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Cu(I)−NHC-Catalyzed (2 + 3)-Annulation of Tetramic Acids with 2*H*-Azirines: Stereoselective Synthesis of Functionalized Hexahydropyrrolo[3,4-*b*]pyrroles

Nikolai V. Rostovskii, Pavel A. Sakharov, Mikhail S. Novikov,* Alexander F. Khlebnikov, and Galina L. Starova

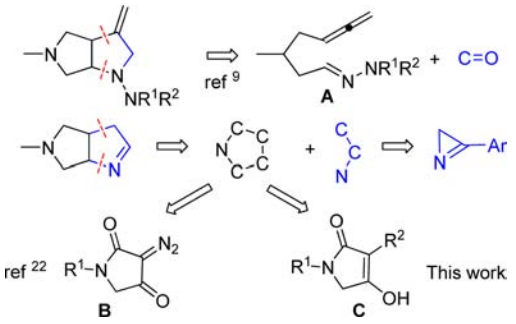
Institute of Chemistry, Saint-Petersburg State University, Universitetskii pr. 26, 198504 St. Petersburg, Russia

Supporting Information

ABSTRACT: A stereoselective and high-yield synthesis of hexahydropyrrolo[3,4-*b*]pyrroles from tetramic acids and 2*H*-azirines under Cu(I)−NHC catalysis is developed. An unusual N−C2 azirine bond cleavage, initiated by a copper enolate, was rationalized in terms of a free radical reaction mechanism.

Various pyrrolopyrrole compounds are attracting a growing attention due to a wide range of biological activities and useful photophysical and optical properties.[1] The pyrrolo[3,4-*b*]pyrrole core is known to be the basic unit of h5-HT_{1D} receptor agonists,[2] which are effective for relieving migraine headache, 5-HT_{2C} receptor agonists,[3] applicable for obesity treatment, and highly selective NK-2 receptor agonists.[4] The pyrrolo[3,4-*b*]pyrrole skeleton is also involved in uracil-based[5] and 4-oxo-4*H*-quinolizine[6] antibacterials. Two principally different strategies for the construction of the bicyclic pyrrolo[3,4-*b*]pyrrole core can be used. The first one makes use of the multistep synthesis of an acyclic or monocyclic precursor, followed by intramolecular cycloaddition[3,7] or cyclization.[4,8] The second approach, involving an intermolecular assembly of the pyrrolo[3,4-*b*]pyrrole backbone, was represented by Ru- or Mo-catalyzed cyclocarbonylation of γ-allenylhydrazones (Scheme 1, structure **A**).[9] In contrast to this reaction the convergent synthetic scheme, which ends with the intermolecular annulation of a pyrroline fragment to pyrrolidine ring, would permit rapid assemblage of the bicyclic pyrrolo[3,4-*b*]pyrrole core from rather simple starting materials if an appropriate C−C−N building block were found. One of the potential synthetic equivalents of a C−C−N synthon are 2*H*-azirines, which have recently been widely used for heterocyclic synthesis[10] and have proven to be especially suitable for the preparation of pyrrole and 2-/3-pyrroline derivatives. Some of these reactions occur intermolecularly via the C=N bond cleavage of an azirine ring providing a C−C−N fragment for the targeted pyrrole or pyrroline system. Various compounds including enamines,[11] ynamines,[12] enols,[13] alkali metal enolates,[14] transition-metal enolates (Cu(I),[15] Cu(II),[16,17] Co(II),[17] Ni(II)[18]), pyridinium,[19] and imidazolium ylides[20] can be used in these annulations as the partners (C−C building blocks) of the azirines. However, only a few examples of the utilization of 2*H*-azirines for the synthesis of *ortho*-fused polycyclic systems via annulation are known.[21] Recently, we have found that 3-aryl-2*H*-azirines are capable of reacting with diazotetramic acids (3-diazopyrrolidine-2,4-diones) (Scheme 1, structure **B**) under $Cu(acac)_2$ catalysis to give 3a-(triazol-2-yl)pyrrolo[3,4-*b*]pyrroles as reaction products.[22]

Scheme 1. Convergent Routes to Pyrrolo[3,4-*b*]pyrroles



We describe herein a facile and stereoselective approach to highly functionalized hexahydropyrrolo[3,4-*b*]pyrrole derivatives based on the Cu(I)-catalyzed (2 + 3)-annulation reaction of tetramic acids (Scheme 1, structure **C**) with 2*H*-azirines.

