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C—H functionalization of (hetero)arenes: Direct selanylation mediated by Selectfluor

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ABSTRACT

The direct selanylation of a diverse array of (hetero)arenes, including imidazo[2,1-*b*]thiazole, imidazo[1,2-*a*]pyridine, 1*H*-indole, 1*H*-pyrazole, isoxazole and naphthalen-2-ol is presented. The reactions are mediated by Selectfluor, as a stable, easy to handle and commercially available oxidant. The methodology features simple, mild and safe reaction conditions to produce non-symmetrical diorganyl selenides in moderate to excellent yields. The reactions were conducted at room temperature in air using $NaHCO_3$ in acetonitrile.

Introduction

Selenium-containing (hetero)arenes have been extensively studied in recent years and several organoselenium compounds play important roles in agrochemistry, organic synthesis and materials science [1]. This class of compounds has also been widely exploited in medicinal chemistry and present numerous promising biological activities, including anti-inflammatory [2], antimicrobial [3], antiproliferative [4] and acetylcholinesterase enzyme inhibition [5]. In 2015, Zhang and co-workers reported a class of bioactive 3-arylselanyl-1*H*-indoles inspired by the Combretastatin core [6]. In this case the selenium-containing indoles were superior to Combretastatin A-4 in preventing tubulin polymerization and also displayed antiproliferative activity against three human cancer cell lines. Two years later, Lenardão and collaborators described the synthesis and antioxidant activity of several 3-arylselanyl-1*H*-indoles and 3-aryl-selanylimidazo[1,2-*a*]pyridines [7]. These authors also highlighted the importance of the selenium moiety for the pharmacological activity, as the parent heterocycles did not present significant antioxidant potential (Fig. 1).

In light of the chemical and biological importance of selenium-containing (hetero)arenes, the development of new and efficient methodologies for their preparation is an important area of research in organic synthesis and medicinal chemistry. Due to these findings, various methods have been developed for the synthesis of selenium-containing (hetero)arenes and the most recent include iodine species-catalyzed reactions [8], transition metal-catalyzed reactions [9], photo-induced reactions [10] and the use of strong oxidizing agents [11].

On the other hand, Selectfluor [12] has emerged as a stable, easy to handle, non-hygroscopic crystalline solid, which acts as a source of positive fluorine. In addition to its wide applicability as an electrophilic fluorinating agent to direct C—H bond functionalization [13], its use as a mild oxidant in transition metal catalysis has been reported [14–18]. Selected examples include the preparation of alkenyl nitriles [14] and 1,2-diketones [15], allylic C—H borylation of alkenes [16], oxyarylation of alkenes [17] and *ortho*-hydroxylation of ethyl benzoates [18].

With regards to organoselenium chemistry, the generation of an electrophilic selenium species using a *N*-F reagent was recently reported by Breder and co-workers. The combination of a catalytic amount of diphenyl diselenide with *N*-fluorobenzenesulfonimide (NFSI) was the first step to achieve a vinylic C(sp^2)–H nitrogenation reaction [19]. Since then, the use of *N*-F reagents to generate electrophilic selenium catalysts has become an attractive method to

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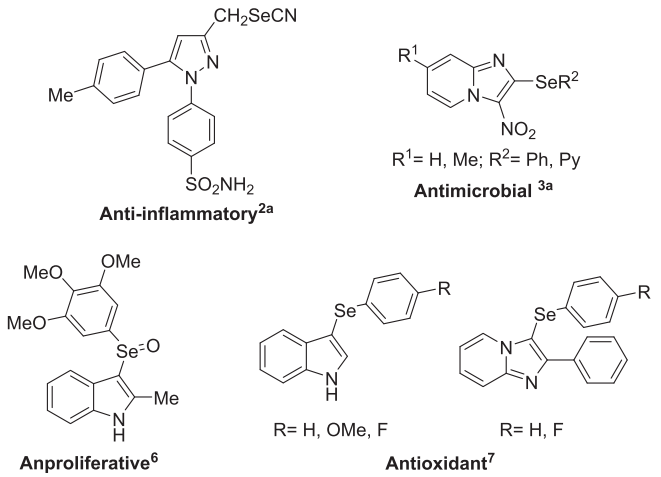


Fig. 1. Selected pharmacologically active selenium-containing heterocycles.

activate and functionalize double bonds through a selenenylation–deselenenylation process [20].

