ACES Asian Chemical Editorial Society

doi.org/10.1002/ajoc.202300545

ASIAN JOURNAL OF ORGANIC CHEMISTRY
Research Article

www.asianjoc.org

การอ้างอิงอยู่ในหน้า 4

Access to [6-7-6]-Icetexanes through Sequential Cascade Cyclization and Biomimetic Ring Expansion

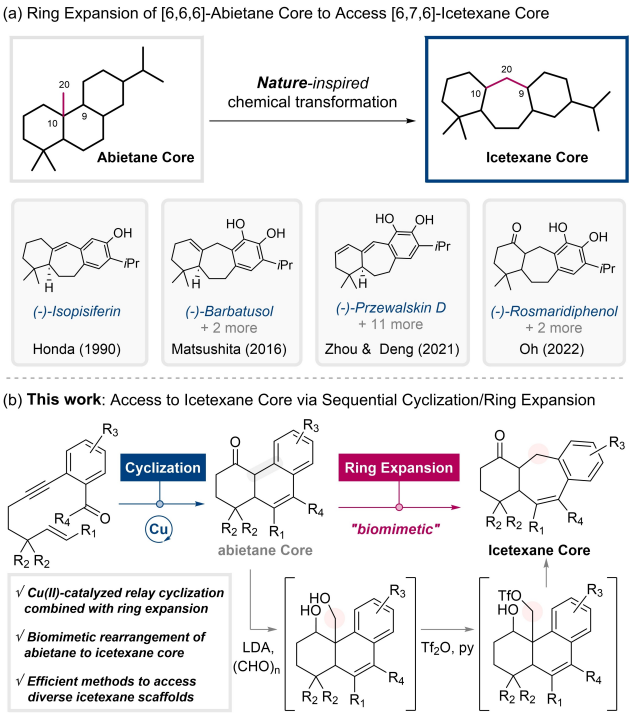
Thuy Quynh Le[+],[a] Niaz Liaba[+],[a] Da In Jeong,[a] Jeonghyo Lee,*[a] and Chang Ho Oh*[a]

We herein report an efficient synthetic method for preparing [6-7-6]-icetexane derivatives. This approach employs our previously designed copper-catalyzed intramolecular cyclization of enyne-aryl carbonyl substrates to generate a [6-6-6]-tricyclic abietane framework and a subsequent ring expansion protocol for the [6-7-6] scaffold. By synergizing these protocols, we established a highly efficient pathway for synthesizing icetexane compounds from readily available enyne-aryl starting materials, exhibiting remarkable versatility in accommodating various functional groups while delivering consistently high yields.

Introduction

Icetexane diterpenes constitute a distinctive family of diterpenoids characterized by their intricate [6-7-6] tricyclic framework. These compounds have been predominantly isolated from terrestrial plants, notably within the Labiatae family.[1] The discovery of icetexone from *S. ballotaeflora* in 1976 marked the inception of an extensive catalogue, encompassing over 70 icetexane diterpenes, each featuring diverse oxygenation and oxidation patterns within their respective rings.[2] The allure of icetexane diterpenoids lies in their compelling biological activities and pharmaceutical potential, which encompass antimicrobial,[3] anti-cancer,[4] antioxidant, [5[anti-inflammatory,[6] antifungal,[7] and anti-HIV[8] properties. As a consequence, these compounds have emerged as highly coveted targets within the domains of synthetic and medicinal chemistry over the past four decades. In light of their unique structural motifs, several sophisticated synthetic strategies have been devised for the construction of icetexane diterpenes. These methodologies encompass diverse approaches, such as Ga(III)-catalyzed cycloisomerization,[9] tandem C–H oxidation/cyclization/rearrangement,[10] intramolecular Marson-type cyclization,[11] Pd-catalyzed intramolecular Heck reactions,[12] $TiCl_4$-catalyzed Friedel–Crafts cycloalkylation,[13] and Pt-mediated cyclization,[14] each playing a pivotal role as key steps in the synthetic routes.

