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Synthetic Methods

Iodine(III)-mediated diazidation and azido-oxyamination of enamides

Sophie Nocquet-Thibault, Anita Rayar, Pascal Retailleau, Kevin Cariou* and Robert H. Dodd*

Abstract: In this study we demonstrate that the combination of bis(*tert*-butylcarbonyloxy)iodobenzene and lithium azide in acetonitrile allows the diazidation of various enamide substrates. The azido-oxyamination of the same substrates can be carried out in the presence of TEMPO.

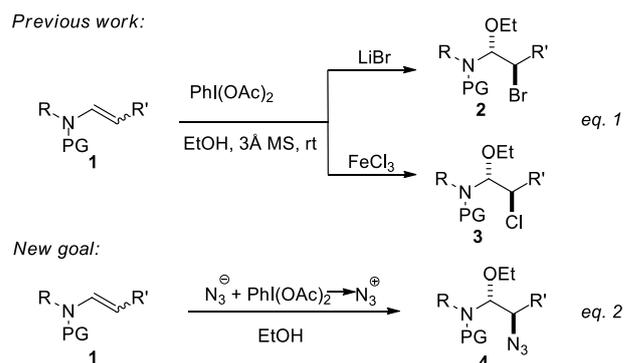
Control experiments strongly suggest that this latter process occurs through a shift in nature of the *in situ* generated electrophilic species from a radical to a cation. Finally, the versatility of the novel compounds synthesized was also assessed by running various selective reactions on them.

Introduction

In recent years hypervalent iodine(III) derivatives have appeared as highly efficient and versatile compounds,^{1,2} notably for oxidative difunctionalization of various alkenes.³ In particular benziodoxole-based reagents have been shown to be superior promoters for transferring a wide range of atoms and functional groups.⁴ However, they suffer from the need to be synthesized beforehand⁵ which limits their general usefulness. This drawback can be overridden by *in situ* generation of the active species through an *umpolung* strategy, relying on the ability of hypervalent iodine(III) ligands to be exchanged, thus generating a novel electrophilic species.⁶ For our part, we have relied on this strategy using a combination of (Diacetoxylo)Benzene (DIB) with lithium bromide and iron(III) chloride to promote the ethoxybromination⁷ and the ethoxychlorination,⁸ respectively, of enamides of type **1**, which permits a regio- and chemoselective access to multipurpose synthons such as **2** and **3** (Scheme 1, eq. 1). In order to further broaden the scope of this strategy we then turned our attention from halogens to pseudohalogens. The azide ion can be considered as a pseudohalide which implies that its behavior can be similar to that of a halide. We thus envisioned that the same *umpolung* process could be applied to azides to give α -azido-hemiaminals **4** (Scheme 1, eq. 2). Given the vast synthetic utility of organic azides⁹ this strategy appeared quite straightforward for the rapid assembly of value-added linchpins.¹⁰

The basis for this study thus relies on the feasibility of combining an azide with a hypervalent iodine(III) derivative to generate an electrophilic species ("N₃⁺") capable of reacting with

various double bonds.



Scheme 1. *Umpolung* strategy for the electrophilic (pseudo)halogenation of enamides.

Indeed, in a series of papers in the early 70s, Zbiral was the first to study and report the reactivity of a DIB-trimethylsilylazide (TMSA) combination with alkenes¹¹ for which he postulated the generation of mixed hypervalent iodine(III) species incorporating an azide ligand. Depending on the reaction conditions employed various difunctionalized compounds could be obtained, although often as mixtures. Fifteen years later, this strategy was expanded upon by Moriarty who described the vicinal diazidation of alkenes using a PhIO-Na₃-AcOH combination.¹² In this case the proposed mechanism involves an electrophilic activation by the iodine and two successive nucleophilic additions of the azide. The most sustained efforts in this area were then deployed by Magnus who first showed that the combination of iodosobenzene and TMSA could trigger the β -azidation or the diazidation of enol ethers,¹³ before thoroughly studying this reaction¹⁴ and applying it to the synthesis of natural products.¹⁵ Similar combinations of reagents were later used by Kirshning as surrogates for haloazides¹⁶ and to synthesize a stable polymer-bound iodine-azide.¹⁷ Adding an organoselenium species to the I(III)-azide

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Supporting information for this article is available on the WWW under <http://www.chemeurj.org/> or from the author.

combination was also shown to be effective for the azido-selenation of various alkenes, including glucals, presumably through the involvement of radical species.¹⁸ Although they need to be prepared beforehand, cyclic azido-benziodoxoles^{5,19} can also act as azido donors in a wide array of reactions with olefins. For instance, they have recently been used for the zinc-catalyzed azidation of silyl enol ethers,²⁰ the intermolecular²¹ and intramolecular²² oxyazidation of alkenes, the copper-catalyzed oxoazidation of indoles²³ and the arylazidation of activated alkenes.²⁴

