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Azidation of *β*-Keto Esters and Silyl Enol Ethers with a Benziodoxole Reagent

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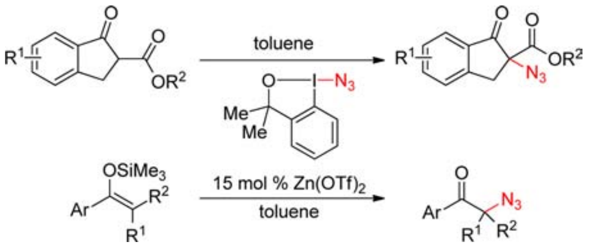
ABSTRACT



The efficient azidation of *β*-keto esters and silyl enol ethers using a benziodoxole-derived azide transfer reagent is reported. The azidation of cyclic *β*-keto esters could be achieved in up to quantitative yields in the absence of any catalyst. In the case of less reactive linear *β*-keto esters and silyl enol ethers, complete conversion and good yields could be obtained by using a zinc catalyst.

Azides are useful functional groups in synthetic chemistry.[1] They are easily reduced to amines, but are themselves nonbasic. They consequently constitute ideal amine precursors in a multistep synthesis. Furthermore, cycloaddition of azides with alkynes, especially catalyzed by copper, has become the most impressive example of "Click" chemistry, as it is completely orthogonal to other functionalities and can proceed under mild conditions without the need to exclude oxygen or moisture. This reaction is now one of the most often used functionalization methods for biomolecules and polymers.[2] In this context, new methods to introduce azides, especially in complex molecules, are needed.

Most approaches to access azides are based on the use of nucleophilic sodium azide. In contrast, the introduction of azides onto nucleophiles is much less developed. Such reactions would be especially useful to access α-azido carbonyl compounds, which are important building blocks in synthetic chemistry as precursors of amino acid derivatives.[3] Sulfonyl azides have been most often used as electrophilic azide sources, but they work best for strongly nucleophilic lithium enolates.[4] For the stabilized enolates derived from dicarbonyl compounds, a mixture of products resulting from competing diazo transfer and subsequent rearrangements has been observed.[5] Another successful approach is based on the in situ *Umpolung* of either the azide or the enolate using a strong oxidant. These reactions often involve the formation of iodoazide or hypervalent iodine reagents and have been usually proposed to proceed via a radical pathway.[6] In the case of the azidation of dicarbonyl compounds, the most general protocol has been reported in 2012 by Kirsch and co-workers based on the use of sodium azide and IBX.[6n] In most oxidative methods, the actual azidation reagent is either unknown or so unstable that it cannot be isolated. This makes the development of catalytic or asymmetric methods difficult. In fact,

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(1) (a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (b) *Organic Azides: Syntheses and Applications*; Bräse, S., Banert, K., Eds.; Wiley: 2009.

(2) (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596. (b) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057. Reviews: (c) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128. (d) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (e) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249. (f) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (g) Amblard, F.; Cho, J. H.; Schinazi, R. F. *Chem. Rev.* **2009**, *109*, 4207. (h) Iha, R. K.; Wooley, K. L.; Nystrom, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J. *Chem. Rev.* **2009**, *109*, 5620.

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(4) Evans, D. A.; Britton, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 6881.

(5) (a) Benati, L.; Calestani, G.; Nanni, D.; Spagnolo, P. *J. Org. Chem.* **1998**, *63*, 4679. (b) Benati, L.; Nanni, D.; Spagnolo, P. *J. Org. Chem.* **1999**, *64*, 5132.

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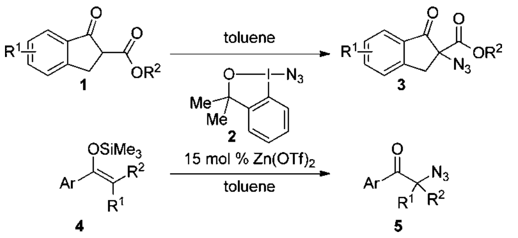
until 2013, no catalytic asymmetric α-azidation of carbonyl compounds had been reported, and the only method to access enantiopure products was based on a chiral auxiliary approach.[4]

