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Azides

Iodine(III)-Mediated Diazidation and Azido-oxyamination of Enamides

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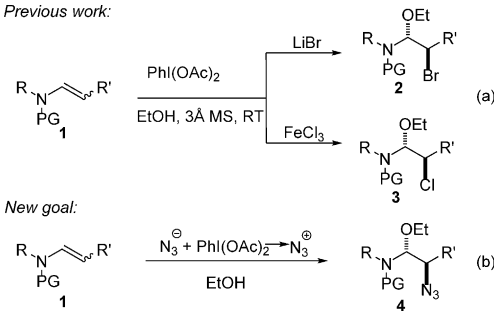
Abstract: In this study we demonstrate that the combination of bis(*tert*-butylcarbonyloxy)iodobenzene and lithium azide in acetonitrile allows the diazidation of various enamide substrates. The azido-oxyamination of the same substrates can be carried out in the presence of 2,2,6,6-tetramethylpiperidine *N*-oxide (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 reagents,[1,2] notably for the 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, their general utility is limited by the need to be synthesized beforehand.[5] This drawback can be overridden by in situ generation of the active species through an "umpolung" strategy, which relies upon the successive exchanges of the hypervalent iodine(III) ligands to generate a novel electrophilic species.[6] We have adopted this strategy to promote the ethoxybromination[7] and the ethoxychlorination of enamides **1** by using a combination of (**D**iacetoxy**I**odo)**B**enzene (DIB) with lithium bromide and iron(III) chloride,[8] respectively, which permitted the regio- and chemoselective access to multipurpose synthons **2** and **3** (Scheme 1 a). To further broaden the scope of this strategy, we turned our attention from halogens to pseudohalogens. The azide ion can be considered as a pseudohalide, which implies that its behavior is similar to that of a halide. Thus, we envisaged that the same umpolung strategy could be applied to azides to give α-azido hemiaminals **4** (Scheme 1 b). Given the vast synthetic utility of organic azides,[9] this straightforward strategy appeared ideal for the rapid assembly of value-added linchpins.[10]



Scheme 1. Umpolung strategy for the electrophilic pseudohalogenation of enamides.

The basis for this study relied upon the feasibility of combining an azide with a hypervalent iodine(III) derivative to generate an electrophilic species ("N_3^+") that is capable of reacting with various double bonds. In a series of papers from the early 70 s, Zbiral was the first to study and report the reactivity of a DIB-trimethylsilylazide (TMSA) combination with alkenes,[11] for which he postulated the generation of mixed hypervalent iodine(III) species that incorporated an azide ligand. Depending on the reaction conditions that were employed, various difunctionalized compounds could be obtained, although often as mixtures. 15 years later this strategy was expanded upon by Moriarty, who described the vicinal diazidation of alkenes by using a PhIO/NaN_3/AcOH combination.[12] In this case, the proposed mechanism involves electrophilic activation by the iodine and two successive nucleophilic additions of the azide. The most sustained efforts in this area were deployed by Magnus, who showed that the combination of iodosobenzene and TMSA could trigger the β-azidation or the diazidation of enol ethers.[13] He went on to study this reaction thoroughly[14] and applied it to the synthesis of natural products.[15] Similar combinations of reagents were later used by Kirshning as surrogates for haloazides[16] and to synthesize a stable polymer-

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bound iodine azide.[17] Furthermore, the addition of an organoselenium species to the iodine(III)-azide combination was 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 intermolecular[21] and intramolecular[22] oxyazidation of alkenes, the copper-catalyzed oxoazidation of indoles,[23] and the arylazidation of activated alkenes.[24]

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 pseudohalides that would only differ by the nature of the salts.[25]

Results and Discussion

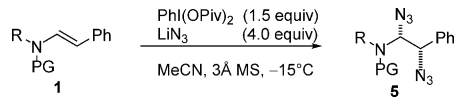
Building on our experience with halide salts, we initially aimed to develop an ethoxy-azidation reaction. Unfortunately, the combination of LiN_3 or NaN_3[26] with DIB in ethanol at various temperatures led to either no conversion or to intractable mixtures, even after prolonged reaction times (Table 1, entries 1 and 2). Using trimethylsilylazide with DIB (entry 3) or with iodosylbenzene (entry 4), or a cyclic azido benziodoxole (entry 5) proved equally unsuccessful.

