OL Organic Letters

pubs.acs.org/OrgLett Letter

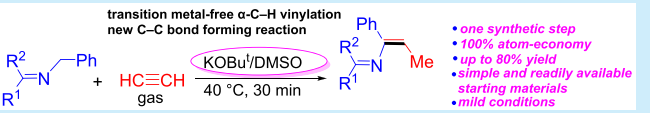
KOBu^t/DMSO-Mediated α-C−H Vinylation of *N*-Benzyl Ketimines with Acetylene Gas: Stereoselective Synthesis of (*E*,*Z*)-2-Azadienes

Ivan A. Bidusenko, Elena Yu. Schmidt, Nadezhda I. Protsuk, Igor A. Ushakov, Alexander V. Vashchenko, Andrei V. Afonin, and Boris A. Trofimov*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00564 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Several imines, readily derived from aryl methyl ketones and benzylamines, react with acetylene gas in KOBu^t/DMSO system to afford 2-azadienes stereoselectively. This new C−C bond constructing reaction involves, instead of the expected ethynylation of the C═N bond, the addition of azaallyl anions to the triple bond of acetylene.

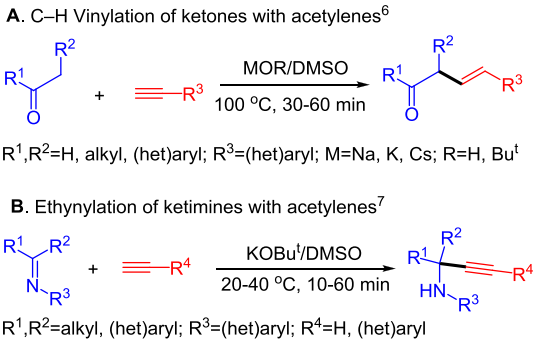


The C−C bond forming reactions are cornerstones of organic chemistry that occupy an important place in its toolkit.[1] In light of growing eco-concerns, research efforts are especially focused on those C−C bond constructing processes that are atom-economic and proceed under nature-mimicking conditions (physiological temperatures, atmospheric pressure) using no heavy metals and toxic solvents. These requirements, also coined as a pot-, atom-, step-economy (PASE) paradigm,[2] well meet the framework of acetylene chemistry. Indeed, acetylene has high and multilateral reactivity. It is industrially manufactured from oil, gas, and coal as well as from calcium carbide, which is now becoming a renewable feedstock (it can be produced from cellulose/lignin).[3] The dual chemistry of acetylene (both electrophilic and nucleophilic reactant) is especially pronounced in basic media (pK_a ∼ 30−32),[4] where acetylene deprotonation, activity of the reacting nucleophiles, and complexing of the triple bond with alkali metal cations are specifically enhanced.[5]

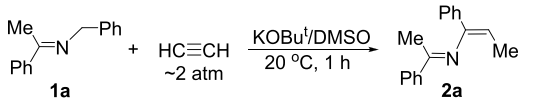
Recently, two transition metal-free involving acetylene Csp^3−Csp^2 and Csp^3−Csp bond-forming reactions occurring in the basic media have been discovered, namely α-C−H vinylation of ketones (Scheme 1, A),[6] where acetylenes behave as electrophiles, and the addition of deprotonated acetylenes as nucleophiles to the C═N bond (Scheme 1, B).[7]

In continuation of this research, we have attempted to extend the latter reaction (Scheme 1, B) to a class of C═N bond containing compounds such as Schiff bases derived from aromatic (heteroaromatic) ketones and benzylamines.[8] However, under the optimum conditions reported for imine alkynylation, instead of the addition of acetylene to the C═N bond of ketimine **1a**, we detected the formation of 2-azadiene **2a** in 34% yield (Scheme 2). This likely results from a higher acidity of the *N*-benzyl ketimines (pK_a ∼ 24)[8b] compared to acetylene. Along this line, transition-metal-free chemo- and regioselective cross-coupling of azaallyls with vinyl bromides has been recently published.[9]

Scheme 1. Transition-Metal-free Csp^3−Csp^2 and Csp^3−Csp Bond-Forming Reactions of Acetylenes in Basic Media



Scheme 2. Reaction of Ketimine 1a with Acetylene Gas in the KOBu^t/DMSO System



Consequently, we studied this reaction in detail to improve yield of the products and to understand the new Csp^2−Csp^2 bond-construction process. This communication is a concise summary and analysis of the results obtained.