In our study we focused on the selanylation reaction of different (hetero)arenes mediated by Selectfluor under mild conditions. Based on previously reported data [20,21], we proposed that an electrophilic selenium species generated *in situ*, could be captured by the electron rich (hetero)arene to form a new C-Se bond. Then, hydrogen displacement would occur to allow rearomatization of the (hetero)arene and generate the unsymmetrical selenide product.

Results and discussion

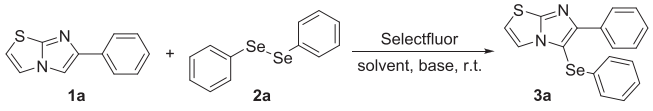
Initially, the model substrates 6-phenylimidazo[2,1-*b*]thiazole **1a** and diphenyl diselenide **2a** were selected for optimization of the reaction conditions. Selectfluor was employed as a mild and safe oxidant, and various conditions were evaluated as depicted in Table 1. Using Selectfluor (0.25 mmol) in acetonitrile at rt, 6-phenyl-5-phenylselanyl-imidazo[2,1-*b*]thiazole **3a** was obtained in 98% yield after column chromatography (Table 1, entry 1). When the reactions were conducted using 0.12 mmol or 0.05 mmol of Selectfluor lower yields were obtained (Table 1, entries 2 and 3). These results demonstrate the dependence of the yield on the amount of Selectfluor. Other solvents such as PEG-400, ethanol, DMSO and ethyl acetate were also tested (Table 1, entries 4–7). However, no improvements were observed, and acetonitrile was considered the most suitable solvent. Finally, we observed that the presence of $NaHCO_3$ as a weak base was important to reduce the reaction time from 2.0 h to 0.5 h (Table 1, entry 8).

With the optimized reaction condition in hand (Table 1, entry 8), we explored the generality and scope of this methodology using different diaryl diselenides **2** as well as (hetero)arenes **1** (Table 2). In addition to diphenyl diselenide **2a**, diaryl diselenides with the electron-donating *para*-methoxy group, the electron-withdrawing *meta*-trifluoromethane group and the sterically bulky substituent 2,4,6-trimethyl group were reacted with imidazo[2,1-*b*]thiazole **1a**. In this regard, we observed that when the electron rich di(4-methoxyphenyl)diselenide was employed, a lower yield was obtained when compared to the non-substituted diselenide **2a**. We propose that the presence of a strong donor group on the diaryl diselenide hinders Se-Se bond cleavage and the generation of an electrophilic selenium species. Conversely, we observed that the presence of an electron-withdrawing group directly attached to the benzene ring favors the formation of the coupling product **3c**, possibly by generating a stronger electrophilic selenium species. When we turned our attention to the bulky di(2,4,6-trimethylphenyl)diselenide, a good yield was obtained for product **3d**. However, this reaction shows evidence that steric hinderance can negatively affect product formation (See Table 2).

In addition to **1a**, 2-phenylimidazo[1,2-*a*]pyridine was also reacted with the four diaryl diselenides under the same reaction conditions. Products **3e**-**h** were obtained in poor to excellent yields. We observed that the electronic and steric effects associated with the diselenides were consistent with the results described for **3a**-**d**. The applicability of this protocol was further demonstrated using different (hetero)arenes, including 1*H*-indole, 1*H*-pyrazole, isoxazole and thiazole. The reaction of 1*H*-indole with diphenyl diselenide in the presence of Selectfluor gave compound **3i** in only 25% yield. This result is consistent with the strong interactions between the electron rich 1*H*-indole and Selectfluor generating different fluorinated compounds and possibly resulting in its degradation [22].