To solve this challenge, we decided to make use of the exceptional stability of benziodoxol(on)e-based hypervalent iodine reagents.[7] Our group has recently demonstrated the exceptional properties of this class of reagents for acetylene transfer onto dicarbonyl compounds,[8] and we wondered if similar azido reagents would be equally successful. In fact, Zhdankin and co-workers have described the synthesis of azido benziodoxol(on)e compounds, which were surprisingly stable.[9] The reactivity of these reagents was studied for the radical-based azidation of aliphatic C−H bonds.[9,10] During completion of our work, Gade and co-workers reported the first catalytic asymmetric method for the azidation of *β*-keto esters and oxindoles using a chiral iron catalyst together with an azidobenziodoxole reagent.[11] This major breakthrough motivated us to report our own preliminary results in the area, including the very efficient azidation of cyclic *β*-keto esters with azidobenziodoxole **2** in the absence of any catalyst and the zinc-catalyzed azidation of less reactive linear keto esters and silyl enol ethers using the same reagent (Scheme 1). Our results demonstrated that the potential of azidobenziodoxole reagents as electrophilic azidation reagents is not limited to cyclic *β*-keto esters.

Scheme 1. Azidation of Keto Esters and Silyl Enol Ethers



We started our studies with the azidation of keto ester **1a** with benzidoxol(on)e reagents **2** and **6** (Scheme 2). Whereas no reaction was observed with benziodoxolone **6**, a complete conversion to azide **3a** was observed with benziodoxole **2** in different solvents, with the best yield (82% by ^{1}H NMR) obtained in toluene.[12] The better result obtained with benziodoxole **2** is probably due to the higher basicity of the alcoholate generated after azide transfer.

Scheme 2. Azidation of Keto Ester **1a**

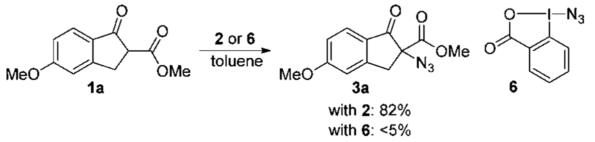
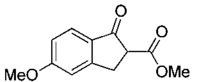
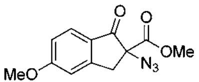
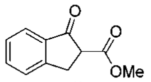
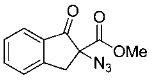
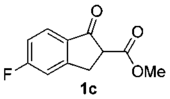
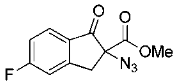
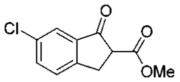
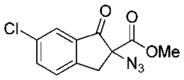
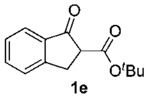
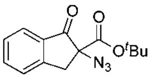
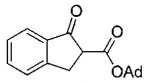
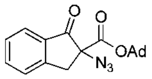
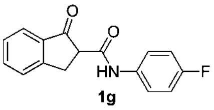
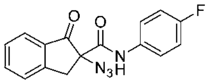
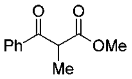
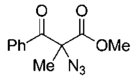
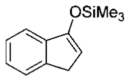
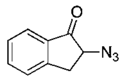


Table 1. Azidation of Cyclic *β*-Keto Esters with Benziodoxole **2**

entry	β-keto ester	product	yield(%)^a
1	 **1a**	 **3a**	94
2	 **1b**	 **3b** **3b**	79
3	 **1c**	 **3c**	quant.
4	 **1d**	 **3d**	92
5	 **1e**	 **3e**	quant.
6	 **1f**	 **3f**	98
7	 **1g**	 **3g**	67
8	 **1h**	 **3h**	<5
9	 **4a**	 **5a**	<5

^{a} Isolated yields with keto ester **1** or enol ether **4a** (0.40 mmol), benziodoxole **2** (0.52 mmol), toluene (0.4 mL), 1−3 h at rt.