As a reference for the investigation, the reaction of imine **1a** with acetylene (Scheme 2) was chosen. In Table 1, the selected

Received: February 13, 2020

https://dx.doi.org/10.1021/acs.orglett.0c00564
Org. Lett. XXXX, XXX, XXX−XXX

representative experimental data illustrating the effect of the reaction conditions on the yield of azadiene **2a** is presented.

Table 1. Effects of the Reaction Conditions on the Yield of 2-Azadiene 2a[a]

entry	**1a**/KOBu^t[b]	T (°C)	*time* (min)	yield of **2a**[c] (%)
1	1:1	25	60	8
2	1:1	40	60	68
3	1:1	40	30	72
4	1:1	40	15	56
5	1:0.5	40	30	66
6	1:0.5	40	120	55
7	1:0.2	40	120	56
8	1:0.2	40	180	43
9	1:1.2	40	30	56
10[d]	1:1	40	30	48
11[e]	1:1	20	30	71
12[f]	1:1	40	30	traces
13[g]	1:1	40	30	14

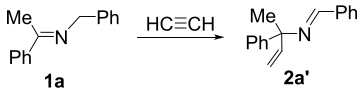
[a]Conditions: **1a** (5 mmol, 1.046 g), KOBu^t (5 mmol), DMSO (50 mL), acetylene (flow rate ~15 cm^3/min). [b]Molar ratio. [c]Isolated yield after column chromatography (SiO_2, *n*-hexane/Et_2O = 20:1). [d]DMSO (20 mL). [e]Acetylene under pressure ~2 atm. [f]NaOBu^t (5 mmol). [g]KOH·0.5H_2O (5 mmol).

The reactions were carried out under atmospheric pressure (a flow reactor) by bubbling of acetylene gas from a commercially available standard cylinder through a stirred solution of ketimine **1a** in the KOBu^t/DMSO system. The reaction was monitored by ^{1}H NMR spectroscopy. Immediately after mixing of ketimine **1a** with KOBu^t/DMSO solution, the reaction mixture turned reddish-purple, which indicated the deprotonation of the substrate to generate semistabilized azaallyl anions that is typical for *N*-benzyl ketimines.[8b] In the course of the process, the color of the reaction mixture faded and became light brown. The optimized conditions providing 72% yield of **2a** can be specified as follows: atmospheric pressure, equimolar ratio of **1a** and KOBu^t, 40 °C, 30 min (entry 3). Performing the reaction at slightly excessive pressure (~2 atm, closed reactor, 20 °C, 30 min) secured 71% yield of **2a** (entry 11). Notably, in the NaOBu^t/DMSO system, only traces of **2a** were observed (entry 12), indicating a crucial role of the alkali metal cation in the reaction. Another characteristic of the process was the need for significant dilution (5 mmol of **1a** in 50 mL of DMSO). This indicated the importance of the dissociation of KOBu^t and prevention of possible interaction of azaallyl anions with nondeprotonated starting ketimines. Carrying the reaction at a higher concentration of **1a** (5 mmol in 20 mL of DMSO) resulted in lowering the yield of **2a** to 48% (entry 10), although the productivity per unit volume became three to four times larger. When the base loading was reduced to 0.5 equiv, the yield of **2a** decreased by only 6% (entry 5). As evident from Table 1, the reaction could be conducted on a gram scale.

