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Visible-Light-Induced Cleavage of C–S Bonds in Thioacetals and Thioketals with Iodine as a Photocatalyst

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A protocol for a visible-light-induced cleavage of thioacetals and thioketals using molecular iodine as a photocatalyst in combination with oxygen as the terminal oxidant is reported. The reaction proceeds with low catalyst loadings and high chemical yields while the most commonly used *N*- and *O*-protecting groups remain untouched in this transformation. Further investigation showed that the reaction also permits the synthesis of unsymmetrical disulfides by cleavage of unsymmetrical thioacetals.

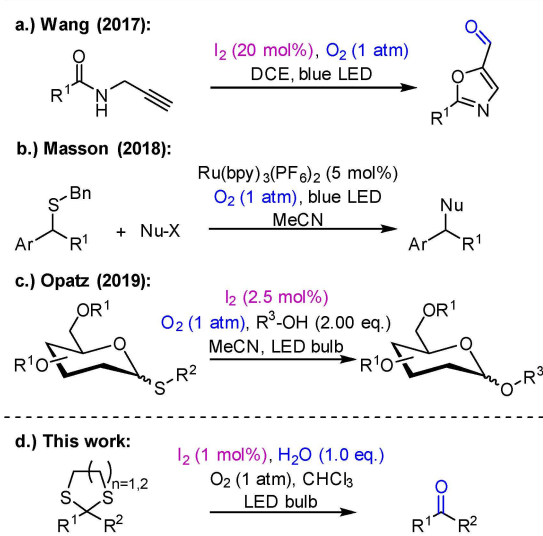
Thioacetals and thioketals have found numerous important applications in organic chemistry and are mostly encountered in form of 1,3-dithianes and 1,3-dithiolanes as protecting groups.^[1] These protecting groups are popular in particular due to their facile introduction and high stability in many chemical transformations.^[2] They have been used in total synthesis^[3] and also found widespread application as substrates in the Corey-Seebach umpolung reaction.^[4] Thioacetals and -ketals can be readily obtained by treatment of carbonyls with thiols in the presence of Lewis or Brønsted acids.^[5] The cleavage of thioacetals and -ketals has also generated attention and made considerable progress over the recent years.^[6]

A series of light-induced transformations based on photoredox catalysis have e.g. been developed.^[7] In particular, the development of new photocatalysts for such reactions has been pursued.^[8] Most of the commonly employed photocatalysts are transition metal complexes or organic dyes, while simple, cost-effective and photoactive main group elements, like molecular iodine, surprisingly are underexplored in this context.^[9] Molecular iodine can absorb visible light to reach its electronically excited state^[10] and can effectively sensitize the formation of singlet oxygen.^[11]

One of the first reports featuring molecular iodine as a photocatalyst in combination with molecular oxygen under irradiation of visible light was the activation of alkynes for electrophilic cyclizations by Wang and co-workers (Scheme 1, a).^[12] In their report, molecular iodine both acted as a photocatalyst for singlet oxygen generation and as a π -Lewis acid. Recently, Masson and coworkers showed that benzylic thioethers can be oxidized to the radical cations through a combination of Ru(bpy)₃(PF₆)₂ and molecular oxygen.^[13] Notably, this report revealed that singlet oxygen cleaves C–S bonds through oxidation.

In this case, energy transfer originates from ruthenium to oxygen and not from iodine. Our lab recently investigated the cleavage of thioglycosides with iodine photocatalysis in combination with oxygen as the terminal oxidant.^[14] Thioglycosides were activated by catalytic amounts of iodine to release glycosyl cation intermediates which reacted with alcohols to produce various *O*-glycosides (Scheme 1, c).

We hypothesized that the combination of iodine with oxygen under irradiation might provide a more general approach for the activation of C–S bonds. Thus, our initial glycosylation work prompted us to investigate whether dithioacetals also were suitable substrates for this system.



Scheme 1. Overview of literature reports employing iodine and oxygen photocatalytic systems (top) and schematic representation of the protocol reported herein (bottom).