Next, 1*H*-pyrazoles and isoxazoles were reacted with diaryl diselenides to produce 4-selanyl-1*H*-pyrazoles **3j**-**n** and 4-selanyl-isoxazole **3o**-**p**, respectively. Compounds **3j**-**m** were obtained in yields ranging from 21% to 60%. The reactions to give **3j** and **3k** needed to be carried without $NaHCO_3$, because the presence of a base reduced the yield. When 5-methyl-3-isoxazolamine was used product **3o** was satisfactorily obtained in 61% yield. 5-Methyl-4-(phenylselanyl)-3-isoxazolamine **3o** has no precedent in the

Table 1
Optimization of the reaction conditions.[a]



Entry	Selectfluor (mmol)	Solvent	Time (h)[b]	Yield **3a** (%)
1	0.25	MeCN	2	98
2	0.12	MeCN	3	77
3	0.05	MeCN	12	27
4	0.25	PEG-400	12	45
5	0.25	DMSO	5	12
6	0.25	EtOH	23	50
7	0.25	AcOEt	12	17
8[c]	0.25	MeCN	0.5	98

[a] Reactions were conducted using **1a** (0.25 mmol), **2a** (0.13 mmol) in solvent (3.0 mL) at room temperature in air.
[b] The consumption of **1a** was monitored by TLC. [c] 0.25 mmol of $NaHCO_3$ was used.

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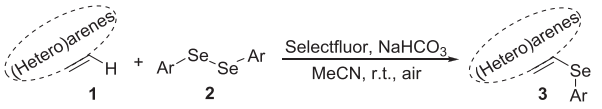
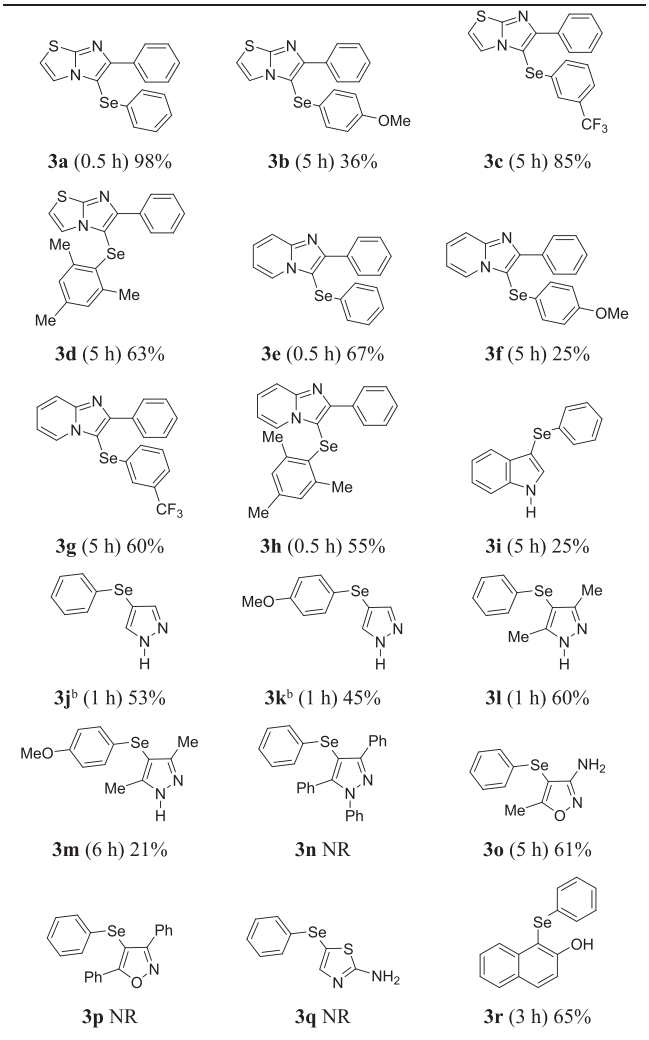
Table 2
Substrate scope of selanyl-(hetero)arenes **3a-r**.[a]





[a]Reactions were conducted using **1** (0.25 mmol), **2** (0.13 mmol), Selectfluor (0.25 mmol) and $NaHCO_3$ (0.25 mmol) in MeCN (3.0 mL) at room temperature in air. [b]Reaction conducted without $NaHCO_3$. NR: No reaction.