For our part, based on our previous studies with enamides, we thought that it would be more general and satisfying to develop a set of conditions for the *umpolung* of (pseudo)halides that would only differ by the nature of the salts.²⁵

Results and Discussion

Building on our experience with halide salts we initially aimed at developing an ethoxy-azidation reaction. Unfortunately the combination of LiN₃ or NaN₃²⁶ with DIB in ethanol at various temperatures either led to no conversion or to intractable mixtures after prolonged reaction times (Table 1, entries 1,2). Using trimethylsilylazide with DIB (entry 3) or iododisylbenzene (entry 4) as well as employing a cyclic azido-benziodoxole (entry 5) as promoters proved equally unsuccessful.

azido compound **5a** in 19 % yield (entry 6). While running the reaction in acetonitrile did not help to improve the reactivity (entry 7), bis(*tert*-butylcarbonyloxy)iodobenzene appeared as a superior promoter (entry 8), which could also be used with LiN₃ (entries 9,10). This latter source of azide was found to be more convenient and robust to use than TMSN₃. Although poorly soluble in DCM, this could be compensated by conducting the reaction in acetonitrile (entry 11). Having found the optimal combination of reagents and solvents, we then assessed the effect of the reaction temperature on the efficiency and the stereoselectivity (entries 11-14). Thus -15°C was shown to offer the best balance with respect to yield, reaction time and diastereoselectivity (entry 13).

At this stage we went on to explore the scope of the reaction in terms of substrate. The benzylamine-derived enamide **1b** behaved similarly (Table 2, entry 2) and so did the mesyl-protected **1c** (entry 3) and the methylamine derivative **1d** (entry 4). While the use of a carbamate protecting group (Boc, entries 5,6) appeared incompatible with this reaction, amides (entries 7-9) were well tolerated. Finally the same conditions were applied to *N*-benzenesulfonyl-indole **1j** and led to the desired product only after a prolonged reaction time and with a mediocre 24% yield (entry 10).¹² It should also be noted that aminoacrylates were found to be unreactive under these conditions, even after extended reaction times.

Table 1. Diazidation optimization.

Entry	R, x	Y ^[a]	Solvent	Temp. [°C]	Time	d.r. ^[b]	Yield [%] ^[c]
1	Ac, 2.0	Na	EtOH	-20	7 d	ND	CM ^[d]
2	Ac, 2.0	Li	EtOH	-40	7 d	ND	CM
3	Ac, 1.5	TMS	MeCN	RT	2 d	ND	CM
4	PhIO, 1.2	TMS	CH ₂ Cl ₂	-50	6 d	ND	CM
5			EtOH	0 to RT	30 h to 5 d	ND	CM
6	COCF ₃ , 1.2	TMS	CH ₂ Cl ₂	RT	15 min	ND	19
7	COCF ₃ , 1.2	TMS	MeCN	RT	15 min	ND	8
8	CO ^t Bu, 1.2	TMS	CH ₂ Cl ₂	RT	1 h	ND	27
9	CO ^t Bu, 1.2	Li	CH ₂ Cl ₂	RT	1 h	ND	21 ^[e]
10	CO ^t Bu, 1.5	Li	CH ₂ Cl ₂	RT	1 h	ND	31
11	CO ^t Bu, 1.5	Li	MeCN	RT	25 min	70/30	52
12	CO ^t Bu, 1.5	Li	MeCN	0	25 min	80/20	42
13	CO ^t Bu, 1.5	Li	MeCN	-15	1 h	80/20	52
14	CO ^t Bu, 1.5	Li	MeCN	-40	24 h	ND	ND

[a] Entries 1-4, y = 2x; entries 6-8, y = 2.0; entries 9-14, y = 4.0. [b] The relative stereochemistry of the major diastereoisomer was attributed by X-ray analysis of a mono crystal of **5a**.²⁸ ND: not determined. [c] Isolated yields. [d] CM: complex mixture. [e] Reaction run with 3.0 equiv of NaHCO₃.

Eventually, the more reactive PhenylIodine-bis(triFluoroAcetate) (PIFA)²⁷ was found to be a suitable promoter when used in conjunction with TMSN₃ in dichloromethane to access the bis

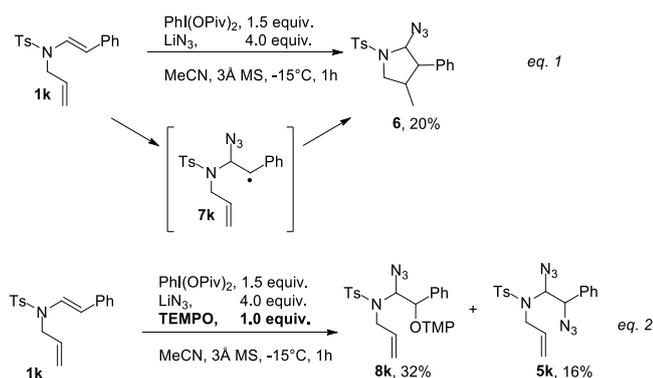
Table 2. Diazidation scope.