While icetexane structure is featured as [6-7-6] core, abietane diterpenoids are characterized by a common [6-6-6]-tricyclic core. A systematic name 9(10→20)-abeo-abietane given to icetexanes indicates that an abietane core could be involved in the biosynthetic origin of icetexanes (Scheme 1a). In 1976, Watson and coworkers were the first to propose a structural connection between abietanes and icetexanes.[15] Since then, research endeavors have been undertaken to establish the connection between abietanes and their structurally rearranged counterparts.[16] In 1990, the Honda group reported a strategy towards the synthesis of (±)-pisiferin (±)-isopisiferin, via key ring expansion of (±)-pisiferol, generated via intramolecular [4 + 2] cycloaddition.[17] Subsequently, the Matsushita group reported the semi-synthesis of icetexanes diterpenoids named (+)- rosmaridiphenol, (−)-barbatusol, and (+)-demethylsalvicanol, from naturally separated (+)-pisiferic acid via B-ring expansion.[18] Recently, Zhou, Deng and co-workers presented an efficient regioselective and scalable synthetic strategy toward (+)-grandione (−)-demethylsalvicanol, (−)-barbatusol



Scheme 1. Ring expansion reaction in the synthesis of icetexane diterpenoids.

[a] *T. Q. Le,[+] N. Liaba,[+] D. I. Jeong, J. Lee, C. H. Oh*
Department of Chemistry and Research Institute of Natural Science, Hanyang University,
Sungdong-Gu, Seoul 04763 (Korea)
E-mail: changho@hanyang.ac.kr
jeonghyolee@hanyang.ac.kr

[+] *These authors contributed equally*

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ajoc.202300545

and other icetexane diterpenes using PPh_3/DIAD-mediated rearrangement of naturally extracted carnosic acid.[19]

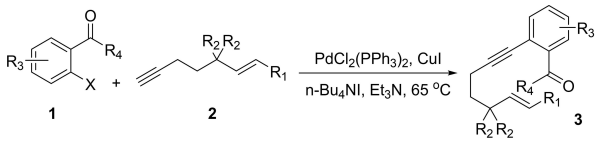
Motivated by existing literature detailing the biological mechanisms and ring-enlargement chemistry associated with the conversion of abietane to icetexane, our group recently contributed to offering a versatile and efficient method for icetexane synthesis. In contrast to prior studies, which typically involve isolating [6-6-6]-abietane compounds from natural or semi-synthetic sources, our icetexane synthesis approach operates through the copper-catalyzed relayed cyclization of enyne-aryl carbonyl substrate[20] to generate abietane [6-6-6]-tricyclic structures (Scheme 1b). Combining this procedure with the B-ring expansion strategy, we successfully synthesized three icetexane diterpenoids, namely (±)-pisiferin, (±)-rosmaridiphenol, and (±)-barbatusol.[21] Our methodology offers versatility in modifying the desired icetexane core through various derivatization routes. In this work, we broaden the application of copper-catalyzed cyclization and ring expansion procedures to access the icetexane core, demonstrating its potential as a foundational precursor for synthesizing a wide range of icetexane natural products featuring diverse functional groups.

Results and Discussion

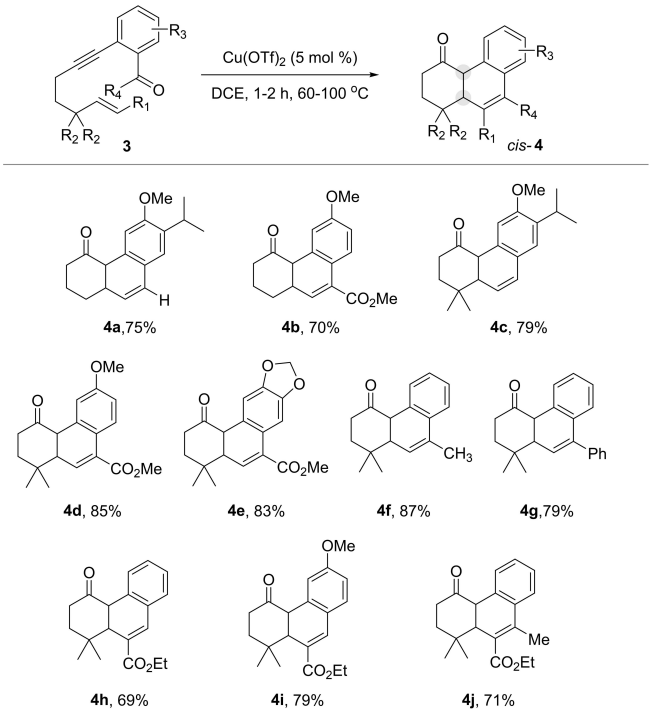
To initiate the creation of the icetexane framework, our initial strategy was centered on establishing the abietane scaffold. This scaffold was derived from aryl-enyne starting material **3**, attainable through a Pd-catalyzed Sonogashira coupling reaction employing readily available starting materials.[20] (Scheme 2). Utilizing this procedure, we can easily introduce aromatic compound **1**, encompassing a diverse array of functional groups like aryl aldehydes, aryl ketones, and aryl oxalates, into the abietane scaffold, thereby incorporating these functional groups as desired.