For the test experiments, we used readily available 3-phenyl-2*H*-azirine **2a** and tetramic acid **1a** (Table 1), which was synthesized from methyl *N*-(*p*-methoxybenzyl)glycinate and methyl phenylacetate. Heating a solution of compound **1a**, azirine **2a** (1.6 equiv), and 5 mol % of copper(II) acetylacetonate (calculated on tetramic acid) in 1,2-dichloroethane (DCE) gave a 1.8:1 mixture of adduct **3a** and bis(pyrrolidinedione) **4a** (Table 1, entry 1). Compound **3a** was isolated by column chromatography in 46% yield, while both diastereomers **4a**, originating from an oxidation of tetramic acid **1a**, were isolated in a further experiment (see Scheme 3, entry 9) and also fully characterized. Trace amounts of two dimerization products of azirine **2a**, 2-methyl-2,4-

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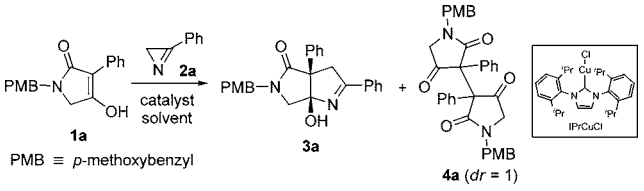
Table 1. Optimization of 3a Synthesis[a]



entry	catalyst	mol %	solvent	ratio 3a:4a[b]
1	$Cu(acac)_2$	5	DCE	1.8:1 (46)[c]
2	$Cu(acac)_2$	5	MeOH	2.4:1
3	CuI	5	MeOH	0.5:1
4	$[Cu(NCMe)_4][PF_6]$	5	MeOH	2.6:1
5	$[Cu(NCMe)_2(PPh_3)_2][BF_4]$	5	MeOH	4.3:1
6	CuC≡CPh	5	MeOH	11:1 (72)[c]
7	IPrCuCl	5	MeOH	12:1 (84)[c]
8	IPrCuCl	2.5	MeOH	8.1:1
9	IPrCuCl	1	MeOH	7.4:1
10	IPrCuCl	0.1	MeOH	2.2:1
11	IPrCuCl	5	MeOH	2.7:1[d]

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.16 mmol), a catalyst, solvent (1.5 mL), 10 min, 100 °C. [b]Ratio was determined by ^{1}H NMR spectroscopy. [c]Isolated yield of adduct **3a**. [d]60 °C, 50 min.

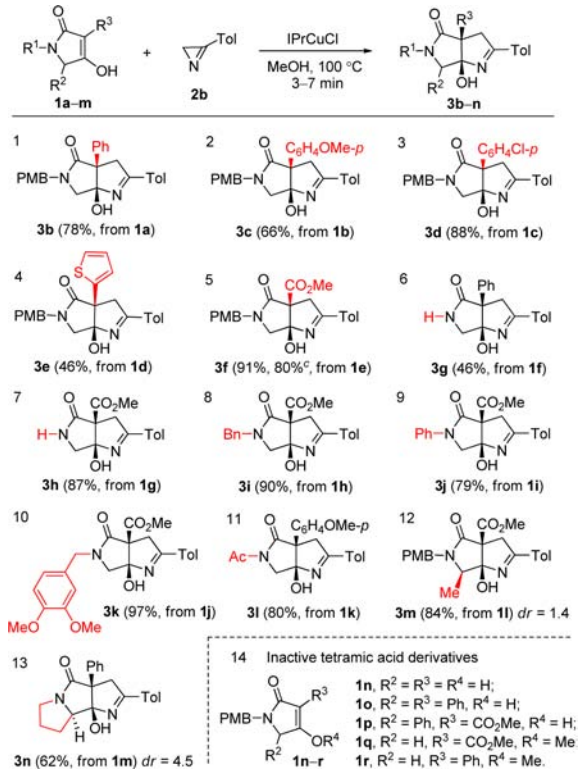
diphenyl-2*H*-imidazole and 2,5-diphenylpyrazine, were also isolated.[23]