Entry	SM ^[a]	R	PG	Time [h]	d.r. ^[b]	Yield [%] ^[c]
1	1a	Ph	Ts	1	80/20	52
2	1b	Bn	Ts	1.25	90/10	47
3	1c	Ph	Ms	1	70/30	40
4	1d	Me	Bs ^[d]	1	75/25	46
5	1e	Ph	Boc	1	ND	CM ^[e]
6	1f	Bn	Boc	1	ND	CM
7	1g	Ph	Ac	1	73/27	18
8	1h	Bn	Ac	1	75/25	61
9	1i	Ph	COCF ₃	3	67/33	43
10	1j	<i>N</i> -(Bs)-indole		7 ^[f]	85/15	24

[a] SM: starting material. [b] The relative stereochemistry of the major diastereoisomer was attributed by analogy with **5a**. ND: not determined. [c] Isolated yields. [d] Bs: benzenesulfonyl. [e] CM: complex mixture. [f] Additional 1 h at RT

Overall this process seems to be quite capricious and hampered by various side-reactions, which hinted towards the *in situ* generation of highly reactive intermediates such as azido radicals, as previously postulated.¹⁴ The involvement of radical species became apparent when tri-substituted pyrrolidine **6** was isolated as the main product, albeit in a modest yield, from the reaction of allylamine-derived enamide **1k** (Scheme 2, eq. 1). In order to account for the formation of this compound we postulated that a *5-exo-trig* cyclization could have occurred from radical intermediate **7k** resulting from the addition of an azido radical to

the starting enamide. To obtain more insight on this particular case we decided to run the same reaction in the presence of 1 equivalent of TEMPO²⁹ as a radical scavenger. In this case, the main product was the oxyaminated adduct **8k**, possibly arising from the trapping of intermediate **7k** by the TEMPO radical (Scheme 2, eq. 2). Moreover, diazido compound **5k** was also isolated, while virtually no traces of cyclized products were detected.



Scheme 2. Reactivity of allylamine-derived enamide **1k**.

Considering the apparently better efficiency of the enamide azido-oxyamination vs. the diazidation,³⁰ we thought that this former transformation could also be worth optimizing. First, by doubling the amount of TEMPO the yield of **8k** went up to 58% (Table 3, entry 2). By lowering the amount of LiN₃ to only 2 equivalents, a complete chemoselectivity was attained along with a further improvement of the yield (entry 3).

Table 3. Azido-Oxyamination optimization.

Entry	SM	x	y	z	T. [°C]	t. [h]	d.r. ^[b]	Yield[%] ^[a]
1	1k	1.5	4	1	-15	1	ND	32 ^[c]
2	1k	1.5	4	2	-15	6	ND	58 ^[d]
3	1k	1.5	2	2	-15	5	ND	75
4	1k	1.5	2	2	0	2	95/5	69
5	1k	1.5	2	2	RT	1	95/5	21
6	1a	1.5	2	2	-15	7	95/5	50 ^[e]
7	1a	1.2	1.2	1.2	RT	6	90/10	51 ^[f]
8	1a	1.2	2	2	0	2.25	90/10	77
9	1k	1.2	2	2	0	1	95/5	67

[a] Isolated yields. [b] The relative stereochemistry of the major diastereoisomer was attributed by analogy with **8a** for which an X-ray analysis of a mono crystal was performed.²⁸ ND: not determined. [c] Along with 16 % of **5k**. [d] Along with 20 % of **5k**. [e] After 6h at -15°C the conversion was not complete so the reaction was warmed up to 0°C for an additional 1 h. [f] After 5.5 h at RT the conversion was not complete so an additional 1.2 equiv. of TEMPO and LiN₃ were added to reach completion in 30 min.

The effect of the temperature was then assessed. Running the reaction at 0°C accelerated it without dramatically affecting its efficiency (entry 4), while operating at room temperature greatly impaired the yield (entry 5). The optimization was continued with enamide **1a**, for which the reaction proceeded sluggishly at -15°C (entry 6). Lowering the amount of all reagents, even at RT, had little effect (entry 7). The better compromise, in terms of yield, reaction time and selectivity was reached by running the reaction at 0°C with only 1.2 equivalents of bis(*tert*-butylcarbonyloxy)iodobenzene and with 2.0 equivalents of both TEMPO and lithium azide (entry 8). Under these conditions enamide **1k** reacted rapidly and cleanly to give **8k** as the sole product with a good 67% yield (entry 9, vs. entry 4: 69% yield with 1.5 equiv. of oxidant).