With this simple protocol for the azidation of keto esters in hand, we investigated the scope of the reaction (Table 1). On a 0.40 mmol scale, azide **3a** could be isolated in 94% yield (entry 1). The azidation proceeded in good yields independent of the electronic properties of the substituent

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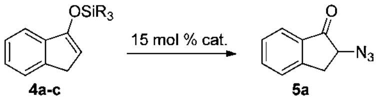
(6) (a) Fowler, F. W.; Hassner, A.; Levy, L. A. *J. Am. Chem. Soc.* **1967**, *89*, 2077. (b) Moriarty, R. M.; Vaid, R. K.; Ravikumar, V. T.; Vaid, B. K.; Hopkins, T. E. *Tetrahedron* **1988**, *44*, 1603. (c) Magnus, P.; Barth, L. *Tetrahedron Lett.* **1992**, *33*, 2777. (d) Magnus, P.; Lacour, J. *J. Am. Chem. Soc.* **1992**, *114*, 767. (e) Magnus, P.; Hulme, C.; Weber, W. *J. Am. Chem. Soc.* **1994**, *116*, 4501. (f) Magnus, P.; Barth, L. *Tetrahedron* **1995**, *51*, 11075. (g) Magnus, P.; Lacour, J.; Evans, P. A.; Roe, M. B.; Hulme, C. *J. Am. Chem. Soc.* **1996**, *118*, 3406. (h) Magnus, P.; Lacour, J.; Evans, P. A.; Rigollier, P.; Tobler, H. *J. Am. Chem. Soc.* **1998**, *120*, 12486. (i) Tohma, H.; Egi, M.; Ohtsubo, M.; Watanabe, H.; Takizawa, S.; Kita, Y. *Chem. Commun.* **1998**, 173. (j) Lee, J. C.; Kim, S.; Shin, W. C. *Synth. Commun.* **2000**, *30*, 4271. (k) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *Org. Biomol. Chem.* **2005**, *3*, 816. (l) Kumar, D.; Sundaree, S.; Rao, V. S. *Synth. Commun.* **2006**, *36*, 1893. (m) Telvekar, V. N.; Patile, H. V. *Synth. Commun.* **2011**, *41*, 131. (n) Harschneck, T.; Hummel, S.; Kirsch, S. F.; Klahn, P. *Chem.—Eur. J.* **2012**, *18*, 1187.

(7) (a) Zhdankin, V. V. *Curr. Org. Synth.* **2005**, *2*, 121. (b) Brand, J. P.; Fernandez Gonzalez, D.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102.

(8) Fernandez Gonzalez, D.; Brand, J. P.; Waser, J. *Chem.—Eur. J.* **2010**, *16*, 9457.

on the benzene ring of indanone (entries 2−4). More sterically hindered esters gave quantitative yields of azide (entries 5 and 6). Azidation of keto amide **1g** was also possible in 67% yield (entry 7).[13] Nevertheless, the reaction did not work for less reactive substrates: no conversion was observed for both acyclic keto ester **1h** (entry 8) or silyl enol ether **4a** (entry 9).

Table 2. Optimization of the Azidation of Silyl Enol Ethers



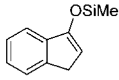
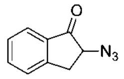
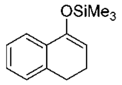
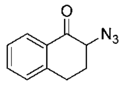
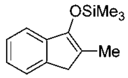
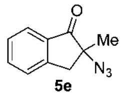
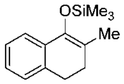
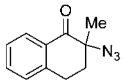
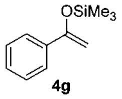
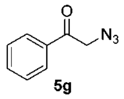
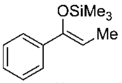
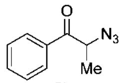
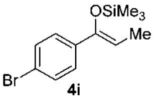
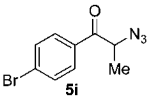
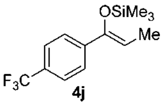
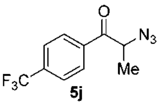
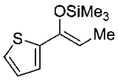
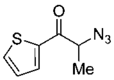
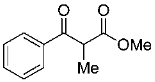
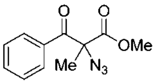
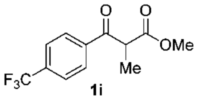
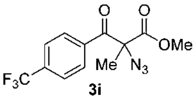
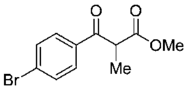
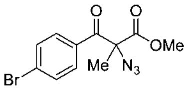
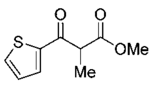
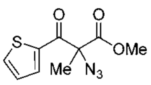
4a-c **5a**