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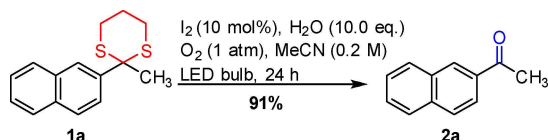
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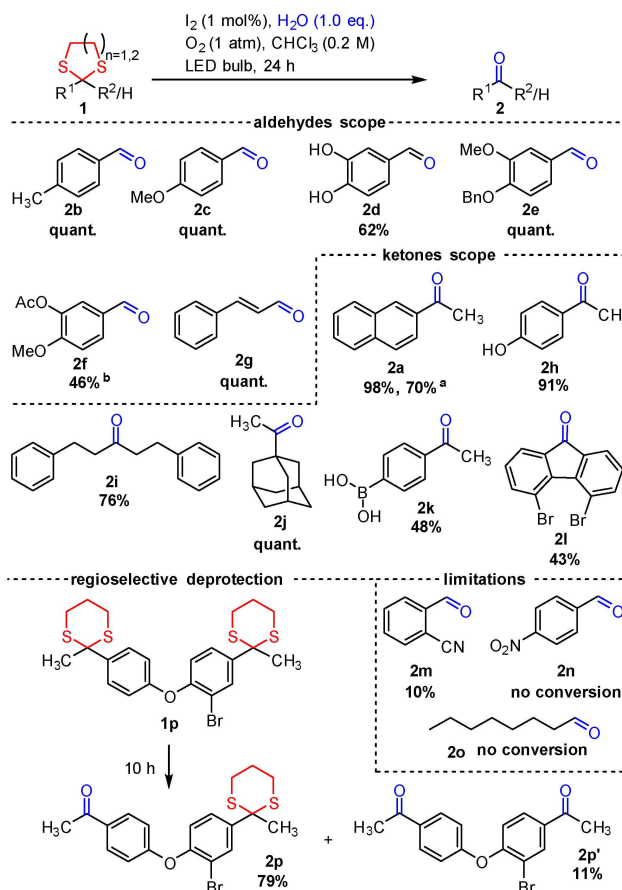
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Herein, the development of a related inexpensive protocol for the mild photocatalytic cleavage of thioacetals and -ketals is reported. Molecular iodine serves as an inexpensive, environmentally benign and widely available photocatalyst in combination with oxygen as the terminal oxidant. The reaction is driven by irradiation with visible light using a common household energy saving LED bulb. In an initial experiment, the cleavage of 1,3-dithiane derivative **1a** was investigated (Scheme 2). The reaction was carried out in acetonitrile with 10 mol% of iodine in the presence of H₂O and O₂ under irradiation with a LED bulb (12 W, warm white color temperature). Cleavage proceeded smoothly and yielded ketone **2a** in 91% yield. In order to reduce the catalyst loading, optimization studies were carried out (for details, see the SI). The catalyst loading was reduced to 1 mol% and the solvent was switched to chloroform, providing a superior solubility of substrate **1a** in comparison to the initially used acetonitrile. Besides the optimization of the reaction conditions, mechanistic experiments were performed (see the SI for details). For example, it was shown that oxidation of dithianes is likely to involve a combination of iodine and singlet oxygen. An ¹⁸O labelling experiment revealed that the oxygen atom in the product originates from the added water. Thus, water and oxygen atoms were highlighted in blue in the reaction schemes.