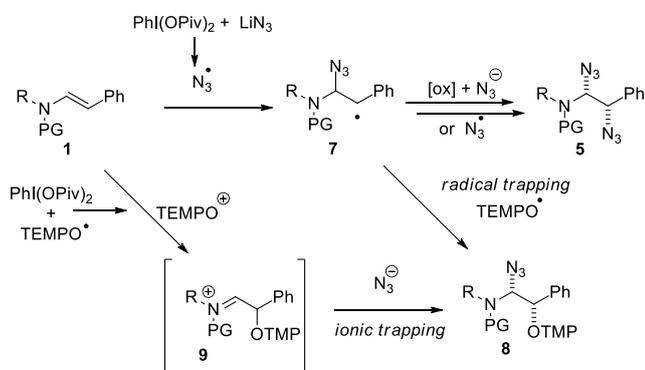
Having determined an optimal and robust set of conditions for the oxy-azidation we began to test them against a range of enamides (Table 4). As already observed with compounds **1a** and **1k**, the yields were found to be consistently higher than for the diazidation of the same substrates. A slightly extended set of sulfonyl-protected enamides (entries 1-6) was first probed and the yields were found to be generally above 70%, the regioselectivity complete and the diastereoselective ratio above 80:20. Moreover, while carbamate-protected enamides **1e** and **1f** could not undergo the diazidation reaction (see Table 2, entries 5,6), their azido-oxyamination did proceed although with moderate yields (entries 7,8). Very good yields and good stereoselectivities were also obtained for amide substrates, whether an acetamide (entries 9,10), a trifluoroacetamide (entry 11) or a caprolactam (entry 12). Finally, cyclic enamides such as *N*-(Bs)-indole (entry 13) and *N*-(Bs)-tetrahydropyridine (entry 14) were also evaluated and yielded the desired product with excellent selectivities and yields.

Table 4. Azido-Oxyamination Scope.

Entry	SM ^[a]	R	PG	time [h]	d.r.	Yield [%] ^[b]
1	1a	Ph	Ts	2.25	90/10	77
2	1b	Bn	Ts	3	95/5	74
3	1c	Ph	Ms	1	80/20	73
4	1d	Me	Bs ^[c]	1	85/15	73
5	1k	allyl	Ts	1	95/5	67
6	1l	Me	Ms	1	83/17	83
7	1e	Ph	Boc	1	74/26	31
8	1f	Bn	Boc	1	83/17	41
9	1g	Ph	Ac	1	81/19	81
10	1h	Bn	Ac	4	60/40	98
11	1i	Ph	COCF ₃	4 ^[d]	77/23	77
12	1m	-(CH ₂) ₅ CO-		1	100/0	67
13	1j	<i>N</i> -(Bs)-indole		7 ^[d]	100/0	97
14	1n	<i>N</i> -(Bs)-tetrahydropyridine		7 ^[e]	100/0	94

[a] SM: starting material. [b]. Isolated yields [c] Bs: benzenesulfonyl. [d] And an additional 1 h at RT. [e] And an additional 1 h at RT, with addition of 1.0 equiv. of both LiN₃ and TEMPO and 0.6 equiv. of PhI(OPiv)₂.

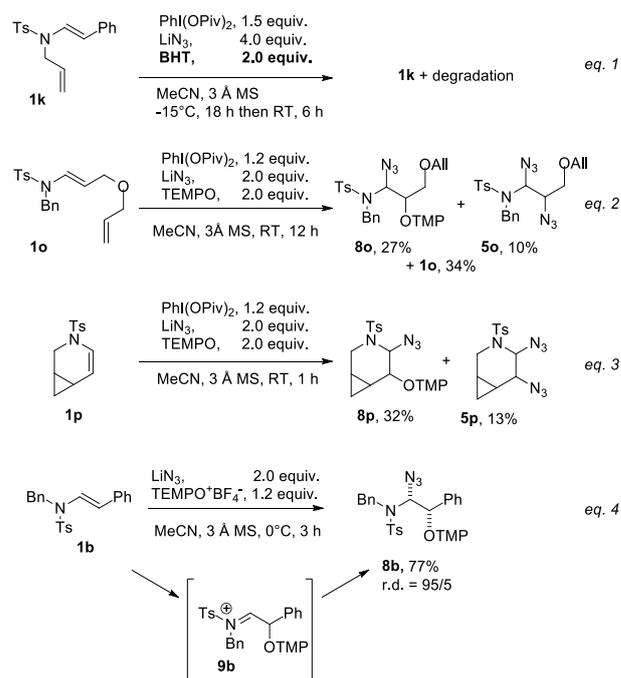
At this stage we sought after a mechanistic rationalization accounting for the formation of both types of products. Our initial assumption, based on the formation of cyclic product **6** (see Scheme 2) was that the combination of $\text{PhI}(\text{OPiv})_2$ and LiN_3 led to the generation of azido radicals that upon reaction with enamide **1** would lead to intermediate **7**. Subsequent recombination with another azido radical or SET oxidation followed by trapping by an azide anion would account for the formation of adduct **5** (Scheme 3). In the presence of TEMPO, interception of **7** by a nitroxyl free radical would lead to compound **8**. Based on the known reactivity of TEMPO with iodine (III) reagents³¹ an alternative scenario can be envisaged.³² In this case, the TEMPO radical would be oxidized to an oxy-ammonium cation that could be trapped to yield iminium **9**.³³ Eventually, nucleophilic trapping by an azide anion would also deliver adduct **8**.