The more reactive **P**henyl**I**odine-bis(tri**F**luoro**A**cetate) (PIFA)[27] was found to be a suitable promoter when it was used in conjunction with $TMSN_3$ in dichloromethane to access the bis-azido compound **5a** in 19% yield (entry 6). Running the reaction in acetonitrile did not help to improve the reactivity (entry 7), whereas bis(*tert*-butylcarbonyloxy)iodobenzene acted as a superior promoter (entry 8), and it could also be used with LiN_3 (entries 9 and 10). This azide source was found to be more convenient and robust to use than $TMSN_3$, although it was poorly soluble in CH_2Cl_2, but this could be overcome 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 of the reaction (entries 11–14). Accordingly, −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 substrate scope of the reaction. The benzylamine-derived enamide **1b** reacted in a similar manner (Table 2, entry 2), as did the mesyl-protected substrate **1c** (entry 3) and the methylamine derivative **1d** (entry 4). The use of a carbamate protecting group (Boc, entries 5 and 6) appeared incompatible with this reaction, whereas amides (entries 7–9) were well tolerated. Finally, the same conditions were applied to *N*-benzenesulfonyl indole **1j** to give the desired product, 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.

Overall, this process seemed to be quite capricious and it was hampered by various side reactions, which indicated the in situ generation of highly reactive intermediates, such as azido radicals, as previously postulated.[14] The involvement of radical species became apparent when trisubstituted pyrrolidine **6** was isolated as the main product, albeit in a modest yield, from the reaction of allylamine-derived enamide **1k** (Scheme 2a). To account for the formation of this compound, we postulated that a *5-exo-trig* cycli-

Table 2. Diazidation scope.

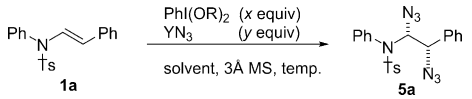


1 → 5

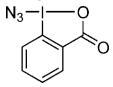
Entry	SM[a]	R	PG	Time [h]	d.r.[b]	Yield [%][c]
1	**1a**	Ph	Ts	1	80:20	52
2	**1b**	Bn	Ts	1.25	90:10	47
3	**1c**	Ph	Ms	1	70:30	40
4	**1d**	Me	Bs[d]	1	75:25	46
5	**1e**	Ph	Boc	1	ND	CM[e]
6	**1f**	Bn	Boc	1	ND	CM
7	**1g**	Ph	Ac	1	73:27	18
8	**1h**	Bn	Ac	1	75:25	61
9	**1i**	Ph	$COCF_3$	3	67:33	43
10	**1j**	*N*-(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] Yield of isolated product. [d] Bs: benzenesulfonyl. [e] CM: complex mixture. [f] Additional 1 h at RT.

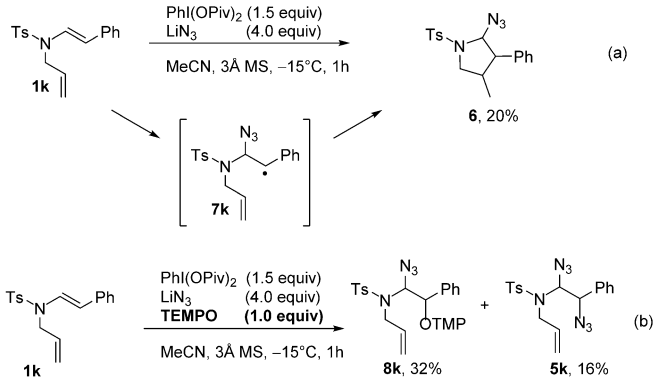
Table 1. Diazidation optimization.



1a → 5a

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_2Cl_2	−50	6 d	ND	CM
5		1.9	–	EtOH	0 to RT	30 h to 5 d	ND	CM
6	$COCF_3$	1.2	TMS	CH_2Cl_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_2Cl_2	RT	1 h	ND	27
9	CO*t*Bu	1.2	Li	CH_2Cl_2	RT	1 h	ND	21[e]
10	CO*t*Bu	1.5	Li	CH_2Cl_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 determined by X-ray diffraction analysis of a mono crystal of **5a**.[28] ND: not determined. [c] Yield of isolated product. [d] CM: complex mixture. [e] Reaction run with 3.0 equiv of $NaHCO_3$.