With the optimized conditions in hand, the substrate scope was investigated (Scheme 3). First experiments showed that the reaction proceeded smoothly in quantitative yield when *p*-toluylaldehyde- (**2b**) or *p*-anisylaldehyde thioacetal derivatives (substrate **2c**) were used. The 1,3-dithiane derivative of 3,4-dihydroxybenzaldehyde (**2d**) was deprotected in 62% yield. When the phenolic hydroxyl groups were protected as ethers as in the case of 4-benzyl-3-methoxybenzaldehyde (**2e**), a quantitative yield was again achieved. A decrease in yield to 46% was found when acetoxy groups as in substrate **2f**, were present. Gratifyingly, olefinic double bonds remain untouched as demonstrated by the release of cinnamaldehyde (**2g**) in quantitative yield. The developed iodine-catalyzed deprotection strategy was also successfully applied to the cleavage of thioketals (Scheme 3, lower part). 2-Acetonaphthone (**2a**) was released from the 1,3-dithiane derivative in 98% yield, while its 1,3-dithiolane derivative yielded the same ketone in 70% yield. The deprotection of *p*-hydroxyacetophenone (**2h**) was achieved in 91% yield. Next, the ability of the method to deprotect aliphatic ketone derivatives was investigated. The deprotection of the 1,3-dithiane derivatives of dibenzylacetone (**2i**) and 1-acetyladamantane (**2j**) was successful. A free boronic acid moiety as demonstrated by substrate **2k** was tolerated without any noticeable deborylation. The doubly bromo-substituted fluorenone **2l** was released in 43% yield. Electron withdrawing groups reduce the reaction rate as demonstrated by the release of 2-cyanobenzaldehyde (**2m**), where only 10% of the desired product could be isolated, while the major component of the reaction mixture was unreacted starting material. 4-Nitrobenzaldehyde (**2n**) could not be released from its 1,3-dithiane derivative. Octanal (**2o**) also showed no conversion to the desired product, which gives evidence that aliphatic aldehydes cannot be deprotected with this protocol. This drawback can be exploited to achieve regioselective deprotection of substrate **1p** (Scheme 3, bottom). Diaryl ether **1p** containing a single bromine atom to differentiate both rings electronically can be deprotected regioselectively with the electron-rich 1,3-dithiane moiety of **1p** reacting more rapidly. If the reaction is stopped after 10 h, the desired product **2p** was isolated in 79% yield, while the undesired doubly deprotected product **2p'** was obtained in only 11% yield. The regioisomeric monodeprotected compound could not be found in the reaction mixture.



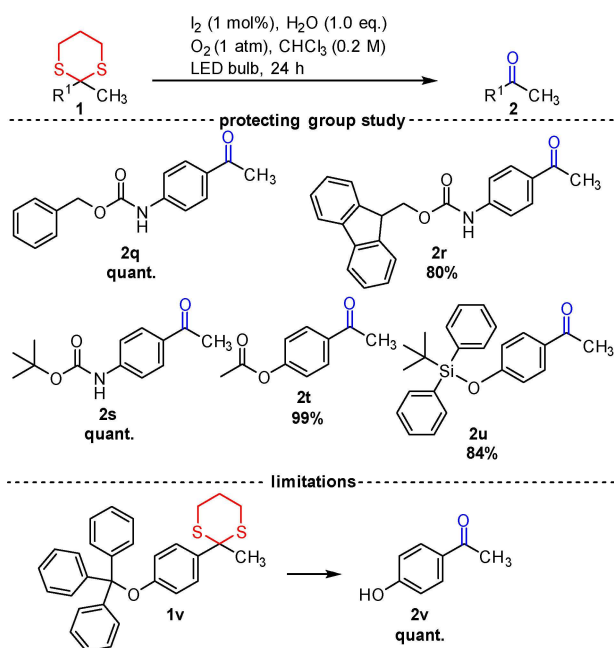
Scheme 2. Cleavage of 2-methyl-2-(naphthalen-2-yl)-1,3-dithiane (**1a**) to form 2-acetonaphthone (**2a**) using molecular iodine and oxygen under visible light irradiation. Yield determined by ¹H NMR spectroscopic analysis with 1,4-bis(trimethylsilyl)benzene as an internal standard. The reaction was performed according to the general procedure on a 0.38 mmol scale.



Scheme 3. Cleavage of 1,3-dithianes. All reactions were performed according to the general procedure on a 0.5 mmol scale. All yields are those of isolated products. All deprotection reactions occur from the 1,3-dithiane derivative unless stated otherwise ($n = 2$). [a] Yield from deprotection of the 1,3-dithiolane derivative ($n = 1$). [b] Reaction on a 0.35 mmol scale.