Scheme 3. Mechanistic proposal.

We thus devised a series of control experiments to verify these hypotheses. First, enamide **1k** was submitted to the diazidation reaction conditions in the presence of two equivalents of BHT as a radical scavenger (Scheme 4, eq. 1). Only unreacted starting material and some degradation products could be observed even after prolonged reaction time, which further supports the involvement of radical species in this case. As for the oxyazidation reaction, two potential radical probes were synthesized and subjected to the reaction conditions to complement the observations made with *N*-allyl derivative **1k**. Both *O*-allyl enamide **1o** (eq. 2) and cyclopropyl enamide **1p** (eq. 3) reacted sluggishly to give the α -TEMPO azido amins **8o** and **8p** as the major compounds in approximately 30% yield along with about 10% of the diazido adducts **5o** and **5p**.

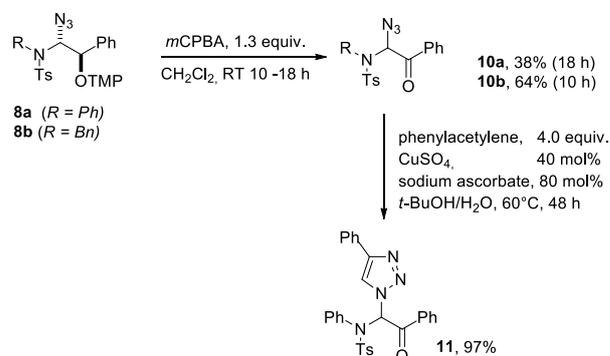
Although not fully conclusive *per se* with regard to the nature (ionic or radical) of the reactive species, these two latter experiments seem to hint towards a mechanistic dichotomy depending on whether or not TEMPO is present in the reaction mixture. Indeed, it would be surprising that trapping by TEMPO would systematically be faster than any possible intramolecular process, cyclization (**1k** and **1o**) or ring-opening (**1p**), the products resulting of which have not been observed. Finally, the oxy-ammonium reagent TEMPOBF_4 was prepared³⁴ and then reacted with enamide **1b** (eq. 4). Oxy-azido adduct **8b** was obtained, presumably through iminium **9b**, with nearly identical yield and selectivity as when using the I(III)-TEMPO combination.



Scheme 4. Control experiments.

This set of experiments converges towards the fact that while for the diazidation process the initial step would involve radical azido species, for the azido-oxyamination it would rather entail oxoammonium species generated *in situ* from TEMPO. The incorporation of the OTMP moiety would thus arise from an ionic manifold, rather than from the final trapping of a free radical.³⁵

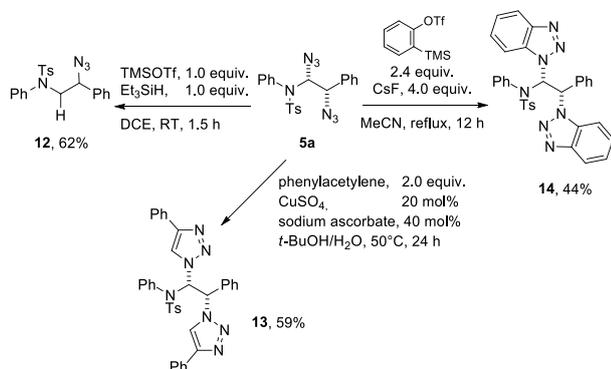
The highly versatile adducts isolated throughout this study were subjected to various transformations. First, the TEMPO moiety was oxidatively removed to give the corresponding ketones **10a** and **10b** with moderate to good yields (Scheme 5).²¹ Subsequently, the azide moiety of ketone **10a** could undergo a copper-catalyzed [3+2] cycloaddition with phenylacetylene to give keto-triazole **11** with an excellent yield.