Analysis of the ^{1}H NMR spectrum of the crude product indicated the formation of the **2a′**, an isomer of **2a**, which can be formed by the addition of more hindered site of the 2-azaallyl anion to acetylene. The azaallyl anions are known to have the negative charge at the both ends (Scheme 3).[8b]

Although isomer **2a′** was present in the crude product in ~13%, it was difficult to isolate probably due to its hydrolysis on silica gel column. However, in one case, the isomer (see Table 3, **2r′**) was isolated in 3% yield and was fully characterized.

Scheme 3. Competitive C−H Vinylation of Ketimine 1a



After optimizing the conditions for the formation of **2a**, it was applied to an array of substituted N-benzyl ketimines. For the convenience of the substituent effect evaluation, we divided the ketimine series into two sets: one derived from various ketones with an amine counterpart fixed as benzylamine (Table 2) and the second having the varying amine moiety with the fixed ketone counterpart as acetophenone (Table 3).

As follows from Table 2, the reaction proceeded well with several *N*-benzyl ketimines obtained from aryl alkyl ketones including heteroaromatic ones affording products **2a−m** in good yields. Reaction of the imine **1n** obtained from cyclohexanone did not take place at all.

A similar trend was observed in the formation of vinylation products **2** from the benzylic counterpart of ketimines **1** (Table 3). In the case when the α-CH_2 group was linked to an aromatic or heteroaromatic substituent, the vinylation occurred, while with a fully aliphatic substituent at the nitrogen atom (ketimine **1t**) no reaction was observed. The azaallyl anion cannot be stabilized by charge distribution, and hence, the intermediate anionic species were not nucleophilic enough to add to acetylene.

The structure and stereochemistry (*E,Z* configuration) of 2-azadienes **2** have been established by NMR spectroscopy (^{1}H, ^{13}C, ^{15}N), including 2D techniques (NOESY, COSY, HSQC, HMBC), and was also confirmed by single-crystal X-ray analysis of **2k** (Figure 1).

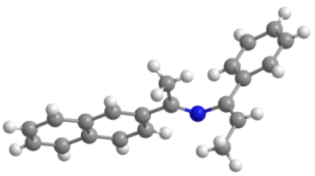
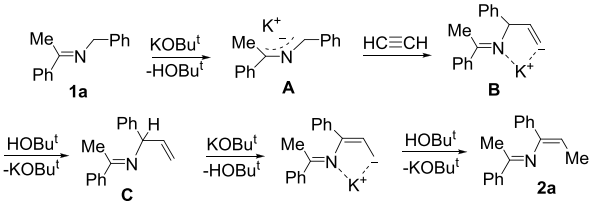


Figure 1. X-ray structure of **2k** (from ethanol; CCDC 1968359)

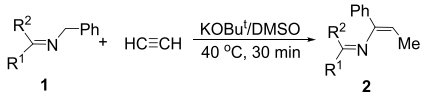
The reaction represents a base-mediated stereoselective α-C−H vinylation of *N*-benzyl ketimines with acetylene gas (Scheme 4, with example of **1a**). Consequently, the key step of the reaction is the addition of the deprotonated substrates (semistabilized azaallyl anions **A**) to the triple bond. Such anions are usually depicted as a three-atom system with the delocalized negative charge. Actually, the electron density delocalization is here extended over the adjacent aromatic or