moiety as demonstrated by substrate **2k** was tolerated without any noticeable deborylation. The doubly bromo-substituted fluorenone **2l** was released in 43% yield. Electron withdrawing groups reduce the reaction rate as demonstrated by the release of 2-cyanobenzaldehyde (**2m**), where only 10% of the desired product could be isolated, while the major component of the reaction mixture was unreacted starting material. 4-Nitrobenzaldehyde (**2n**) could not be released from its 1,3-dithiane derivative. Octanal (**2o**) also showed no conversion to the desired product, which gives evidence that aliphatic aldehydes cannot be deprotected with this protocol. This drawback can be exploited to achieve regioselective deprotection of substrate **1p** (Scheme 3, bottom). Diaryl ether **1p** containing a single bromine atom to differentiate both rings electronically can be deprotected regioselectively with the electron-rich 1,3-dithiane moiety of **1p** reacting more rapidly. If the reaction is stopped after 10 h, the desired product **2p** was isolated in 79% yield, while the undesired doubly deprotected product **2p'** was obtained in only 11% yield. The regioisomeric monodeprotected compound could not be found in the reaction mixture.

As 1,3-dithianes and 1,3-dithiolanes are frequently used as protecting groups in total synthesis,^[15] the functional group tolerance of the method was evaluated (Scheme 4). The most

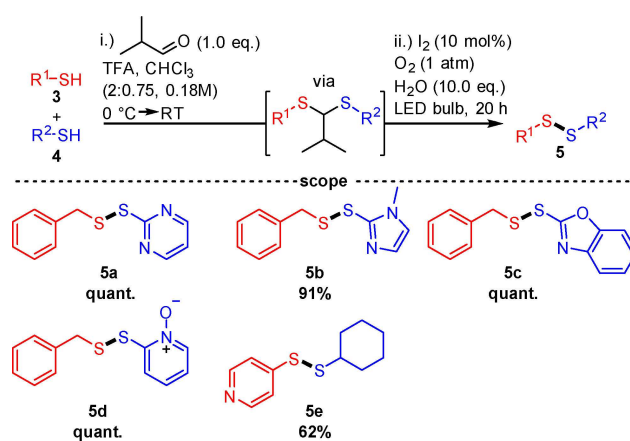


Scheme 4. Investigation of protecting group tolerance. All ketones were released from the corresponding 1,3-dithiane derivatives. All reactions were performed according to the general procedure on a 0.5 mmol scale. All yields are those of isolated products.

common *N*-protecting groups were well tolerated: The Cbz-protected derivative **2q** and Fmoc-protected derivative **2r** were selectively deprotected in quantitative and 80% yield, respectively. Surprisingly, even the acid sensitive Boc-protection was tolerated well, and ketone **2s** was isolated in quantitative yield. *O*-protecting groups such as acetyl (substrate **2t**) and TBDPS (substrate **2u**) proved to be tolerated as well and yielded the ketones in 99% and 84%, respectively. The trityl protecting group in substrate **1v** however turned out to be labile and the doubly deprotected alcohol **2v** was obtained in quantitative yield.

Unsymmetrical disulfides have been employed as a structural element in the synthesis of a variety of biologically active molecules.^[16] Thus, a series of methods for a direct dehydrogenative coupling of thiols to unsymmetrical disulfides have been reported.^[17] A major drawback of direct dehydrogenative coupling of thiols is the competing formation of the homocoupling products. However, studies investigating the formation of unsymmetrical thioacetals showed that a combination of electron-rich and electron-deficient thiols furnishes unsymmetrical thioacetals in the presence of a strong acid in high yields, while homothioacetalization is suppressed.^[18] We assumed that this preformation of an unsymmetric thioacetal could be beneficial for the formation of unsymmetrical disulfides upon cleavage of the C–S bond from these thioacetals.