In order to reduce the amount of side product **4a**, an optimization of reaction conditions was performed (Table 1). In the absence of a catalyst or in the presence of $Rh_2(OAc)_4$ no reaction was observed. No traces of adduct **3a** were detected in the ^{1}H NMR spectra of the reaction mixtures obtained with the additives of Fe(III), Ni(II), and Co(III) acetylacetonates. It was also found that the catalysis with $Cu(acac)_2$ in methanol instead of DCE gives less side product **4a** (entry 2), and further optimization was carried out in this solvent. All of the tested copper(I) compounds showed catalytic activity (entries 3−7), with *N*-heterocyclic carbene−copper(I) complex (IPrCuCl) providing the best yield of **3a** and highest **3a**:**4a** ratio (entry 7). The low catalyst (IPrCuCl) loading as well as the decrease of the reaction temperature led to the increase of the side product quantity (entries 8−11). Thus, the optimal conditions were found to be the heating of a 1.6:1 mixture of azirine **2a** and tetramic acid **1a** in MeOH (concentration of **1a** 0.067 mol/L) at 100 °C in the presence of IPrCuCl (5 mol %).

With the optimized conditions in hand, we examined the scope of the reaction. The reaction of azirine **2b** with variously substituted tetramic acids **1a−m** provided pyrrolo[3,4-*b*]-pyrroles **3b−n** in good to high yields (Scheme 2). 3-Aryl-, 3-hetaryl-, and 3-alkoxycarbonyl-substituted as well as *N*-unsubstituted, *N*-acetyl-, and *N*-phenyl-substituted tetramic acids are compatible with this transformation (entries 1−12). The reaction also proceeds well with fused tetramic acid **1m** giving rise to tricyclic pyrrolo[2,3-*a*]pyrrolizine derivative **3n**[24] (entry 13). Attempts, however, to accomplish the annulation of 3-unsubstituted **1n** and bulkier 5-phenyl-substituted tetramic acids **1o**,**p** failed (entry 14). The presence of an OH group in substrate **1** proved to be a necessary requisite for the reaction to occur, as no pyrrolo[3,4-*b*]pyrrole derivatives were obtained when *O*-methylated derivatives **1q**,**r** were used (entry 14).

It was also shown that 3-aryl-2*H*-azirines with electron-donating and electron-withdrawing substituents in the *para* position of the phenyl ring provide the corresponding

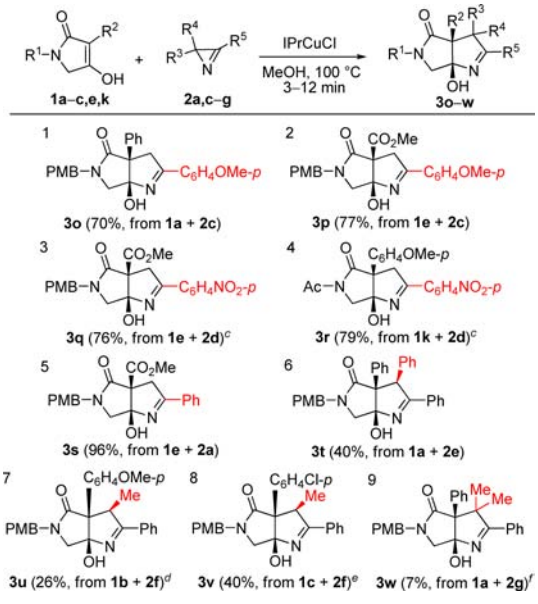
Scheme 2. Scope of Tetramic Acids 1[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2b** (0.32 mmol), IPrCuCl (5 mol %), MeOH (3 mL). [b]Isolated yields. [c]$Cu(acac)_2$ (5 mol %) was used as a catalyst.

pyrrolo[3,4-*b*]pyrroles **3o−r** in good yields (Scheme 3, entries 1−4). In the reactions of 3-(*p*-nitrophenyl)-2*H*-azirine **2d** (entries 3 and 4), DCE was used as solvent because of the

Scheme 3. Scope of 2*H*-Azirines[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.32 mmol), IPrCuCl (5 mol %), solvent (3 mL). [b]Isolated yields. [c]DCE was used as a solvent. [d]**4b** was also isolated in 33% yield. [e]**4c** was also isolated in 20% yield. [f]**4a** was also isolated in 40% yield.