Scheme 4. Tentative Mechanism of C−H Vinylation of Ketimines 1 with Acetylene

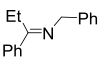
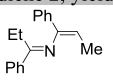
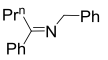
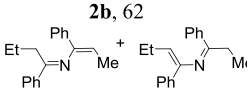
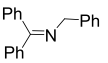
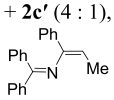
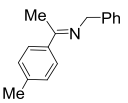
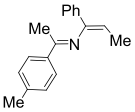
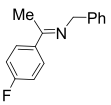
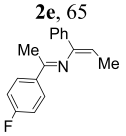
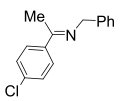
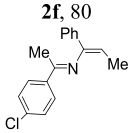
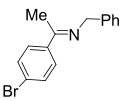
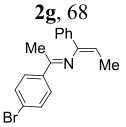
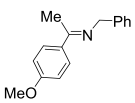
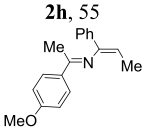
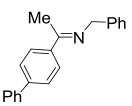
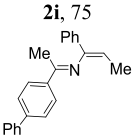
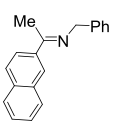
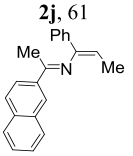
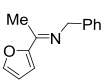
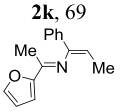
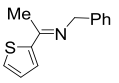
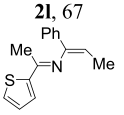
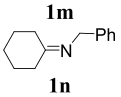


https://dx.doi.org/10.1021/acs.orglett.0c00564
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Effect of the Ketone Counterpart Structure of Ketimines 1 on the Yield of Vinylation Products 2[a]

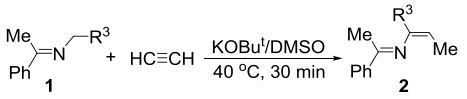


1 2

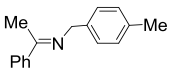
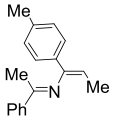
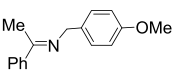
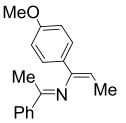
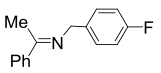
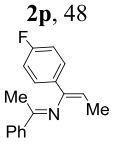
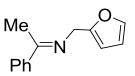
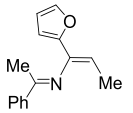
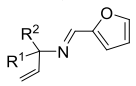
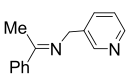
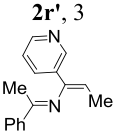
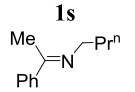
imine **1**	2-azadiene **2**, yield (%)[b]
 **1b**	 **2b**, 62
 **1c**	 **2c** + **2c′** (4 : 1), 79
 **1d**	 **2d**, 67
 **1e**	 **2e**, 65
 **1f**	 **2f**, 80
 **1g**	 **2g**, 68
 **1h**	 **2h**, 55
 **1i**	 **2i**, 75
 **1j**	 **2j**, 61
 **1k**	 **2k**, 69
 **1l**	 **2l**, 67
 **1m**	 **2m**, 64
 **1n**	**2n**, no reaction

[a]Conditions: **1** (5 mmol), KOBu^t (5 mmol), DMSO (50 mL), acetylene (flow rate ∼15 cm^3/min). [b]Isolated yield.

Table 3. Effect of the Benzylamine Counterpart Structure of Ketimines 1 on the Yield of Vinylation Products 2[a]



1 2

imine **1**	2-azadiene **2**, yield (%)[b]
 **1o**	 **2o**, 43
 **1p**	 **2p**, 48
 **1q**	 **2q**, 51
 **1r**	 **2r**, 61
	 **2r'**, 3
 **1s**	 **2s**, 53
 **1t**	**2t**, no reaction

[a]Reactions were carried out under conditions as in Table 2. [b]Isolated yield.

heteroromatic substituent that additionally stabilizes these anionic systems. This increases the concentration of anions **A** in the reaction mixture, thereby making the α-C−H vinylation possible.

An interesting feature of the reaction is the *E,Z* stereochemistry of the azadiene product. Formation of the azadiene can be explained by the following. The intermediate **A** obtained from **1a** reacts with acetylene to form the vinyl carbanion **B**, which leads to the formation of the 2-aza-1,4-diene **C**. The latter prototropically isomerizes, still retaining in the coordination sphere of the K^+ that warrants the *Z* orientation of the forming Me group to finally afford conjugated (*E,Z*) 2-aza-1,3-diene **2a** and recover the base.