With the aryl-enyne substrates in our possession, we proceeded to investigate their applications in the synthesis of the [6-6-6]-tricyclic abietane framework through our copper-catalyzed intramolecular cyclization reaction protocol.[20d] This method distinguishes itself by enabling the efficient preparation of the abietane core in a straightforward and highly effective manner, in stark contrast to previous approaches that often relied on natural or semi-synthetic processes, rendering structural derivatization challenging.

Under the optimized Cu-catalytic conditions (utilizing 5 mol% of $Cu(OTf)_2$ in 1,2-dichloroethane at temperatures ranging from 60 to 100 °C),[20d] the relayed cyclization reaction efficiently furnished the tricyclic abietane core with various functional groups attached (Scheme 3). The presence of oxygen



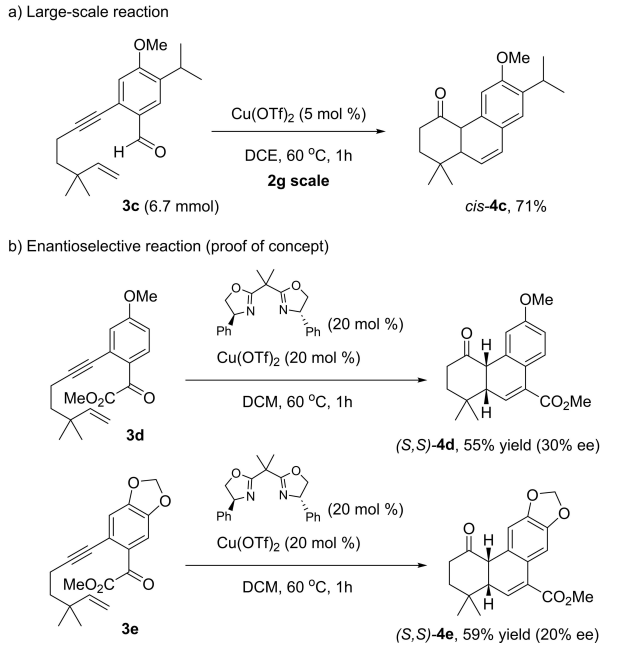
Scheme 2. Preparation of aryl-enyne substrate **3**.



Scheme 3. Copper-catalyzed cyclization of aryl-enyne towards [6,6,6]-tricyclic abietane derivatives.

functionalities in the aromatic ring (methoxy in **4a**-**4d** and **4i** and a methylenedioxy bridge in **4e**) was well-tolerated, and it was observed that *iso*-propyl groups could also be incorporated into the aromatic ring (**4a** and **4c**), yielding the desired tricyclic product in respectable yields. Furthermore, the resulting alkene in product **4** displayed compatibility with ester, alkyl, and phenyl groups (**4b** and **4d**-**4j**), highlighting the robustness of our cyclization reaction toward electronic variations. It is noteworthy that all tricyclic abietane products formed in this reaction adopted a *cis*-configuration, a fact corroborated by previous studies.[20d,e]

Next, we conducted a scale-up experiment to assess the potential application of Cu-catalyzed relay-cyclization on enyne-carbonyl substrates (Scheme 4a). To our delight, 2 grams (6.7 mmol) of aryl-enyne **3c** underwent a successful transformation, yielding the desired tricyclic structure **4c** in a 71% yield, a result comparable to the 0.1 mmol scale reaction. Encouraged by this success in large-scale synthesis, we then turned our attention to the possibility of achieving copper catalysis in an asymmetric fashion, utilizing a chiral ligand. Among the various chiral ligands available, we selected the BOX ligand, (4S,4′S)-2,2′-(propane-2,2-diyl)bis(4-phenyl-4,5-dihydrooxazole), as outlined in Scheme 4b. In the presence of the BOX ligand, aryl enyne substrates **3d** and **3e** underwent conversion into the tricyclic structures **4d** and **4e** with moderate yields, yielding 30% and 20% *ee (enantiomeric excess)*, respectively. While high enantioselectivity was not achieved in this reaction, it still stands as a meaningful proof of concept, demonstrating the potential for asymmetric synthesis of abietane. It should be noted that the chiral copper system also