Scheme 5. Functionalization of the oxyamino-azido adducts.

The particular structure of the diazido adducts could also serve as the basis for further transformations. First, taking advantage of

the hemiaminal moiety, a Lewis acid-induced reduction with triethylsilane was performed to give α -azido-amide **12** (Scheme 6).



Scheme 6. Functionalization of the diazido adducts.

While this strategy allows discrimination of the two azide groups, a double copper-catalyzed [3+2] cycloaddition could also be performed to deliver bis-triazole **13**. Alternatively, reaction with *in situ* generated benzyne formed the bis-benzotriazole **14**.²¹

Conclusion

We have shown that the *in situ umpolung* of halide salts for the oxidative difunctionalization of enamides could be extended to pseudo-halide salts, such as lithium azide, thereby enabling a diazidation reaction. In order to better understand the mechanism of this reaction, TEMPO was used as a radical scavenger which ultimately led to the triggering of a divergent but ultimately interesting reaction pathway. This discovery showcases that caution must be taken when highly reactive species such as TEMPO are used as mechanistic probes for processes involving hypervalent iodine(III) species. Nevertheless, it also permitted the development of a highly efficient azido-oxyamination of enamides. Both lines of research, *ie* the *umpolung* of pseudo-halide salts and the *in situ* generation of electrophilic oxyammonium species, appear as highly promising and are currently being pursued in our laboratory.

Experimental Section

Representative procedure for diazidation

To a suspension of (*E*)-*N*-phenyl-*N*-styryl-*N*-(4-methylbenzenesulfonamide) **1a** (50 mg, 0.14 mmol, 1.0 equiv.), LiN₃ (28 mg, 0.57 mmol, 4 equiv.) and 3Å molecular sieves (50 mg) in MeCN at -15°C was added Ph(OPiv)₂ (87 mg, 0.22 mmol, 1.5 equiv.). After 1 h, the reaction mixture was diluted with EtOAc, filtered over alumina (EtOAc) and concentrated under reduced pressure. ¹H NMR indicated the formation of two diastereoisomers in a 80/20 ratio. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 95/05) to afford 32 mg (52%) of the desired product **5a** as a colorless oil.

Representative procedure for azido-oxyamination

To a suspension of (*E*)-*N*-phenyl-*N*-styryl-*N*-(4-methylbenzenesulfonamide) **1a** (300 mg, 0.86 mmol, 1.0 equiv.), LiN₃ (84 mg, 1.72 mmol, 2.0 equiv.), TEMPO (268 mg, 1.72 mmol, 2.0 equiv.) and 3Å molecular sieves (300 mg) in MeCN at 0°C was added Ph(OPiv)₂ (419 mg, 1.03 mmol, 1.2 equiv.). After 2.25 h, the reaction mixture was diluted with EtOAc, filtered over alumina (EtOAc) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 95/05) to afford 360 mg (77%) of the desired product **8a** as a white powder.

All synthetic methods including spectroscopic and analytical data are included in the Supplementary Information.

Acknowledgements

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Keywords: hypervalent iodine • umpolung • azide • TEMPO • enamides

