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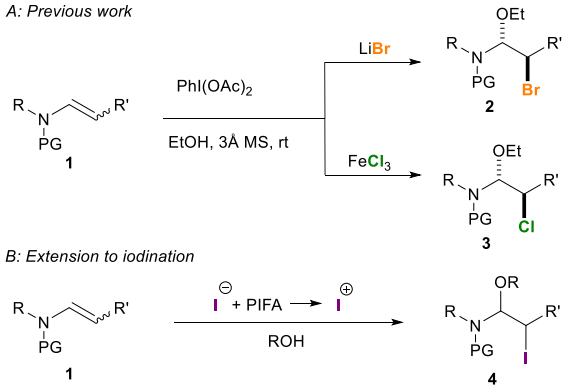
The regioselective ethoxyiodination of enamides was developed using PIFA in combination with potassium iodide in ethanol. The reaction proceeds regioselectively with excellent yields and diastereoselectivities, providing valuable synthons for further functionalisations. Control experiments were conducted, indicating that the transformation occurs through an ionic manifold involving an *in situ* generated hypoiodite species.

Enamides constitute a readily accessible[1] and versatile class of nitrogen-containing building blocks which can be used in a wide array of transformations.[2] For our part, we recently focused our attention on their regioselective oxidative double functionalisation using hypervalent iodine(III) reagents[3] as the promoter.[4] For instance, combinations of (diacetoxyiodo)benzene (DIB) with lithium bromide or iron(III) chloride in ethanol efficiently convert enamides **1** into the corresponding α-bromo-[4a] (**2**) and α-chloro-hemiaminals (**3**),[4b] respectively (Scheme 1A).



Scheme 1 Iodine(III)-mediated halogenation of enamides

This strategy relies on the *in situ* oxidation of the halide salt and constitutes a mild and selective alternative to the use of electrophilic halogenation reagents such as dihalides or succinimide derivatives.[3h] Inasmuch as the alkoxy-iodination of enamides[5] yields extremely useful synthons,[6] we thus considered extending our halogenation strategy to the oxy-iodination of enamides (Scheme 1B). Iodide anions are more readily oxidised than bromides or chlorides by iodine(III) reagents,[7] yet this couple has only been rarely used.[8] Instead, iodination has been performed using the iodine(III) reagents as the iodide donor[9] or in conjunction with I_2.[10,11] Based on our previous experience[4] we postulated that using a simple iodide salt in conjunction with a suitable iodine(III) compound would be sufficient to trigger the desired transformation.

Indeed, using *N*-benzyl-*N*-tosyl enamide **1a** as a model substrate, the desired adduct **4a** could be formed upon reaction with 1.2 equivalents of DIB and 2.0 equivalents of potassium iodide in ethanol at room temperature (Table 1, entry 1). However, the extended reaction time needed to reach full conversion (8 h) led to the formation of a complex mixture that was difficult to purify. A major improvement was witnessed when using a larger excess of DIB in combination with KI, giving the desired adduct **4a** in 1 h with a 68% yield (entry 2). Using 1.2 equivalents of [bis(trifluoroacetoxy)iodo]-benzene (PIFA) essentially gave the same results, although unwanted by-products, such as diethoxy adduct **5a**, were also detected (entry 3).[12] Replacing potassium iodide by sodium iodide did not improve the reactivity (entry 4). When 1.5 equivalents of PIFA and 2.4 equivalents KI were employed the reaction proceeded more rapidly and allowed the isolation of **4a** in 64% yield (entry 5). While PIFA seemed to be the best choice, its reactivity needed to be tempered. By adding the reagent in portions over two hours an excellent 92% yield of **4a** was obtained (entry 6). Finally, a controlled addition of a PIFA solution to the reaction mixture (containing all other reagents), gave a rapid (10 min) and clean reaction that led to the isolation of the difunctionalised adduct **4a** with a 91% yield and a 90:10 diastereoisomeric ratio (entry 7).