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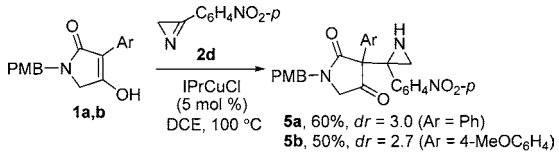
instability of the azirine in methanol under the reaction conditions. 2,3-Disubstituted azirines **2e,f** react slower and provide the annulation products **3t−v** in moderate yield (entries 6−8). Compounds **3t**,[24] **3u**,[24] and **3v** are formed stereoselectively as a single (3*RS*,3a*SR*)-isomer with *cis*-oriented substituents at the C3 and C3a positions. The use of the more hindered 2,2-dimethyl-3-phenyl-2*H*-azirine **2g** resulted in a lower yield of the desired product (entry 9) and an increase of the amount of side product **4a** (ratio **3w**:**4a** is 1:1.4 according to ^{1}H NMR). For the reactions with di- and trisubstituted azirines **2e−g** the presence of an aryl group at C3 of a tetramic acid seems to be crucial, as tetramic acids **1e,g−j,l** with an ester group at C3 did not give pyrrolo[3,4-*b*]pyrroles **3** at all.

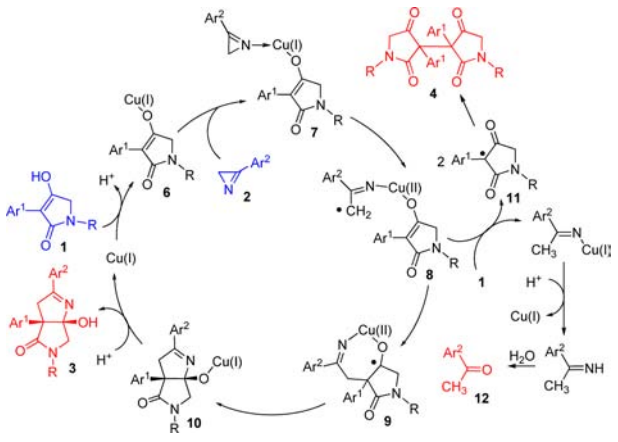
Unexpectedly, tetramic acids **1a,b**, not containing at least one strong electron-withdrawing substituent at N1 or C3, react with 3-(*p*-nitrophenyl)-2*H*-azirine **2d** to give a diastereomeric mixture of aziridines **5a,b**,[24] but not the corresponding pyrrolo[3,4-*b*]pyrroles (Scheme 4). This reaction occurs under heating without a catalyst but slowly, providing lower yields of the desired product.

Scheme 4. Aziridine Formation



The reaction of the rather nucleophilic **1a,b** with highly electrophilic **2d** can be rationalized in terms of a nucleophilic addition over the C═N bond. Such additions are postulated for the Cu(II)- or Ni(II)-catalyzed reactions of azirines with acyclic 1,3-dicarbonyl compounds to produce pyrrole derivatives via the azirine N═C bond cleavage.[17,18] The results presented in Schemes 2 and 3 are in sharp contrast to the outcome of the above-mentioned reactions: under similar conditions, a cleavage of the azirine N−C2 single bond occurs. This unusual outcome, along with the fact that there is a formation of dimerization products **4**, has led us to the assumption that the formation of adducts **3** from tetramic acids **1** and 2*H*-azirine **2** proceeds via a radical pathway (Scheme 5). First, Cu(I) enolate **6** coordinates with azirine **2**, producing the azirine complex **7** which then is transformed to the open-chain radical species **8** via an azirine N−C2 bond cleavage.

Scheme 5. Proposed Reaction Mechanism



Cyclization of intermediate **8** gives a key cyclic radical intermediate **9**. This cyclization likely controls the stereochemical outcome of the reactions of 2,3-disubstituted azirines **2e,f** providing the sole stereoisomer of **3** (Scheme 3, entries 6−8). Finally, transformation of **9** to intermediate **10** and the release of the catalyst furnishes adduct **3**. The formation of the coupling product **4** can be rationalized in terms of the competing reaction of intermediate **8** with tetramic acid **1**, the formation of two radical species **11**, and subsequent dimerization. This undesirable route becomes dominant when sterically hindered azirines are used. It is worth noting that among the byproducts of the reaction acetophenones **12** were also detected, which have been previously reported as the products of an azirine radical decomposition.[23] The reason for the inability of some acyclic enols to react with azirines[15−18] via a radical pathway may be both the chelated structure of its metal enolates which are unable to provide intermediate **7** and the absence of additional radical-stabilizing substituent R^3 (Scheme 2).