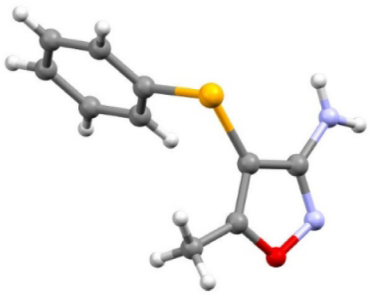


Fig. 2. Molecular structure of compound **3o** obtained by X-ray crystallography. Carbon (grey), red (oxygen), blue (nitrogen), orange (selenium) and white (hydrogen). CCDC number 1992256.

literature and a single-monocrystal was obtained from a mixture of dichloromethane and hexane (1:1) after five days. The structure of **3o** is showed in Fig. 2.

Unfortunately, when 1,3,5-triphenyl-1*H*-pyrazole, 2,5-diphenylisoxazole and 2-aminothiazole were used, products **3n**, **3p** and **3q** were not formed and the starting materials were completely recovered.

In addition to the (hetero)arenes, naphthalen-2-ol was reacted with diphenyl diselenide **2a**. In this case, tolerance of the highly reactive hydroxyl group was observed under the reaction conditions. The direct selanylation occurred at position-1 of the naphthyl ring and 1-(phenylselanyl)naphthalen-2-ol **3r** was obtained in 65% yield after 3 h.

Attempts to improve the yields with a number of diverse heteroarenes proved not to be fruitful with generally incomplete consumption of starting material being observed. Despite this, we believe that the incorporation of an organoselenium group in the structure of the heteroarenes makes them attractive for future applications.

To help understand the reaction mechanism, a control experiment was conducted (Scheme 1) in the presence of the radical inhibitor 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) under the standard reaction conditions. In this case product **3a** was obtained in 65% yield. For us, this outcome suggests that the reaction mechanism is predominantly ionic, but also can follow a radical pathway.

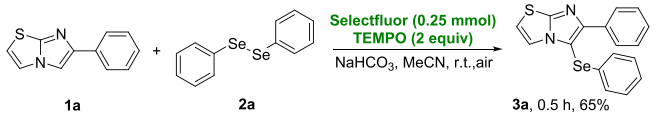
In addition, ^{77}Se NMR analysis previously described by our research group[21a] supports the formation of an electrophilic selenium species during the reaction of diaryl diselenides with Selectfluor, possibly as the result of Se-F bond formation.

Based on the above results and on information from the literature, we propose the reaction mechanism outlined in Scheme 2 for the model substrates **1a** and **2a**. According to this proposal, the reaction of diphenyl diselenide **2a** with Selectfluor gives the electrophilic species **A** and **B** (Step I), as a consequence of Se-F bond formation and nucleophilic attack by a Lewis base [23] on the neighboring selenium atom. These species undergo attack from the electron rich (hetero)arene **1a** to produce the cationic intermediate **C**. Finally, deprotonation of the imidazolium ion **C** by the base leads to formation of the desired product **3a** (Step II).

Finally, to verify the possibility to form a C-F bond and produce 5-fluoro-6-phenyl-imidazo[2,1-*b*]thiazole **4a**, a reaction was conducted in the absence of the diaryl diselenide (Scheme 3). It was possible to obtain **4a** in 23% yield under non-optimized conditions. It is important to note that when diaryl diselenides are present in the reaction media no fluorination products are observed. This result demonstrates that under the optimized reaction conditions Selectfluor has a higher preference to react with diselenides than with the electron rich heterocycles. In general, it also suggests that the direct fluorination was not a competing reaction.