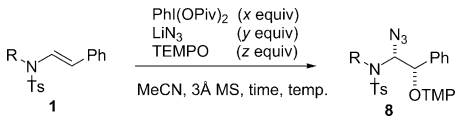


Scheme 2. Reactivity of allylamine-derived enamide **1k**.

zation could have occurred from the radical intermediate **7k**, which resulted from the addition of an azido radical to the starting enamide. To obtain more insight into this particular case, we decided to run the same reaction in the presence of 1 equivalent of TEMPO[29] as a radical scavenger. In this case, the main product was the oxyaminated adduct **8k**, which possibly arose from the trapping of intermediate **7k** by the TEMPO radical (Scheme 2b). Moreover, diazido compound **5k** was also isolated, whereas virtually no traces of cyclized products were detected.

Considering the apparent improved efficiency of the enamide azido-oxyamination versus the diazidation,[30] we thought that optimization of the former transformation would also be worthwhile. By doubling the amount of TEMPO, the yield of **8k** went up to 58% (Table 3, entry 2). By using only 2 equivalents of LiN_3, complete chemoselectivity was attained along with a further improvement of the yield (entry 3).

Table 3. Azido-oxyamination optimization.



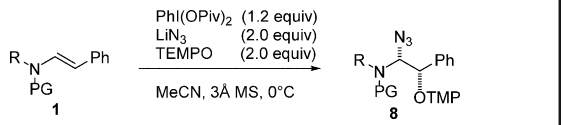
Entry	SM	*x*	*y*	*z*	Temp. [°C]	Time [h]	d.r.[b]	Yield [%][a]
1	**1k**	1.5	4	1	−15	1	ND	32[c]
2	**1k**	1.5	4	2	−15	6	ND	58[d]
3	**1k**	1.5	2	2	−15	5	ND	75
4	**1k**	1.5	2	2	0	2	95:5	69
5	**1k**	1.5	2	2	RT	1	95:5	21
6	**1a**	1.5	2	2	−15	7	95:5	50[e]
7	**1a**	1.2	1.2	1.2	RT	6	90:10	51[f]
8	**1a**	1.2	2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

[a] Yield of isolated product. [b] The relative stereochemistry of the major diastereoisomer was determined by analogy with **8a**, for which X-ray diffraction 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 6 h 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 LiN_3 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), whereas operating at room temperature greatly reduced 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 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 in 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 evaluated the enamide substrate scope (Table 4). As we had observed with compounds **1a** and **1k**, the reaction yields were consistently higher than for the diazidation of the same substrates. A range of sulfonyl-protected enamides (entries 1–6) were first tested; the yields were generally above 70%, the regioselectivity was complete, and the diastereoselective ratio was above 80:20. Moreover, although the carbamate-protected enamides **1e** and **1f** could not undergo the diazidation reaction (see Table 2, entries 5 and 6), their azido-oxyamination did proceed though with moderate yields (entries 7 and 8). Very good yields and good levels of stereoselectivity were also obtained for amide substrates, including acetamides **1g** and **h** (entries 9 and 10), a trifluoroacetamide **1i** (entry 11), and a caprolactam **1m** (entry 12). Finally, cyclic enamides, such as *N*-(Bs)-indole **1j** (entry 13) and *N*-(Bs)-tetrahydropyridine **1n** (entry 14), gave the desired products with excellent levels of selectivity and yields.

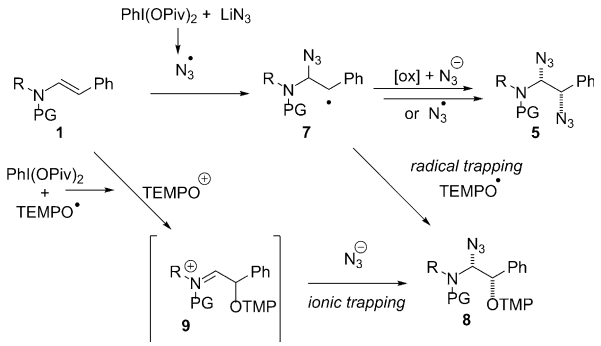
Table 4. Azido-oxyamination scope.