We found that compound **1a** virtually did not oxidize into **4a** in MeOH when heated at 100 °C in the presence of IPrCuCl or $Cu(acac)_2$, but an additive of sterically hindered 2,2-dimethyl-3-phenyl-2*H*-azirine (**2g**) strongly accelerates this process. It is noteworthy that oxidation of **1a** into **4a** under the action of 2,2-diphenyl-1-picrylhydrazyl radical at room temperature or molecular iodine under heating occurs very rapidly, but the addition of azirine **2a** to a mixture of **1a** and the radical initiator does not provide **3a**. From this result, it follows that the ordinary radical addition of species **11** to azirines **2** should be excluded from the sequence leading to pyrrolo[3,4-*b*]pyrroles **3**.

In conclusion, we have developed an effective method for the preparation of hexahydropyrrolo[3,4-*b*]pyrroles from easily accessible tetramic acids and 2*H*-azirines. The reaction is catalyzed both by Cu(I) and Cu(II) compounds, but the best results were obtained with the use of the imidazole-based NHC−Cu(I) complex. 3-Aryltetramic acids stereoselectively react with 2,3-disubstituted 2*H*-azirines, furnishing exclusively (3*RS*,3a*SR*)-isomer. The annulation of a new pyrroline ring proceeds via the N−C2 azirine bond cleavage, which can be explained by a free-radical reaction mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01883.

Experimental procedures, characterization data, X-ray structures, and ^{1}H, ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: m.s.novikov@chem.spbu.ru.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Kaur, M.; Choi, D. H. *Chem. Soc. Rev.* **2015**, *44*, 58. (b) Bijleveld, J. C.; Gevaerts, V. S.; Di Nuzzo, D.; Turbiez, M.; Mathijssen, S. G. J.; de Leeuw, D. M.; Wienk, M. M.; Janssen, R. A. J. *Adv. Mater.* **2010**, *22*, E242. (c) Schrimpf, M. R.; Tietje, K. R.; Toupence, R. B.; Ji, J.; Basha, A.; Bunnelle, W. H.; Daanen, J. F.; Pace, J. M.; Sippy, K. B. Patent WO0181347, 2001.

(2) Russell, M. G. N.; Beer, M. S.; Stanton, J. A.; Sohal, B.; Mortishire Smith, R. J.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2491.

(3) Huck, B. R.; Llamas, L.; Robarge, M. J.; Dent, T. C.; Song, J.; Hodnick, W. F.; Crumrine, C.; Stricker-Krongrad, A.; Harrington, J.; Brunden, K. R.; Bennani, Y. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2891.

(4) Deal, M. J.; Hagan, R. M.; Ireland, S. J.; Jordan, C. C.; McElroy, A. B.; Porter, B.; Ross, B. C.; Stephens-Smith, M.; Ward, P. *J. Med. Chem.* **1992**, *35*, 4195.

(5) Petersen, U.; Schenke, T.; Krebs, A.; Grohe, K.; Scheriewer, M.; Haller, I.; Mezger, K. G.; Endermann, R.; Zeiler, H. J. U.S. Patent 5 416 096, 1996.

(6) Ma, Z.; Chu, D. T. W.; Cooper, C. S.; Li, Q.; Fung, A. K. L.; Wang, S.; Shen, L. L.; Flamm, R. K.; Nilius, A. M.; Alder, J. D.; Meulbroek, J. A.; Or, S. R. *J. Med. Chem.* **1999**, *42*, 4202.

(7) (a) Henke, B. R.; Kouklis, A. J.; Heathcock, C. H. *J. Org. Chem.* **1992**, *57*, 7056. (b) Marx, M. A.; Grillot, A.-L.; Louer, C. T.; Beaver, K. A.; Bartlett, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 6153. (c) Peng, G.; Sohn, A.; Gallop, M. A. *J. Org. Chem.* **1999**, *64*, 8342. (d) Pedrosa, R.; Andres, C.; de las Heras, L.; Nieto, J. *Org. Lett.* **2002**, *4*, 2513. (e) Garner, P.; Kaniskan, H. U. *Tetrahedron Lett.* **2005**, *46*, 5181. (f) Aurich, H. G.; Gentes, C.; Harms, K. *Tetrahedron* **1995**, *51*, 10497.