Scheme 4. Synthetic viability of Cu(II)-catalyzed cyclization

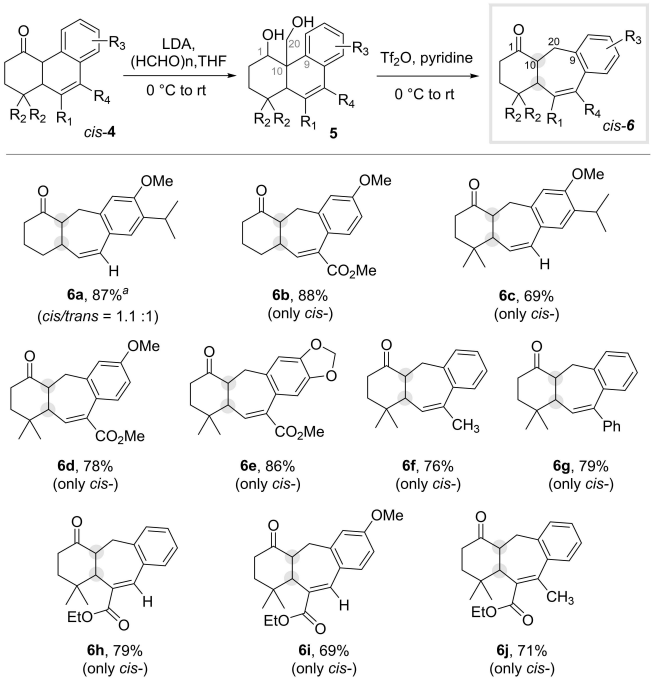
produced the cyclic structure with A and B rings in a *cis*-configuration with each other, but the (*S,S*)-configuration was favored.

Following the successful creation of the [6-6-6]-abietane scaffold **4**, our subsequent focus was on converting it into the [6-7-6]-icetexane structure using a B-ring expansion reaction (Scheme 5). In the presence of a C1 carbonyl group in compound **4**, we explored the possibility of hydroxymethylation at the C10 position through kinetic enolate formation, followed by the addition of paraformaldehyde. Interestingly, this reaction resulted in an overreaction, yielding diol compound **5**, which had been observed in our previous study.[20b] Consecutively, diol compound **5** underwent primary alcohol triflation and subsequent a 1,2-carbon rearrangement, leading to the formation of the ring-expanded [6-7-6]-icetexane product **6** (for a specific mechanism, refer to Scheme 6).

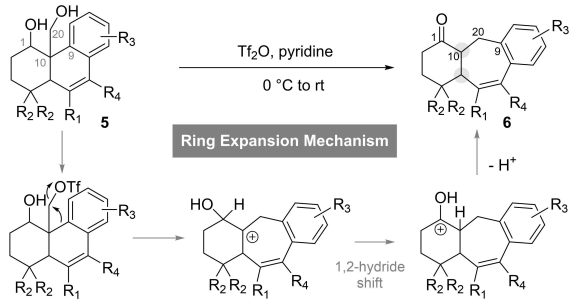
It is worth noting that all the abietane substrates **4**, encompassing diverse functional groups as described in Scheme 3, proved to be well-suited for these stepwise procedures, resulting in the transformation into icetexane **6**. Importantly, the *cis*-configuration of compound **4** remained intact throughout these transformations, yielding selectively *cis*-icetexane scaffold **6**.[22] To verify the stereochemical structure, we conducted ^{1}H NMR, ^{13}C NMR, DEPT, and COSY NMR experiments (detailed in the Supplementary Information).

Acknowledging the prior transformation from the [6-6-6]-abietane scaffold to the [6-7-6]-icetexane structure, which encompassed alkene formation at either the C9-C10 or C1-C10 positions,[17–19] our current protocol has retained the sp^3 carbon configuration at C10 position of the icetexane core. This underscores the unique mechanistic features of our reaction. We postulate that the hydroxy group at the C1 position of compound **5** contributes to the stability of the presumed carbocation intermediates that form following the removal of the triflate leaving group (Scheme 6). While there is the potential for these carbocation intermediates to undergo deprotonation and give rise to alkene products,[17–19] the presence of the alcohol group serves as a protective mechanism by facilitating the transformation into a ketone. This ensures the successful formation of the desired icetexane core.