Conclusion

In conclusion, we have developed a simple and efficient methodology for the functionalization of different (hetero)arene systems *via* C-Se bond formation. The selanylation reactions were performed in MeCN as the solvent at r.t. in air. Selanylation of imidazo[2,1-*b*]thiazole, imidazo[1,2-*a*]pyridine, 1*H*-pyrazole, 1*H*-



Scheme 1. Control experiment.

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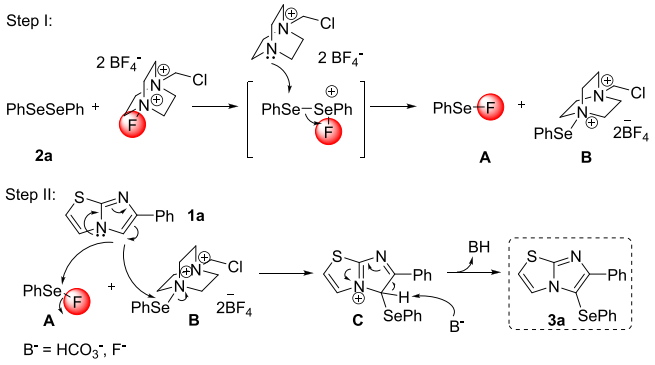
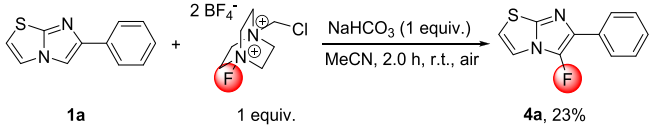


Scheme 2. Ionic mechanism proposal for the formation of selanyl(hetero)arenes **3**.



Scheme 3. Direct fluorination reaction of **1a** with Selectfluor.

pyrazole, 1*H*-indole and naphthalen-2-ol gave the expected products in moderate to excellent yields. The novel compound 5-methyl-4-(phenylselanyl)-3-isoxazolamine was obtained and characterized by X-ray diffraction. Finally, this methodology represents a simple method to access a wide range of non-symmetrical (hetero)aryl selenides under mild conditions, using Selectfluor as a stable, easy to handle and safe oxidizing agent.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152035.