Thus, a one-pot procedure for the synthesis of unsymmetrical disulfides directly from thiols was developed (Scheme 5). Two electronically different thiols react with isobutyraldehyde to the unsymmetrical thioacetal in the presence of TFA. Then, molecular iodine and oxygen were



Scheme 5. Formation of unsymmetrical disulfides from thiols using unsymmetrical thioacetals as intermediates. All reactions were performed according to the general procedure on a 0.5 mmol scale. All yields are those of isolated products.

added, and the reaction mixture was irradiated with visible light. This cleaved the thioacetal and released an unsymmetrical disulfide as the major product while homocoupling could be largely suppressed. When a direct coupling of thiols without prior thioacetalization was performed under the same reaction conditions, the unsymmetrical disulfide was formed as the minor and the symmetrical disulfide as the major product. A cross-over experiment, in which a mixture of two different unsymmetrical thioacetals was reacted, revealed an intermolecular mechanism through appearance of the unsymmetrical crossover products while homocoupling product formation was completely suppressed (see SI for details). The developed reaction proceeds well when benzyl mercaptan is used as the electron-rich thiol component, which is shown by the combination with the electron-deficient 2-mercaptopyrimidine to the unsymmetrical disulfide **5a** in quantitative yield. Equally high yields were obtained when 2-mercapto-1-methylimidazole (disulfide **5b**) or 2-mercaptobenzoxazole (disulfide **5c**) were used. In addition, 2-mercapto-pyridin-*N*-oxide as a potentially reactive component was tolerated (disulfide **5d**) and the corresponding disulfide was obtained in quantitative yield. When 4-mercaptopyridine and cyclohexanethiol were used, the corresponding mixed disulfide **5e** was isolated in 62% yield.

The combination of catalytic amounts of molecular iodine and oxygen under irradiation with visible light was shown to be an effective system for the cleavage of C–S bonds. An operationally simple protocol for the mild and catalytic cleavage of thioacetals and -ketals in high yields was developed. A series of 1,3-dithianes was effectively deprotected to release the corresponding carbonyl compounds. The protocol was further demonstrated to be compatible with common *N*- and *O*-protecting groups. In addition, the described reaction showed to be suitable for generation of unsymmetrical disulfides from thiols using unsymmetrical thioacetals as the intermediates.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Iodine · dithiane cleavage · photocatalysis · protecting groups · unsymmetrical disulfides