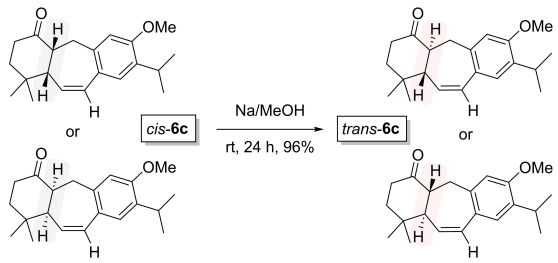
Finally, the *cis* isomer of compound **6c** underwent a successful epimerization reaction when treated with sodium methoxide in methanol at room temperature for 24 hours (Scheme 7). This transformation primarily yielded the thermodynamically stable *trans*-**6c** in an impressive 96% yield. This approach allows for the efficient preparation of both the *cis*- and *trans*- versions of the icetexane core, demonstrating a highly effective method for constructing the icetexane derivatives.



Scheme 5. Ring expansion of [6-6-6]-abietane core to afford [6-7-6]-icetexane derivatives. [a]*cis*/*trans* mixture was obtained (see SI for detail)



Scheme 6. Plausible ring expansion mechanism involving carbocation intermediates.



Scheme 7. Isomerization of *cis*-**6c** to *trans*-**6c**.

Conclusions

In summary, we developed a streamlined approach for the efficient synthesis of icetexane core which can be used to construct natural products. Commencing with the creation of the abietane scaffold, the formation of the tricyclic abietane core is achieved, accommodating diverse functional groups, demonstrating scalability, and showing potential for asymmetric synthesis. The abietane scaffold is then expanded into the icetexane structure while preserving its distinctive sp^3 carbon configuration, with a key role played by a hydroxy group at the C1 position. The successful asymmetric cyclization and epimerization of the *cis* isomer into the stable *trans* form was also demonstrated as a proof of concept. This work offers a practical means for the production of both icetexane isomers, thus contributing to advancements in natural product synthesis.

Supporting Information

The authors have included additional references within the Supporting Information ([23])

Acknowledgements

This work was supported by a Basic Science Research Program through the National Research Foundation of Korea (NRF), funded by the Ministry of Education (NRF-2021R1F1A1049992).

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: biomimetic reaction · carbocation rearrangement · copper · cyclization · ring expansion