References

[1] (a) F.-Y. Cao, F.-Y. Lin, C.-C. Tseng, K.-E. Hung, J.-Y. Hsu, Y.-C. Su, Y.-J. Cheng, ACS Appl. Mater. Interfaces 11 (2019) 11674–11683;
(b) C. Depken, F. Krätzschmar, R. Rieger, K. Rode, A. Breder, Angew. Chem., Int. Ed. 57 (2018) 2459–2463;
(c) V.K. Jain, K.I. Priyadarsini, Organoselenium Compounds in Biology and Medicine: Synthesis, RSC Publishing, Biological and Therapeutic Treatments, 2018;
(d) R. Montis, M. Arca, M.C. Aragoni, A.J. Blake, C. Castellano, F. Demartin, F. Isaia, V. Lippolis, A. Pintus, E.J. Lenardão, G. Perin, A.E. O'Connor, S. Thurow, New J. Chem. 42 (2018) 10592–10602.
[2] (a) D. Desai, N. Kaushal, U.H. Gandhi, R.J. Arner, C. D'Souza, G. Chen, H. Vunta, K. El-Bayoumy, S. Amin, K.S. Prabhu, Chem. Biol. Interact. 188 (2010) 446–456;
(b) M.H.M. Sari, A.C.G. Souza, S.G. Rosa, P.M. Chagas, S.C.A. da Luz, O.E.D. Rodrigues, C.W. Nogueira, Eur. J. Pharmacol. 781 (2016) 25–35.
[3] (a) S. Kumar, N. Sharma, I.K. Maurya, A.K.K. Bhasin, N. Wangoo, P. Brandão, V. Félix, K.K. Bhasin, R.K. Sharma, Eur. J. Med. Chem. 123 (2016) 916;
(b) M. Giurg, A. Gołab, J. Suchodolski, R. Kaleta, A. Krasowska, E. Piasecki, M. Piętka-Ottlik, Molecules 22 (2017) 974.
[4] (a) M. Álvarez-Pérez, W. Ali, M.A. Marć, J. Handzlik, E. Domínguez-Álvarez, Molecules 23 (2018) 628;
(b) S. Shaaban, A.M. Ashmawy, A. Negm, L.A. Wessjohann, Eur. J. Med. Chem. 179 (2019) 515–526;
(c) D. de Souza, D.O.C. Mariano, F. Nedel, E. Schultze, V.F. Campos, F. Seixas, R. S. da Silva, T.S. Munchen, V. Ilha, L. Dornelles, A.L. Braga, J.B.T. Rocha, T. Collares, O.E.D. Rodrigues, J. Med. Chem. 58 (2015) 3329–3339.
[5] (a) R.F.S. Canto, F.A.R. Barbosa, V. Nascimento, A.S. de Oliveira, I.M.C. Brighente, A.L. Braga, Org. Biomol. Chem. 12 (2014) 3470–3477;
(b) T.J. Peglow, R.F. Schumacher, R. Cargnelutti, A.S. Reis, C. Luchese, E.A. Wilhelm, G. Perin, Tetrahedron Lett. 58 (2017) 3734–3738.
[6] Z. Wen, J. Xu, Z. Wang, H. Qi, Q. Xu, Z. Bai, Q. Zhang, K. Bao, Y. Wu, W. Zhang, Eur. J. Med. Chem. 90 (2015) 184–194.
[7] B.M. Vieira, S. Thurow, M. da Costa, A.M. Casaril, M. Domingues, R.F. Schumacher, G. Perin, D. Alves, L. Savegnago, E.J. Lenardão, J. Asian, Org. Chem. 6 (2017) 1635–1646.
[8] (a) C. Ding, Y. Yu, Q. Yu, Z. Xie, Y. Zhou, J. Zhou, G. Liang, Z. Song, ChemCatChem 10 (2018) 5397–5401;
(b) J. Rafique, S. Saba, A.R. Rosario, A.L. Braga, Chem. Eur. J. 22 (2016) 11854;
(c) M. Xu, X.H. Zhang, P. Zhong, Synth. Commun. 42 (2012) 3472–3481.
[9] (a) Z. Li, J. Hong, X. Zhou, Tetrahedron 67 (2011) 3690–3697;
(b) B.M. Vieira, S. Thurow, J.S. Brito, G. Perin, D. Alves, R.G. Jacob, C. Santi, E.J. Lenardão, Ultrason. Sonochem. 27 (2015) 192–199;
(c) K.S. Santos, E.M.A. Sandagorda, R. Cargnelutti, T. Barcellos, R.G. Jacob, D. Alves, R.F. Schumacher, ChemistrySelect 2 (2017) 10793–10797;