This mechanism was supported by the following experiments: (i) In the ^{13}C NMR spectrum of **1a**/KOBu^t/DMSO system, the carbon atom signals of azaallyl anion [C═N−CH]$^-$ were almost equivalent (107.8 and 104.7 ppm, correspondingly) as compared to the ^{13}C NMR spectrum of neutral ketimine **1a** (164.0 and 54.0 ppm, correspondingly), see the SI for details. (ii) The determining effect of alkali metal

https://dx.doi.org/10.1021/acs.orglett.0c00564
Org. Lett. XXXX, XXX, XXX−XXX

cation nature on the reaction course (no reaction with $NaOBu^t$) implies the specific coordination of K^+ with the reacting species. The latter was additionally confirmed by the especially positive role of high dilution of the reaction mixture that rendered a better separation of the K^+/Bu^tO^- ion pair. (iii) The competitive α-C−H vinylation (in a smaller degree) of ketone site of azaallyl system. (iv) The treatment of the reaction mixture with D_2O did not lead to incorporation of deuterium in the target product.

In summary, we have developed a transition-metal-free Csp^2-Csp^2 bond construction reaction comprising the addition of azaallyl anions to acetylene. The methodology meets pot-, atom-, step-economy (PASE)[2] paradigm requirements. Apart from a contribution to fundamental organic chemistry, this reaction offers a convenient and operationally simple stereoselective synthesis of 2-azadienes, important building blocks[10] for creating molecular complexity and diversity of medicinal and biological importance.[11]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00564.

Experimental procedures, compound characterizations, NMR spectra, and crystallographic data (PDF)

Accession Codes

CCDC 1968359 contains 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 emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Boris A. Trofimov − *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences 664033 Irkutsk, Russia;* orcid.org/0000-0002-0430-3215; Email: boris_trofimov@irioch.irk.ru

Authors

Ivan A. Bidusenko − *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences 664033 Irkutsk, Russia;* orcid.org/0000-0003-0783-6233

Elena Yu. Schmidt − *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences 664033 Irkutsk, Russia*

Nadezhda I. Protsuk − *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences 664033 Irkutsk, Russia*

Igor A. Ushakov − *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences 664033 Irkutsk, Russia*

Alexander V. Vashchenko − *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences 664033 Irkutsk, Russia*

Andrei V. Afonin − *A. E. Favorsky Irkutsk Institute of Chemistry, Siberian Branch, Russian Academy of Sciences 664033 Irkutsk, Russia;* orcid.org/0000-0001-7916-2421

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00564

Notes

The authors declare no competing financial interest.

Please be aware of potential safety hazards associated with the use of a $KOBu^t$/DMSO system at increased temperatures.[12]

■ ACKNOWLEDGMENTS

We thank the Baikal Analytical Centre of collective use for the equipment.

■ REFERENCES

(1) For recent reviews, see: (a) Rao, B.; Kinjo, R. *Chem. - Asian J.* **2018**, *13*, 1279−1292. (b) Heravi, M. M.; Ghanbarian, M.; Ghalavand, N.; Nazari, N. *Curr. Org. Chem.* **2018**, *22*, 1420−1457. (c) Santos, A. S.; Mortinho, A. C.; Marques, M. M. B. *Molecules* **2018**, *23*, 2673. (d) Akhtar, R.; Zahoor, A. F.; Parveen, B.; Suleman, M. *Synth. Commun.* **2019**, *49*, 167−192. (e) Hyatt, I. F. D.; Dave, L.; David, N.; Kaur, K.; Medard, M.; Mowdawalla, C. *Org. Biomol. Chem.* **2019**, *17*, 7822−7848.

(2) (a) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438−440. (b) Xiang, H.; Chen, Y.; He, Q.; Xie, Y.; Yang, C. *RSC Adv.* **2013**, *3*, 5807−5810.

(3) (a) Lehmann, J. *Nature* **2007**, *447*, 143−144. (b) Li, G.; Liu, Q.; Liu, Z.; Zhang, Z. C.; Li, C.; Wu, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 8480−8483.