[1] a) J. L. Fernandez-Alonso, N. Vega, J. J. Filgueira, G. Pérez, *Biochem. Syst. Ecol.* **2003**, *31*, 617–633; b) M. C. G. Vallejo, L. Moujir, J. Burillo, L. L. Guerra, M. Gonzalez, R. D. Penate, L. S. Andrés, J. G. Luis, F. L. Blanco, C. R. de Galarreta, *Flavour Fragrance J.* **2006**, *21*, 72–76.
[2] a) E. M. Simmons, R. Sarpong, *Nat. Prod. Rep.* **2009**, *26*,1195–1217; b) M. A. Gonzalez, *Nat. Prod. Rep.* **2015**, *32*, 684–704; c) A. A. Naeini, A. A. Ziegelmeier, W. J. Chain, *J. Chem. Biodiversity.* **2022**, *19*, e202200793; d) J. Kang, T. Q. Le, C. H. Oh, *Tetrahedron Lett.* **2022**, *108*, 154133.
[3] a) M. C. Bonito, C. Cicala, M. C. Marcotullio, F. Maione, N. Mascolo, *Nat. Prod. Commun.* **2011**, *6*, 1205–1215; b) A. M. El-Lakany, M. S. Abdel-Kader, N. N. Sabri, F. R. Stermitz, *Planta Med.* **1995**, *61*, 559–560.
[4] G. Zheng, A. Kadir, X. Zheng, P. Jin, J. Liu, M. Maiwulanjiang, G. Yao, H. A, *A. Org. Chem. Front.* **2020**, *7*, 3137–3145.
[5] V. G. M. Naidu, H. Atmakurb, S. B. Katragadda, B. Devabakthuni, A. Kota, S. C. K. Reddy, M. Kuncha, M. V. P. S. V. Vardhan, P. Kulkarni, M. R. Janaswamy, R. Sistla, *Phytomedicine.* **2014**, *21*, 497–505.
[6] A. Salae, A. Rodjun, C. Karalai, C. Ponglimanont S Chantrapromma, A. Kanjana-Opas, S. Tewtrakul, H. Fun, *Tetrahedron* **2012**, *68*, 819–829.
[7] A. Khan, M. Rahman, M. S. Islam, *Pharm. Biol.* **2009**, *47*, 1187–1191.
[8] F. Xia, S. Z. Du, M. K. Wu, R. Liu, Y. S. Ye, J. Yang, G. Xu, Y. Nian, *Bioorg. Chem.* **2022**, *128*, 106059.
[9] E. M. Simmons, J. R. Yen, R. Sarpong, *Org. Lett.* **2007**, *9*, 2705–2708.
[10] Z. W. Jiao, Q. Zhang, W. X. Liu, S. Y. Zhang, S. H. Wang, F. M. Zhang, S. Jiang, Y. Q. Tu, *Nat. Commun.* **2015**, *6*, 7332.
[11] D. Martinez-Solorio, M. P. Jennings, *Org. Lett.* **2009**, *11*, 189–192.
[12] S. Sengupta, M. G. B. Drew, R. Mukhopadhyay, B. Achari, A. K. Banerjee, *J. Org. Chem.* **2005**, *70*, 7694–7700.
[13] a) G. Majetich, J. Yu, Y. Li, *Heterocycles.* **2007**, *73*, 227–235; b) G. Majetich, Y. Li, G. Zou, *Heterocycles.* **2007**, *73*, 217–225.
[14] C. H. Oh, L. Piao, J. Jung, J. Kim, *Asian J. Org. Chem.* **2016**, *5*, 1237–1241.
[15] W. H. Watson, Z. Taira, X. A. Dominguez, H. Gonzales, M. Guiterrez, R. Aragon, *Tetrahedron Lett.* **1976**, *17*, 2501–2502.
[16] S. Hasegawa, Y. Hirose, M. Yatagai, T. Takahashi, *Chem. Lett.* **1984**, *13*, 1837–1838.
[17] T. Kametani, H. Kondoh, M. Tsubuki, T. Honda, *J. Chem. Soc.-Perkin Trans.* **1990**, *1*, 5–10.
[18] E. Nisigaki, K. Sugamoto, M. Nishida, Y. Matsushita, *Chem. Lett.* **2016**, *45*, 746–748.
[19] W. Cao, T. Liu, S. Yang, M. D. Liu, Z. Pan, Y. Zhou, X. J. Deng, *Nat. Prod.* **2021**, *84*, 2012–2019.
[20] a) C. Seong, J. Kang, U. Chai, D. H. Mac, C. H. Oh, *Synlett.* **2020**, *31*, 1953–1956; b) C. Seong, J. Kang, J. Lee, C. H. Oh, *Bull. Korean Chem. Soc.* **2021**, *42*, 517–520; c) J. Kang, S. Ham, C. Seong, C. H. Oh, *Synlett* **2021**, *32*, 1039–1043; d) J. Kang, J. H. Lee, J. Lee, C. H. Oh, *Asian J. Org. Chem.* **2022**, *11*, e202200244; e) N. Asao, Y. Yamamoto, Gold-Catalyzed Benzannulations: Asao-Yamamoto Benzopyrylium Pathway, in Modern Gold Catalyzed Synthesis, ed. A. S. K. Hashmi, F. D. Toste, Wiley-VCH, Weinheim, 1st edn. **2012**, 35–75.
[21] T. Q. Le, J. H. Lee, C. H. Oh, *Synlett.* **2022**, *33*, 983–987.
[22] In the case of **6a**, exceptionally, a *cis*/*trans* mixture was obtained in 45% and 42% yield, respectively.
[23] a) N. R. Cichowicz, W. Kaplan, Y. Khomutnyk, B. Bhattarai, Z. Sun, P. Nagorny, *J. Am. Chem. Soc.* **2015**, *137*, 14341; b) Y. You, T. T. Li, T. J. Sun, Y. P. Zhang, Z. H. Wang, J. Q. Zhao, W. C. Yua, *Org. Lett.* **2022**, *24*, 7671–7676.

Manuscript received: October 15, 2023
Revised manuscript received: November 20, 2023
Accepted manuscript online: November 21, 2023
Version of record online: December 7, 2023