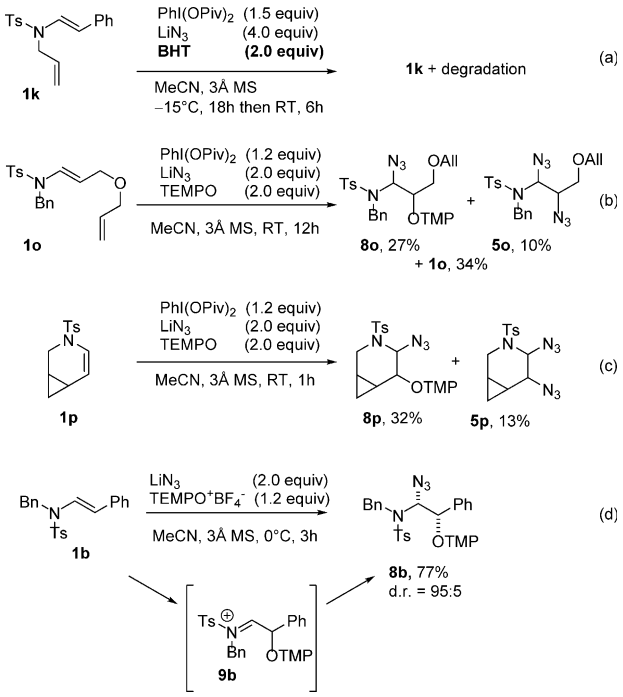
Entry	SM[a]	R	PG	Time [h]	d.r.	Yield [%][b]
1	**1a**	Ph	Ts	2.25	90:10	77
2	**1b**	Bn	Ts	3	95:5	74
3	**1c**	Ph	Ms	1	80:20	73
4	**1d**	Me	Bs[c]	1	85:15	73
5	**1k**	allyl	Ts	1	95:5	67
6	**1l**	Me	Ms	1	83:17	83
7	**1e**	Ph	Boc	1	74:26	31
8	**1f**	Bn	Boc	1	83:17	41
9	**1g**	Ph	Ac	1	81:19	81
10	**1h**	Bn	Ac	4	60:40	98
11	**1i**	Ph	$COCF_3$	4[d]	77:23	77
12	**1m**	$-(CH_2)_5CO-$		1	100:0	67
13	**1j**	*N*-(Bs)-indole		7[d]	100:0	97
14	**1n**	*N*-(Bs)-tetrahydropyridine		7[e]	100:0	94

[a] SM: starting material. [b] Yield of isolated product. [c] Bs: benzenesulfonyl. [d] And an additional 1 h at RT. [e] And an additional 1 h at RT, 1.0 equiv of both LiN_3 and TEMPO, and 0.6 equiv of $PhI(OPiv)_2$.

At this stage, we sought after a mechanistic rationalization to account 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 $PhI(OPiv)_2$ 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,



Scheme 3. Mechanistic proposal.



Scheme 4. Control experiments.

interception of **7** by a nitroxyl free radical would lead to compound **8**. Based on the known reactivity of TEMPO with iodine (III) reagents,[31] an alternative scenario can be envisaged.[32] In this case, the TEMPO radical would be oxidized to an oxy-ammonium cation, which could be trapped to yield iminium intermediate **9**.[33] Eventually, nucleophilic trapping by an azide anion would also deliver adduct **8**.

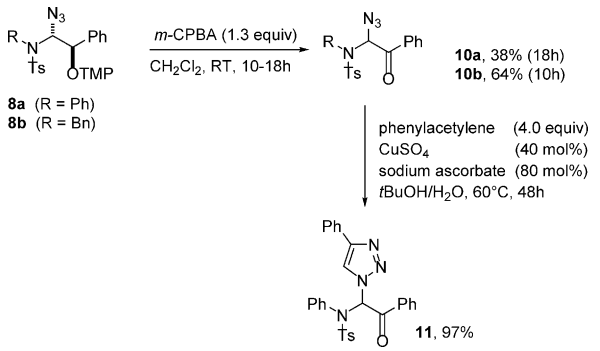
We devised a series of control experiments to verify these hypotheses. Initially, enamide **1k** was submitted to the diazidation reaction conditions in the presence of two equivalents of BHT as a radical scavenger (Scheme 4a). However, only unreacted starting material and some degradation products were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

Although they are not fully conclusive with regard to the nature (ionic or radical) of the reactive species, the two latter experiments intimate a mechanistic dichotomy that depends 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 intramolecular process, cyclization (**1k** and **1o**), or ring-opening (**1p**), the products of which have not been observed. Finally, the oxy-ammonium reagent $TEMPOBF_4$ was prepared[34] and reacted with enamide **1b** (Scheme 4d). Oxy-azido adduct **8b** was obtained, presumably via iminium intermediate **9b**, with nearly identical yield and selectivity as when using the I(III)/TEMPO combination.