- [1] a) V. V. Zhdankin, *Hypervalent Iodine Chemistry*, Wiley, Chichester **2014**; b) *Hypervalent Iodine Chemistry*, (Ed.: T. Wirth), *Top. Curr. Chem.* **2003**, *224*, Springer, Berlin.
- [2] a) M. Brown, U. Farid, T. Wirth, *Synlett* **2013**, 424; b) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; c) T. Wirth, *Angew. Chem.* **2005**, *117*, 3722; *Angew. Chem., Int. Ed.* **2005**, *44*, 3656; d) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2002**, *102*, 2523; e) A. Varvoglis, *Tetrahedron* **1997**, *53*, 1179; f) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **1996**, *96*, 1123.
- [3] R. M. Romero, T. H. Wöste, K. Muñoz *Chem. Asian J.* **2014**, *9*, 972.
- [4] a) J. P. Brand, D. Fernández González, S. Nicolai, J. Waser *Chem. Commun.*, **2011**, *47*, 102; b) V. V. Zhdankin, *Curr. Org. Synth.* **2005**, *2*, 121.
- [5] a) S. Akai, T. Okuno, T. Takada, H. Tohma, Y. Kita, *Heterocycles* **1996**, *42*, 47; b) G. A. Rabah, G. F. Koser, *Tetrahedron Lett.* **1996**, *37*, 6453
- [6] R. M. Moriarty, *J. Org. Chem.* **2005**, *70*, 2893.
- [7] S. Nocquet-Thibault, P. Retaillieu, K. Cariou, R. H. Dodd, *Org. Lett.* **2013**, *15*, 1842.
- [8] S. Nocquet-Thibault, C. Minard, P. Retaillieu, K. Cariou, R. H. Dodd, *Tetrahedron* **2014**, *70*, 6769.
- [9] S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem.* **2005**, *117*, 5320; *Angew. Chem. Int. Ed.* **2005**, *44*, 5188.
- [10] For recent reviews on *N,O*-acetals, see: a) A. O. Kataja, G. Masson *Tetrahedron* **2014**, *70*, 8783; for illustrations of the synthetic versatility of α -halo-hemiaminals, see: b) M. R. P. Norton Matos, C. A. Afonso, R. A. Batey, *Tetrahedron* **2001**, *61*, 1221; c) M. R. P. Norton Matos, C. A. Afonso, T. McGarvey, P. Lee, R. A. Batey, *Tetrahedron Lett.* **1999**, *40*, 9189; d) ref 7.
- [11] a) F. Cech, E. Zbiral, *Tetrahedron* **1975**, *31*, 605; b) J. Ehrenfreund, E. Zbiral, *Liebigs Ann. Chem.* **1973**, 290; c) J. Ehrenfreund, E. Zbiral, *Tetrahedron* **1972**, *28*, 1697; d) E. Zbiral, J. Ehrenfreund, *Tetrahedron* **1971**, *27*, 4125; e) E. Zbiral, G. Nestler, *Tetrahedron* **1970**, *26*, 2945.
- [12] R. M. Moriarty, J. S. Khosrowshahi, *Tetrahedron Lett.* **1986**, *27*, 2809.
- [13] a) P. Magnus, J. Lacour, *J. Am. Chem. Soc.* **1992**, *114*, 767; b) P. Magnus, J. Lacour, *J. Am. Chem. Soc.* **1992**, *114*, 3993.
- [14] a) P. Magnus, J. Lacour, P. A. Evans, P. Rigollier, H. Tobler, *J. Am. Chem. Soc.* **1998**, *120*, 12486; b) P. Magnus, J. Lacour, P. A. Evans, M. B. Roe, C. Hulme, *J. Am. Chem. Soc.* **1996**, *118*, 3406.
- [15] a) P. Magnus, I. K. Sebhat, *Tetrahedron* **1998**, *54*, 15509; b) P. Magnus, I. K. Sebhat, *J. Am. Chem. Soc.* **1998**, *120*, 5341.