(8) (a) Xu, Z.; De Moliner, F.; Cappelli, A. P.; Hulme, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8037. (b) Jeannotte, G.; Lubell, W. D. *J. Org. Chem.* **2004**, *69*, 4656. (c) Hogan, P. C.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 15386. (d) Rowley, M.; Leeson, P. D.; Williams, B. J.; Moore, K. W.; Baker, R. *Tetrahedron* **1992**, *48*, 3557.

(9) (a) Kang, S.-K.; Kim, K.-J.; Hong, Y.-T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1584. (b) Kim, S.-H.; Kang, E.; Yu, C.-M. *Synlett* **2007**, *2007* (15), 2439.

(10) (a) Huang, C.-Y.; Doyle, A. G. *Chem. Rev.* **2014**, *114*, 8153. (b) Khlebnikov, A. F.; Novikov, M. S. *Tetrahedron* **2013**, *69*, 3363.

(11) (a) Auricchio, S.; Bini, A.; Pastormerlo, E.; Truscello, A. M. *Tetrahedron* **1997**, *53*, 10911. (b) Auricchio, S.; Truscello, A. M.; Lauria, M.; Meille, S. V. *Tetrahedron* **2012**, *68*, 7441.

(12) Zhu, L.; Yu, Y.; Mao, Z.; Huang, X. *Org. Lett.* **2015**, *17*, 30.

(13) Alves, M. J.; Gilchrist, T. L.; Sousa, J. H. *J. Chem. Soc., Perkin Trans. 1* **1999**, *21*, 1305.

(14) (a) Palacios, F.; Ochoa de Retana, A. M.; Vélez del Burgo, A. *J. Org. Chem.* **2011**, *76*, 9472. (b) Ben Cheikh, R.; Bouzouita, N.; Ghabi, H.; Chaabouni, R. *Tetrahedron* **1990**, *46*, 5155. (c) Laurent, A.; Mison, P.; Nafti, A.; Pellissier, N. *Tetrahedron Lett.* **1982**, *23*, 655.

(15) Li, T.; Xin, X.; Wang, C.; Wang, D.; Wu, F.; Li, X.; Wan, B. *Org. Lett.* **2014**, *16*, 4806.

(16) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313.

(17) Galenko, A. V.; Khlebnikov, A. F.; Novikov, M. S.; Avdontceva, M. S. *Tetrahedron* **2015**, *71*, 1940.

(18) (a) Galenko, E. E.; Galenko, A. V.; Khlebnikov, A. F.; Novikov, M. S. *RSC Adv.* **2015**, *5*, 18172. (b) Dos Santos Filho, P. F.; Schuchardt, U. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 647.

(19) Khlebnikov, A. F.; Golovkina, M. V.; Novikov, M. S.; Yufit, D. S. *Org. Lett.* **2012**, *14*, 3768.

(20) Khlebnikov, A. F.; Tomashenko, O. A.; Funt, L. D.; Novikov, M. S. *Org. Biomol. Chem.* **2014**, *12*, 6598.

(21) (a) Mei, Y.; Bentley, P. A.; Wang, W. *Tetrahedron Lett.* **2006**, *47*, 2447. (b) Candito, D. A.; Lautens, M. *Org. Lett.* **2010**, *12*, 3312. (c) Dähler, M.; Prewo, R.; Bieri, J. H.; Heimgartner, H. *Helv. Chim. Acta* **1983**, *66*, 1456. (d) Schläpfer-Dähler, M.; Heimgartner, H. *Helv. Chim. Acta* **1993**, *76*, 2321.

(22) Rostovskii, N. V.; Novikov, M. S.; Khlebnikov, A. F.; Korneev, S. M.; Yufit, D. S. *Org. Biomol. Chem.* **2013**, *11*, 5535.

(23) Auricchio, S.; Grassi, S.; Malpezzi, L.; Sartori, A. S.; Truscello, A. M. *Eur. J. Org. Chem.* **2001**, *2001*, 1183.

(24) CCDC 1061210 (**3f**), CCDC 1061136 ((3a*RS*,8a*SR*,8b*SR*)-**3n**), CCDC 1061124 (**3o**), CCDC 1061125 (**3t**), CCDC 1407546 (**3u**), and CCDC 1061137 ((*RS*,*SR*)-**5b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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