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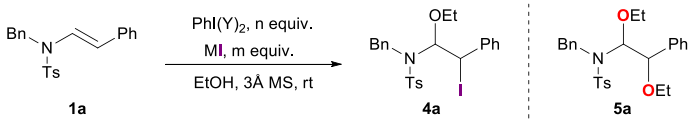
Table 1 Optimisation of the reaction



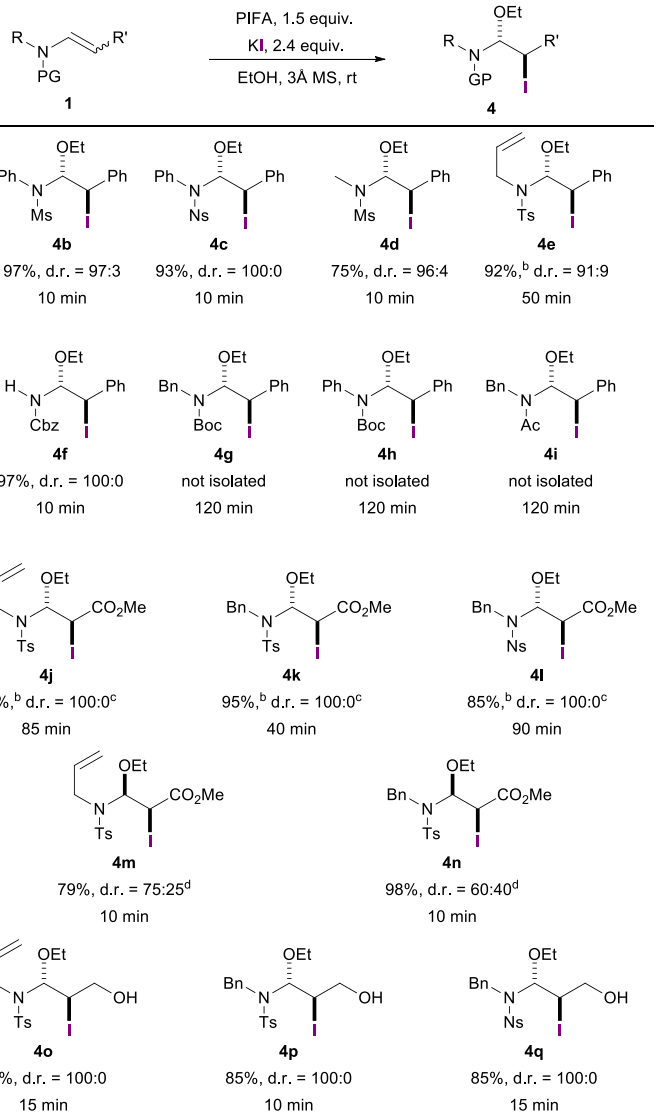
entry	Reagent, n	MI, m	t (min)	yield[a]
1	DIB, 1.2	KI, 2.0	480[b]	ND
2	DIB, 1.5[c]	KI, 2.4	60	68%
3	PIFA, 1.2	KI, 2.0[c]	60	66%
4	PIFA, 1.2	NaI, 2.0	120[b]	ND
5	PIFA, 1.5	KI, 2.4	10	64%
6	PIFA, 1.5[d]	KI, 2.4	120	92%
7	PIFA, 1.5[e]	KI, 2.4	10	91%[f]

[a] Isolated yields. [b] Time necessary to reach full conversion, determined by ^{1}H NMR monitoring. [c] Adding another 0.4 equiv. was necessary to reach completion. [d] In four portions, every 30 min. [e] Dropwise addition of a 0.14 M solution in EtOH. [f] d.r. = 90:10.