This set of experiments implies that, although the initial step of the diazidation process would involve a radical azido species, the azido-oxyamination reaction involves an 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]

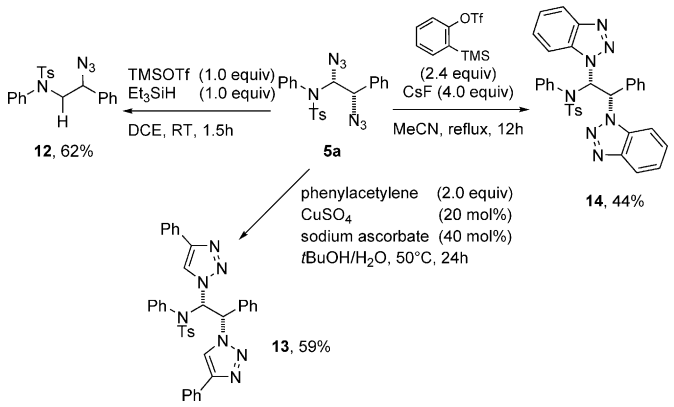
The highly versatile adducts that were isolated throughout this study were then subjected to various transformations. Initially, the TEMPO moiety was oxidatively removed to give the corresponding ketones **10a** and **10b** with moderate to good yields (Scheme 5).[21] Subsequently, the azide moiety of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

The particular structure of the diazido adducts could also serve as the basis for further transformations. By taking advantage of the hemiaminal moiety, a Lewis acid-induced reduction



Scheme 5. Functionalization of the oxyamino-azido adducts.

with triethylsilane was performed to give α-azido-amide **12** (Scheme 6). Although 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, the reaction with benzyne, generated in situ, formed the bis-benzotriazole **14**.[21]



Scheme 6. Functionalization of the diazido adducts.

Conclusion

We have shown that the in situ umpolung of halide salts for the oxidative difunctionalization of enamides could be extended to pseudohalide salts, such as lithium azide, thereby enabling a diazidation reaction. 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 that involve hypervalent iodine(III) species. Nevertheless, it also permitted the development of a highly efficient azido-oxyamination of enamides. Both lines of research, the umpolung of pseudohalide salts and the in situ generation of electrophilic oxyammonium species, appear to be highly promising reactions and are currently being pursued further in our laboratory.

Experimental Section

Representative procedure for diazidation

$PhI(OPiv)_2$ (87 mg, 0.22 mmol, 1.5 equiv) was added to a suspension of (*E*)-*N*-phenyl-*N*-styryl-*N*-(4-methylbenzenesulfonamide) **1a** (50 mg, 0.14 mmol, 1.0 equiv), LiN_3 (28 mg, 0.57 mmol, 4.0 equiv) and 3 Å molecular sieves (50 mg) in MeCN at −15 °C. After 1 h, the reaction mixture was diluted with EtOAc, filtered over alumina (EtOAc), and concentrated under reduced pressure. ^1H NMR spectroscopy 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 the desired product **5a** (32 mg, 52%) as a colorless oil.

Representative procedure for azido-oxyamination

$PhI(OPiv)_2$ (419 mg, 1.03 mmol, 1.2 equiv) was added to a suspension of (*E*)-*N*-phenyl-*N*-styryl-*N*-(4-methylbenzenesulfonamide) **1a** (300 mg, 0.86 mmol, 1.0 equiv), LiN_3 (84 mg, 1.72 mmol, 2.0 equiv), TEMPO (268 mg, 1.72 mmol, 2.0 equiv) and 3 Å molecular sieves (300 mg) in MeCN at 0 °C. 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 the desired product **8a** (360 mg, 77%) as a white powder.

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

Acknowledgements

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Keywords: azides · enamides · hypervalent iodine · tempo · umpolung

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