(4) (a) Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295−3299. (b) Yuan, Y.; Thome, I.; Kim, S. H.; Chen, D.; Beyer, A.; Bonnamour, J.; Zuidema, E.; Chang, S.; Bolm, C. *Adv. Synth. Catal.* **2010**, *352*, 2892−2898.

(5) Trofimov, B. A.; Schmidt, E. Yu. *Acc. Chem. Res.* **2018**, *51*, 1117−1130.

(6) Trofimov, B. A.; Schmidt, E. Yu.; Zorina, N. V.; Ivanova, E. V.; Ushakov, I. A. *J. Org. Chem.* **2012**, *77*, 6880−6886.

(7) (a) Bidusenko, I. A.; Schmidt, E. Yu.; Ushakov, I. A.; Trofimov, B. A. *Eur. J. Org. Chem.* **2018**, *2018*, 4845−4849. (b) Schmidt, E. Yu.; Bidusenko, I. A.; Protsuk, N. I.; Demyanov, Y. V.; Ushakov, I. A.; Trofimov, B. A. *Eur. J. Org. Chem.* **2019**, *2019*, 5875−5881.

(8) For recent examples, see: (a) Wu, Y.; Hu, L.; Li, Z.; Deng, L. *Nature* **2015**, *523*, 445−450. (b) Tang, S.; Zhang, X.; Sun, J.; Niu, D.; Chruma, J. *Chem. Rev.* **2018**, *118*, 10393−10457.

(9) Li, M.; Gutierrez, O.; Berritt, S.; Pascual-Escudero, A.; Yeşilçimen, A.; Yang, X.; Adrio, J.; Huang, G.; Nakamaru-Ogiso, E.; Kozlowski, M. C.; Walsh, P. J. *Nat. Chem.* **2017**, *9*, 997−1004.

(10) For recent reviews, see: (a) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379−471. (b) Monbaliu, J.-C. M.; Masschelein, K. G. R.; Stevens, C. V. *Chem. Soc. Rev.* **2011**, *40*, 4708−4739.

(11) For examples, see: (a) Nicolaou, K. C.; Nevalainen, M.; Safina, B. S.; Zak, M.; Bulat, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1941−1945. (b) Moody, C. J.; Hughes, R. A.; Thompson, S. P.; Alcaraz, L. *Chem. Commun.* **2002**, 1760−1761. (c) Stocking, E. M.; Williams, R. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078−3115. (d) Nicolaou, K. C.; Safina, B. S.; Zak, M.; Lee, S. H.; Nevalainen, M.; Bella, M.; Estrada, A. A.; Funke, C.; Zecri, F. J.; Bulat, S. *J. Am. Chem. Soc.* **2005**, *127*, 11159−11175. (e) Shao, X.; Li, K.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 7083−7087. (f) Li, K.; Shao, X.; Tseng, L.; Malcolmson, S. J. *J. Am. Chem. Soc.* **2018**, *140*, 598−601. (g) Malcolmson, S. J.; Li, K.; Shao, X. *Synlett* **2019**, *30*, 1253−1268.

(12) (a) Lam, T. T.; Vickery, T.; Tuma, L. *J. Therm. Anal. Calorim.* **2006**, *85*, 25−30. (b) Wang, Z.; Richter, S. M.; Gates, B. D.; Grieme, T. A. *Org. Process Res. Dev.* **2012**, *16*, 1994−2000. (c) Wang, Z.; Richter, S. M.; Bellettini, J. R.; Pu, Y.-M.; Hill, D. R. *Org. Process Res. Dev.* **2014**, *18*, 1836−1842. (d) Yang, Q.; Sheng, M.; Henkelis, J. J.; Tu, S.; Wiensch, E.; Zhang, H.; Zhang, Y.; Tucker, C.; Ejeh, D. E. *Org. Process Res. Dev.* **2019**, *23*, 2210−2217.