Having determined the most efficient reaction conditions, the scope of the reaction was explored (Table 2). Other sulfonylated enamides such as aniline derivatives (**1b**,**c**) or alkylamine derivatives (**1d**,**e**) reacted equally well, giving the corresponding hemiaminals (**4b–e**) with excellent yields and diastereoselectivities.[13] The latter case is noteworthy since, despite a slightly prolonged reaction time, the allyl chain remained untouched. Carbonyl-based protecting groups were then evaluated. While enecarbamate **1f** furnished the desired compound (**4f**) in near quantitative yield and with perfect selectivity, *N*-Boc and *N*-Ac-substituted enamides (**1g–i**) only led to complex mixtures.[14] *E*-Aminoacrylates (R' = CO_2Me) were found to be somewhat less reactive but good yields and excellent diastereoselectivities were nevertheless observed (**4j–l**). When the *Z*-aminoacrylates were employed, similar results were observed albeit with a reversal of diastereoselectivity (**4m**,**n**). Finally, a free alcohol group (R' = CH_2OH) was also well tolerated despite the oxidative nature of the reagents, yielding the corresponding 1,2-iodoalcohols with yields between 85% and 98% (**4o–q**).

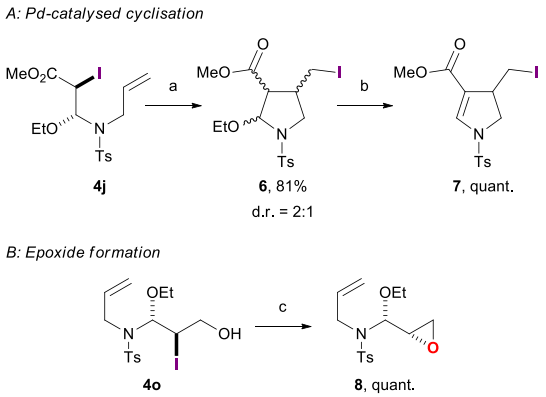
These α-iodo-hemiaminals constitute extremely modular scaffolds for further synthetic opportunities.[8] We have already shown that their α-bromo counterparts could be cyclised using organometallic- or free radical-based strategies.[4a] Here the iodo analogue not only constitutes a more reactive species but also a more versatile one. Therefore, taking inspiration from a method developed by Mori,[15] we subjected substrate **4j** to Pd(0)-catalysis, which triggered the desired cyclisation along with iodine transfer to give pyrrolidine **6** (Scheme 2A). Presumably because of minor acid traces in the NMR solvent, elimination of ethanol could be observed in deuterated chloroform to yield 2-pyrroline **7**.

Table 2 Reaction scope[a]



[a] Isolated yields; dropwise addition of a 0.14 M solution of PIFA in EtOH; d.r. calculated from the ^{1}H NMR spectrum; the stereochemistry of the major isomer was attributed by analogy with **4l** and **4q** for which an X-ray structure was obtained (see ESI for details).[13] [b] Adding another 0.2 equiv. of PIFA were necessary to reach completion. [c] Starting from the *E*-aminoacrylate. [d] Starting from the *Z*-aminoacrylate.

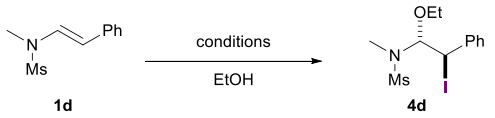
The reactive nature of the iodide could also be used to advantage to transform 1,2-iodoalcohol **4o** into epoxide **8** in quantitative yield (Scheme 2B).



Scheme 2 Examples of further transformations
[a] $Pd(PPh_3)_4$ 10 mol%, THF, rt, 3h [b] $CDCl_3$, rt, 15h [c] NaOH 1.1 equiv., MTBE:THF, 1:1, rt, 24h.

From a mechanistic point of view, it has been proposed that acetoxyhypoiodite is the active electrophilic species generated from the combination of DIB with iodine[10d,g,16] or an iodide[8a,c,17] salt. Alternatively, oxidation of the iodide could eventually lead to iodine. We decided to test these hypotheses by reacting enamide **1d** with either iodine or a hypoiodite and compare the results with those obtained with the PIFA+KI combination (Table 2, entry 1). Following a well-known protocol[18] we prepared acetoxyhypoiodite by mixing iodine with silver acetate and reacted it immediately with enamide **1d**. Indeed, a similar reactivity could be witnessed as hemi-aminal **4d** was readily obtained, although with a longer reaction time (entry 2). In contrast, using only iodine, the reaction yielded the same adduct **4d** but could not reach full conversion even after 2 h (entry 3). Finally the intervention of free radical species in this transformation was ruled out since adding 1 equivalent of BHT, a radical scavenger, left the overall process unchanged (entry 4).