(d) J. Zhu, W. Zhu, P. Xie, C.U. Pittman Jr., A. Zhou, Tetrahedron 74 (2018) 6569–6576.
[10] (a) Q.-B. Zhang, Y.-L. Ban, P.-F. Yuan, S.-J. Peng, J.-G. Fang, L.-Z. Wu, Q. Liu, Green Chem. 19 (2017) 5559–5563;
(b) S. Saba, J. Rafique, M.S. Franco, A.R. Schneider, L. Espíndola, D.O. Silva, A.L. Braga, Org. Biomol. Chem. 16 (2018) 880–885.
[11] (a) C. Ding, Y. Yu, Q. Yu, Z. Xie, Y. Zhou, J. Zhou, G. Liang, Z. Song, ChemCatChem 10 (2018) 5397–5401;
(b) I. Rodrigues, A.M. Barcellos, A.L. Belladona, J.A. Roehrs, R. Cargnelutti, D. Alves, G. Perin, R.F. Schumacher, Tetrahedron 74 (2018) 4242–4246;
(c) S. Vásquez-Céspedes, A. Ferry, L. Candish, F. Glorius, Angew. Chem., Int. Ed. 54 (2015) 5772–5776;
(d) G. Cera, L. Ackermann, Chem.–Eur. J. 22 (2016) 8475–8478.
[12] (a) R.E. Banks, M.K. Besheesh, S.N. Mohialdin-Khaffaf, I. Sharif, J. Chem. Soc., Perkin Trans. 1 (1996) 2069–2076;
(b) G.S. Lal, G.P. Pez, R.G. Syvret, Chem. Rev. 96 (1996) 1737–1756;
(c) P.T. Nyffeler, S.G. Durón, M.D. Burkart, S.P. Vincent, C.-H. Wong, Angew. Chem. Int. Ed. 44 (2005) 192–212.
[13] (a) D. Heeran, G. Sandford, Tetrahedron 72 (2016) 2456–2463;
(b) J.-B. Xia, C. Zhu, C. Chen, J. Am. Chem. Soc. 135 (2013) 17494–17500;
(c) S. Bloom, C.R. Pitts, R. Woltornist, A. Griswold, M.G. Holl, T. Lectka, Org. Lett. 15 (2013) 1722–1724;
(d) S.I. Mirallai, P.A. Koutentis, F. Aldabbagh, Molecules 24 (2019) 282.
[14] D.-W. Gao, E.V. Vinogradova, S.J. Nimmagadda, J.M. Medina, Y. Xiao, R.M. Suciu, B.F. Cravatt, K.M. Engle, J. Am. Chem. Soc. 140 (2018) 8069–8073.
[15] W. Zhang, J. Zhang, Y. Liu, Z. Xu, Synlett 24 (2013) 2709–2714.
[16] L. Mao, R. Bertermann, K. Emmert, K.J. Szabó, T.B. Marder, Org. Lett. 19 (2017) 6586–6589.
[17] L.T. Ball, M. Green, G.C. Lloyd-Jones, C.A. Russell, Org. Lett. 12 (2010) 4724–4727.
[18] Y. Yang, Y. Lin, Y. Rao, Org. Lett. 14 (2012) 2874–2877.
[19] J. Trenner, C. Depken, T. Weber, A. Breder, Angew. Chem. Int. Ed. 52 (2013) 8952–8957.
[20] (a) R. Guo, L. Liao, X. Zhao, Molecules 22 (2017) 835;
(b) L. Shao, Y. Li, J. Lu, X. Jiang, Org. Chem. Front. 6 (2019) 2999–3041;
(c) Y. Kawamata, T. Hashimoto, K. Maruoka, J. Am. Chem. Soc. 138 (2016) 5206–5209.
[21] (a) M.C.P.F. Xavier, E.M.A. Sandagorda, J.S.S. Neto, R.F. Schumacher, M.S. Silva, RSC Adv. 10 (2020) 13975–13983;
(b) J.S. Yadav, B.V.S. Reddy, Y.J. Reddy, Tetrahedron Lett. 48 (2007) 7034–7037.
[22] (a) R. Lin, S. Ding, Z. Shi, N. Jiao, Org. Lett. 13 (2011) 4498–4501;
(b) L. Shi, D. Zhang, R. Lin, C. Zhang, X. Li, N. Jiao, Tetrahedron Lett. 55 (2014) 2243–2245;
(c) Y. Takeuchi, T. Tarui, N. Shibata, Org. Lett. 2 (2000) 639–642.
[23] A. Thupyai, C. Pimpasri, S. Yotphan, Org. Biomol. Chem. 16 (2018) 424–432.