- [16] a) A. Kirschning, M. Abul Hashem, H. Monenschein, L. Rose, K.-U. Schoening, *J. Org. Chem.* **1999**, *64*, 6522. This method was later employed for the synthesis of (\pm)-dibromophakellstatin, see: b) R. Chung, E. Yu, C. D. Incarvito, D. J. Austin, *Org. Lett.* **2004**, *6*, 3881.
- [17] A. Kirschning, H. Monenschein, C. Schmeck, *Angew. Chem.* **1999**, *111*, 2720; *Angew. Chem., Int. Ed.* **1999**, *38*, 2594.
- [18] a) Yu. V. Mironov, A. A. Sherman, N. E. Nifantiev, *Mendeleev Commun.*, **2008**, *18*, 241; b) Yu. V. Mironov, A. A. Sherman, N. E. Nifantiev, *Tetrahedron Lett.*, **2004**, *45*, 9107; c) S. Czernecki, D. Randriamandimby, *Tetrahedron Lett.*, **1993**, *34*, 7915; d) M. Tingoli, M. Tiecco, D. Chianelli, R. Balducci, A. Temperini, *J. Org. Chem.*, **1991**, *56*, 6809.
- [19] a) V. V. Zhdankin, R. M. Arbit, M. McSherry, B. Mismash, V. G. Young Jr., *J. Am. Chem. Soc.* **1997**, *119*, 7408; b) V. V. Zhdankin, A. P. Krasutsky, C. J. Kuehl, A. J. Simonsen, J. K. Woodward, B. Mismash, J. T. Bolz, *J. Am. Chem. Soc.* **1996**, *118*, 5192
- [20] M. V. Vita, J. Waser, *Org. Lett.* **2013**, *15*, 3246.
- [21] TEMPO_{Na}-mediated: B. Zhang, A. Studer, *Org. Lett.* **2013**, *15*, 4548.
- [22] Copper(II)-catalyzed: L. Zhu, H. Yu, Z. Xu, X. Jiang, L. Rin, R. Wang, *Org. Lett.* **2014**, *16*, 1562.
- [23] H. Yin, T. Wang, N. Jiao, *Org. Lett.* **2014**, *16*, 2302.
- [24] a) N. Fuentes, W. Kong, L. Fernández-Sánchez, E. Merino, C. Nevado, *J. Am. Chem. Soc.* **2015**, *137*, 964; b) W. Kong, E. Merino, C. Nevado, *Angew. Chem.* **2014**, *126*, 5178; *Angew. Chem., Int. Ed.* **2014**, *53*, 5078.
- [25] Following a similar reasoning, Ibrahim recently reported that a Bu₄NX-DIB combination was suitable to perform either halogenation (X = Cl, Br or I) or azidation (X = N₃) of 1,3-dicarbonyl compounds, see: a) M. J. Galligan, R. Akula, H. Ibrahim, *Org. Lett.* **2014**, *16*, 600; see also: b) R. Akula, M. J. Galligan, H. Ibrahim, *Chem. Commun.* **2009**, 6991
- [26] This combination (DIB/NaN₃) was recently used for the preparation of azide-containing polymers: H. Han, N. V. Tsarevsky, *Chem. Sci.* **2014**, *5*, 4599.
- [27] Compared to DIB PIFA was found to be a superior *umpolung* promoter for the intramolecular arylazidation of activated alkenes with TMSN₃: K. Matcha, R. Narayan, A.P. Antonchick, *Angew. Chem.* **2013**, *125*, 8143; *Angew. Chem., Int. Ed.* **2013**, *52*, 7985.
- [28] CCDC 1405684 (**5a**) and CCDC 1059677 (**8a**) 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/.
- [29] T. Vogler, A. Studer, *Synthesis* **2008**, 1979.
- [30] Moreover, this reaction formally gives the regioisomer opposite to the one obtained through the copper-catalyzed alkoxyamination we recently developed: M. Nakanishi, C. Minard, P. Retailleau, K. Cariou, R. H. Dodd, *Org. Lett.* **2011**, *13*, 5792.
- [31] a) N. Ambreen, R. Kumar T. Wirth, *Beilstein J. Org. Chem.* **2013**, *9*, 1437; b) A. De Mico, R. Margarita, L. Parlanti A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974.
- [32] In the case of Fe(III)-catalyzed dioxygenation of enamides with an alcohol and TEMPO both radical and ionic manifolds have been proposed, see : F. Drouet, J. Zhu, G. Masson, *Adv. Synth. Catal.* **2013**, *355*, 3563.
- [33] a) Kano, T.; Mii, H.; Maruoka, K. *Angew. Chem.* **2010**, *122*, 6788; *Angew. Chem. Int. Ed.* **2010**, *49*, 6638; b) Schämamm, M.; Schäfer, H. J. *Electrochim. Acta.* **2005**, *50*, 4956; c) T. Takata, Y. Tsujino, S. Nakanishi, K. Nakamura, E. Yoshida, T. Endo, *Chem. Lett.* **1999**, 937.
- [34] H. Richter, O. García Mancheño *Eur. J. Org. Chem.* **2010**, 4460.
- [35] While in this case the TEMPO free radical would be oxidized by SET to the corresponding cation, Studer proposed a radical mechanism for the azido-oxyamination he recently developed.²¹ In this latter study, however, TEMPO_{Na} was used as a reducing agent in combination with a cyclic azido-benziodoxole derivative. The SET process thus generates two free radical species: TEMPO and N₃. For a related strategy using Togni's reagent to promote the trifluoromethylaminoxylation of alkenes, see: a) Y. Li, A. Studer, *Angew. Chem.* **2012**, *124*, 8345; *Angew. Chem., Int. Ed.* **2012**, *51*, 8221. A similar azido-oxyamination of alkenes using N-hydroxyphthalimide, TMSN₃ and DIB has very recently been reported: b) X.-F. Xia, Z. Gu, W. Liu, H. Wang, Y. Xia, H. Gao, X. Liu, Y.-M. Liang *J. Org. Chem.*, **2015**, *80*, 290.

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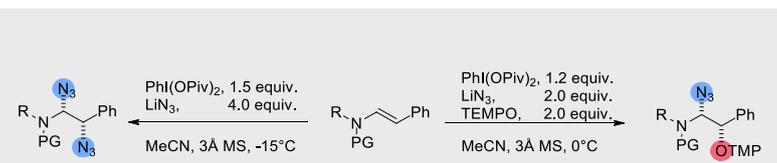
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TEMPO Change: Two complementary difunctionalizations of enamides are described. While the use of bis(*tert*-butylcarboxyloxy)iodobenzene in conjunction with lithium azide triggers a radical diazidation process, adding TEMPO to the mixture leads to the ionic azido-oxyamination of the same substrates.

Synthetic Methods

Sophie Nocquet-Thibault, Anita Rayar, Pascal Retailleau, Kevin Cariou and Robert H. Dodd**

■■ - ■■

Iodine(III)-mediated diazidation and azido-oxyamination of enamides