- [1] a) M. Schelhaas, H. Waldmann, *Angew. Chem. Int. Ed.* **1996**, *35*, 2056–2083; b) M. Yus, C. Nájera, F. Foubelo, *Tetrahedron* **2003**, *59*, 6147–6212.
- [2] a) A. K. Banerjee, M. S. Laya, *Russ. Chem. Rev.* **2000**, *69*, 947–955; b) T. E. Burghardt, *J. Sulfur Chem.* **2005**, *26*, 411–427.
- [3] P. C. Bulman Page, M. B. van Niel, J. C. Procter, *Tetrahedron* **1989**, *45*, 7643–7677.
- [4] B.-T. Gröbel, D. Seebach, *Synthesis* **1977**, *1977*, 357–402.
- [5] a) S. K. De, *Tetrahedron Lett.* **2004**, *45*, 2339–2341; b) P. G. Wuts, T. W. Greene, *Greene's protective groups in organic synthesis*, John Wiley & Sons, **2006**; c) Y.-C. Wu, J. Zhu, *J. Org. Chem.* **2008**, *73*, 9522–9524; d) W. Du, L. Tian, J. Lai, X. Huo, X. Xie, X. She, S. Tang, *Org. Lett.* **2014**, *16*, 2470–2473.
- [6] a) E. J. Corey, B. W. Erickson, *J. Org. Chem.* **1971**, *36*, 3553–3560; b) G. Stork, K. Zhao, *Tetrahedron Lett.* **1989**, *30*, 287–290; c) F. F. Fleming, L. Funk, R. Altundas, Y. Tu, *J. Org. Chem.* **2001**, *66*, 6502–6504; d) Y. Wu, X. Shen, J.-H. Huang, C.-J. Tang, H.-H. Liu, Q. Hu, *Tetrahedron Lett.* **2002**, *43*, 6443–6445; e) N. Iranpoor, H. Firouzabadi, H. R. Shaterian, *Tetrahedron Lett.* **2003**, *44*, 4769–4773; f) N. S. Krishnaveni, K. Surendra, Y. V. D. Nageswar, K. R. Rao, *Synthesis* **2003**, *2003*, 2295–2297; g) N. F. Langille, L. A. Dakin, J. S. Panek, *Org. Lett.* **2003**, *5*, 575–578; h) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.
- [7] a) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; b) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166; c) M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898–6926.
- [8] a) D. Ravelli, M. Fagnoni, *ChemCatChem* **2012**, *4*, 169–171; b) J. Xuan, W.-J. Xiao, *Angew. Chem. Int. Ed.* **2012**, *51*, 6828–6838; c) S. Fukuzumi, K. Ohkubo, *Chem. Sci.* **2013**, *4*, 561–574; d) D. A. Nicewicz, T. M. Nguyen, *ACS Catalysis* **2014**, *4*, 355–360.
- [9] a) P. Becker, T. Duhamel, C. J. Stein, M. Reiher, K. Muñoz, *Angew. Chem.* **2017**, *56*, 8004–8008; b) T. Ishikawa, M. Kimura, T. Kumoi, H. Iida, *ACS Catalysis* **2017**, *7*, 4986–4989; c) Y. Sudo, E. Yamaguchi, A. Itoh, *Org. Lett.* **2017**, *19*, 1610–1613; d) N. N. K. Reddy, D. Rawat, S. Adimurthy, *J. Org. Chem.* **2018**.
- [10] a) R. L. Brown, W. Klemperer, *The Journal of Chemical Physics* **1964**, *41*, 3072–3089; b) F. Wilkinson, A. Farmilo, *Journal of the Chemical Society, Faraday Transactions 2: Molecular and Chemical Physics* **1984**, *80*, 1117–1124.
- [11] a) L. F. Meadows, R. M. Noyes, *J. Am. Chem. Soc.* **1960**, *82*, 1872–1876; b) J. Olmsted, G. Karal, *J. Am. Chem. Soc.* **1972**, *94*, 3305–3310; c) G. W. Luther, J. Wu, J. B. Cullen, *Aquatic Chemistry, Vol. 244*, American Chemical Society, **1995**, pp. 135–155; d) S. Lee, W. Terry Rawlins, S. J. Davis, *Chem. Phys. Lett.* **2009**, *469*, 68–70.
- [12] Y. Liu, B. Wang, X. Qiao, C.-H. Tung, Y. Wang, *ACS Catalysis* **2017**, 4093–4099.
- [13] M. Lanzi, J. Merad, D. V. Boyarskaya, G. Maestri, C. Allain, G. Masson, *Org. Lett.* **2018**, *20*, 5247–5250.
- [14] M. Krumb, T. Lucas, T. Opatz, *Eur. J. Org. Chem.*, **2019**, 4517–4521.
- [15] a) E. J. Corey, M. G. Bock, *Tetrahedron Lett.* **1975**, *16*, 2643–2646; b) P. S. Jones, S. V. Ley, N. S. Simpkins, A. J. Whittle, *Tetrahedron* **1986**, *42*, 6519–6534.
- [16] a) R. K. Ramanathan, D. L. Kirkpatrick, C. P. Belani, D. Friedland, S. B. Green, H.-H. S. Chow, C. A. Cordova, S. P. Stratton, E. R. Sharlow, A. Baker, T. Dragovich, *Clinical Cancer Research* **2007**, *13*, 2109–2114; b) T. R. DiRaimondo, N. M. Plugis, X. Jin, C. Khosla, *J. Med. Chem.* **2013**, *56*, 1301–1310.
- [17] a) D. H. Dethe, A. Srivastava, B. D. Dherange, B. V. Kumar, *Adv. Synth. Catal.* **2018**, *360*, 3020–3025; b) P. Huang, P. Wang, S. Tang, Z. Fu, A. Lei, *Angew. Chem. Int. Ed.*, **2018**, *57*, 8115–8119; c) W. Wang, Y. Lin, Y. Ma, C.-H. Tung, Z. Xu, *Org. Lett.* **2018**, *20*, 3829–3832.
- [18] a) J. Y. Gauthier, N. Zajac, D. L. Mayhew, G. J. Hughes, E. Martins, D. Guay, R. N. Young, R. J. Zamboni, *Synlett* **1998**, *09*, 289–291; b) J. Y. Gauthier, E. O. Martins, R. N. Young, R. J. Zamboni, *Synlett* **2002**, *2002*, 0984–0986.

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