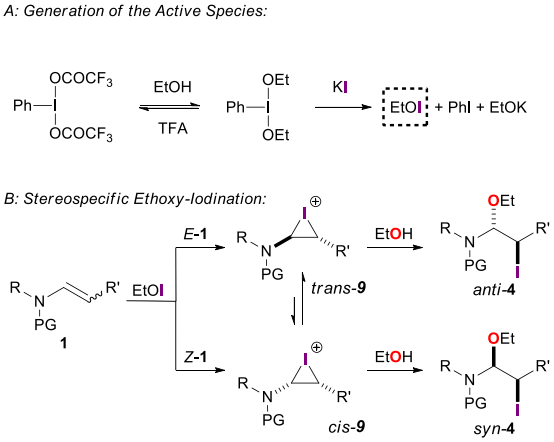
Table 2 Control experiments



entry	conditions	t (min)	conv. (%)[a]
1	(PIFA + KI)[b]	10	100
2	IOAc[c]	60	100
3	I_2[d]	120	60
4	(PIFA + KI)[b] + BHT[e]	10	100

[a] Determined by analysis of the crude ^1H NMR spectrum. [b] Dropwise addition of a 0.14 M solution of PIFA (1.5 equiv.) in EtOH at 0°C to the mixture already containing KI (2.4 equiv.). [c] At 0°C, dropwise addition of a freshly prepared mixture obtained by adding a solution of I_2 (0.14 M in $CHCl_3$, 1.5 equiv.) to a suspension of AgOAc (0.14 M in $CHCl_3$, 1.5 equiv.). [d] Dropwise addition of a 0.14 M solution of I_2 (1.5 equiv.) in EtOH at 0°C. [e] BHT (1.0 equiv.) was added to the reaction mixture before addition of the oxidant.

Based on these additional data we can thus propose a reasonable mechanism for this transformation. While a hypoiodite seems to be the active species, solvolysis of the hypervalent species in ethanol must be envisaged as a plausible initial step.[19] This would eventually lead to ethoxyhypoiodite[15a,20,21] as the actual active iodination reagent (Scheme 3A). Only ionic intermediates should be considered from this point, since, as demonstrated, adding BHT does not affect the outcome. Reaction with enamide **1** would give iodonium **9**, which would undergo S_N2-type opening with ethanol to furnish hemiaminal **4** (Scheme 3B). This latter step is supported by the stereospecificity of the difunctionalisation which would not be consistent with the intermediacy of an iodo-iminium, in which case both *E* and *Z* enamides would give hemiaminal **4** with the same diastereoisomeric ratio.



Scheme 3 Mechanistic proposal

To conclude, we have developed a convenient protocol for the rapid, efficient and selective ethoxyiodination of enamide derivatives. The reaction tolerates a broad range of substrates, thus giving access to various synthons that can, in turn, be useful for further transformations. Compared to the related ethoxybromination[4a] and ethoxychlorination[4b] that we previously developed, the reaction is faster, the yields higher and the stereoselectivity better. Control experiments point to the intermediacy of a hypoiodite active species and rule out the involvement of free radicals. Since this methodology provides a valuable alternative to classical iodination reagents, its application to other types of substrates is currently ongoing in our laboratory and will be reported in due course.

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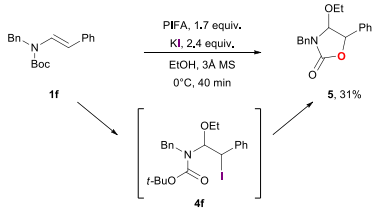
13 The stereochemistry of the major isomer was attributed by analogy with **4l** and **4q** for which an X-ray structure was obtained.Crystallographic data for **4l** and **4q** have been deposited with the Cambridge Crystallographic Data Centre (deposit no. CCDC 1488802 - 1488803). Copies of the data can be obtained, free of charge, from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

14 In the case of **2f**, oxazolidinone **5**, presumably arising from an intramolecular reaction of **4f** could be isolated in 31% yield.



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