entry	R	catalyst	solvent	yield (%)[a]
1	Me (**4a**)	$Sc(OTf)_3$	toluene	23
2	Me (**4a**)	$Cu(OTf)_2$	toluene	36
3	Me (**4a**)	$In(OTf)_3$	toluene	58
4	Me (**4a**)	$Sn(OTf)_2$	toluene	68
5	Me (**4a**)	$Hf(OTf)_4 \cdot 4H_2O$	toluene	71
6	Me (**4a**)	$Zn(OTf)_2$	toluene	67
7	Me (**4a**)	$Zn(NTf_2)_2$	toluene	41
8	Me (**4a**)	$Zn(OAc)_2$	toluene	22
9	Me (**4a**)	$Zn(BF_4)_2$	toluene	47
10	Me (**4a**)	HOTf	toluene	28
11	Me (**4a**)	$Zn(OTf)_2$	CH_3CN	53
12	Me (**4a**)	$Zn(OTf)_2$	Et_2O	52
13	Me (**4a**)	$Zn(OTf)_2$	CH_2Cl_2	30
14	Me (**4a**)	$Zn(OTf)_2$	THF	26
15	Me (**4a**)	$Zn(OTf)_2$	^{i}PrOH	0
16	Et (**4b**)	$Zn(OTf)_2$	toluene	44
17	^{i}Pr (**4c**)	$Zn(OTf)_2$	toluene	23

[a] **4** (0.1 mmol), **2** (0.13 mmol), catalyst (15 mol %), solvent (2 mL). Yield obtained by ^{1}H NMR using 1,3,5-trimethoxybenzene as a standard.

The low reactivity of **2** with silyl enol ethers is in contrast with the fast reaction reported for in situ generated noncyclic reagents.[6c−h] We wondered if the reactivity of the reagent could be further enhanced in the presence of a Lewis acid. In fact, several Lewis acids were able to catalyze the reaction of silyl enol ether **4a** with benziodoxole **2** in toluene (Table 2). Moderate yields were obtained with $Sc(OTf)_3$, $Cu(OTf)_2$, and $In(OTf)_3$ as catalysts (entries 1−3). The best results were obtained when using $Sn(OTf)_2$, $Hf(OTf)_4 \cdot 4H_2O$, or $Zn(OTf)_2$, which gave nearly identical yields (67−71%, entries 4−6).When considering that zinc is cheap and nontoxic, we decided to continue with this metal as the catalyst. Other zinc salts gave inferior results (entries 7−9). Triflic acid was also able to catalyze the reaction, but in only 28% yield (entry 10).

Table 3. Scope of the Zinc-Catalyzed Azidation

entry	indole	product	yield(%)[a]
1	 **4a**	 **5a**	58
2	 **4d**	 **5d**	58
3	 **4e**	 **5e**	62
4	 **4f**	 **5f**	55
5	 **4g**	 **5g**	73
6	 **4h**	 **5h**	72
7	 **4i**	 **5i**	82
8	 **4j**	 **5j**	75
9	 **4k**	 **5k**	81
10	 **1h**	 **3h**	73
11	 **1i**	 **3i**	58
12	 **1j**	 **3j**	55
13	 **1k**	 **3k**	64

[a] Isolated yields with keto ester **1** or enol ether **4** (0.40 mmol), benziodoxole **2** (0.52 mmol), $Zn(OTf)_2$ (0.060−0.12 mmol), toluene (0.8 mL), 12 h at rt.

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(9) (a) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Formaneck, M. S.; Bolz, J. T. *Tetrahedron Lett.* **1994**, *35*, 9677. (b) Krasutsky, A. P.; Kuehl, C. J.; Zhdankin, V. V. *Synlett* **1995**, 1081. (c) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192.

(10) In their first communication,[9a] Zhdankin and co-workers indicated that these reagents may also react with nucleophiles derived from carbonyls, but the result of such reactions was never reported.

(11) Deng, Q. H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356.

(12) Yield obtained in other solvents: CH_2Cl_2, 79%; CH_3CN, 75%; Et_2O, 69%; THF, 63%; ^{i}PrOH, 49%. See Supporting Information (SI) for further details.

(13) In the case of a tetralone-derived keto-ester, only a low yield (10%) of azidation was obtained, due to the favored formation of an aromatic product. A simple cyclopentanone could also be azidated in moderate yield (54%). See SI for further details.

Lower yields were also obtained in solvents different from toluene (entries 11−15). Finally, more sterically hindered silyl enol ethers **4b** and **4c** led to inferior results when compared to trimethylsilyl enol ether **4a** (entries 16 and 17). We consequently decided to examine the scope of the reaction with trimethysilyl enol ethers and zinc triflate as the catalyst (Table 3, entries 1−9).

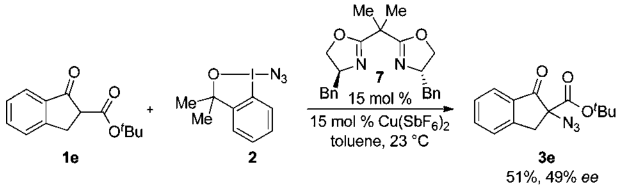
On a 0.40 mmol scale, the azidation worked for silyl enol ethers derived from indanone and tetralone (Table 3, entries 1 and 2). Complete conversion was achieved within a few hours. The reaction could also be applied to the synthesis of tertiary azides (entries 3 and 4). The silyl enol ethers of acetophenone derivatives also worked in the reaction (entries 5−8), giving access to both primary and secondary azides. The azidation also proceeded well in the presence of a thiophene heterocycle (entry 9).

At this point, we wondered if the zinc-catalyzed conditions could also be used to extend the scope of azidation for keto ester substrates. Indeed, acyclic keto ester **1h**, which did not react in the presence of azidobenziodoxole **2** only, could now be azidated in 73% yield (Table 3, entry 10). The reaction was also successful for keto esters bearing a more functionalized benzene ring (entries 11 and 12) or a thiophene heterocycle (entry 13).

Cyclic keto esters are a privileged class of substrates for the development of asymmetric reactions, as two-point binding of a chiral catalyst can lead to good enantioselectivity. However, the high background rate observed with reagent **2** for cyclic keto esters constituted an important challenge for asymmetric induction. Nevertheless, an interesting preliminary result was obtained using a copper catalyst and bisoxazoline **7** as a chiral ligand for the azidation of keto ester **1e** with 49% *ee* (Scheme 3). The results of Gade and co-workers obtained simultaneously along with our own investigations demonstrated the higher efficiency of a tridentate bisoxazoline ligand with iron as the catalyst.[11]

Several mechanisms can be envisaged for the azidation reaction. One possibility is nucleophilic attack of either the oxygen or the carbon atom of the enolate on the iodine atom of benziodoxole **2**, followed by C−N bond formation. An alternative possibility would involve a radical chain reaction, as has been proposed by Magnus and co-workers.[6c−h] However, several observations make the latter less probable: in contrast to what was reported by Magnus and co-workers, no reaction was observed in the absence of a catalyst in the case of silyl enol ethers. Furthermore, diazidation products resulting from radical pathways were not obtained, and the reaction did not require the presence of a bulky triisopropylsilyl group on the oxygen. Finally, the addition of TEMPO to the reaction mixture had no influence on the reaction outcome, neither with keto esters nor with silyl enol ethers. These results are consequently more in accordance with an electrophilic azidation, as has been proposed recently by Muniz and co-workers for the transfer of the NTs group using a hypervalent iodine reagent.[14] The role of the zinc catalyst is also intriguing, as it may act either through nucleophilic activation by formation of a zinc enolate or by electrophilic activation of benziodoxole **2**. Further investigations will be required to gain a better understanding of the reaction mechanism.

Scheme 3. Enantioselective Azidation of Keto-Ester **1e**



In conclusion, we have described that the azidation of cyclic keto esters with benziodoxole reagent **2** proceeded in excellent yield in the absence of any catalyst. For less reactive acyclic keto esters and silyl enol ethers, an efficient zinc-catalyzed method could be developed, which gave access to primary, secondary, and tertiary azides. Further extension of the scope of the reaction and development of asymmetric protocols not limited to cyclic keto esters are currently under investigation, and the results will be reported in due course.

Supporting Information Available. Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Souto, J. A.; Martinez, C.; Velilla, I.; Muniz, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 1324.

The authors declare no competing financial interest.