Direct synthesis of oxazolines from olefins and amides using *t*-BuOI†

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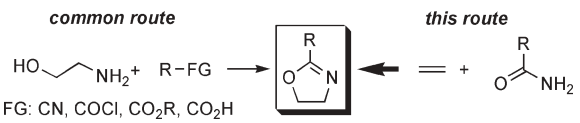
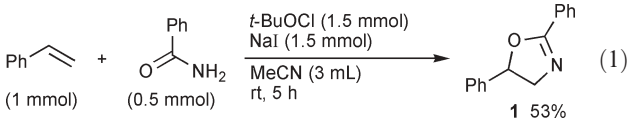
A new and simple method for the synthesis of oxazolines from readily accessible olefins and amides using *tert*-butyl hypoiodite is described; aromatic/aliphatic olefins and amides can be used in the reaction to give a variety of oxazolines.

A great number of oxazoline-containing natural products and biologically active compounds are present in marine organisms.[1] Moreover, enantiomerically pure oxazolines act as efficient chiral sources or ligands for asymmetric transformations,[2] and achiral oxazolines are also valuable intermediates in organic synthesis.[3] Thus, the development of a practical and convenient method for the construction of an oxazoline ring is an important goal. A general route to oxazolines is the reaction of hydroxyamides, prepared from β-aminoalcohols and acid chlorides, with thionyl chloride *via* cyclization.[4] Oxazolines are also directly formed by the reaction of β-aminoalcohols with nitriles, acid chlorides, esters or carboxylic acids.[4] We recently reported on the direct synthesis of oxazolines from olefins using a nitridomanganese complex and acid chlorides,[5] which was accomplished by changing the activator of the complex.[6] Although the method is crucial for the asymmetric synthesis of a variety of chiral oxazolines, a stoichiometric amount of a metal nitride complex is required for a successful reaction. It would be desirable to develop a method for the synthesis of oxazolines from readily accessible resources such as olefins and amides, but to our knowledge, there are no examples of this type of procedure to date.[7] Quite recently, we reported[8] on the novel aziridination of olefins with readily available sulfonamides using *tert*-butyl hypoiodite (*t*-BuOI).[9] The potential of this reagent prompted us to further investigate alternative unprecedented organic transformations. Based on this background, we report here the direct synthesis of oxazolines from unfunctionalized olefins and simple amides using *t*-BuOI.



To explore the possibility of the proposed [3 + 2] type synthesis of oxazolines, a model reaction between styrene and benzamide was performed in the presence of *t*-BuOI, prepared *in situ* from *t*-BuOCl and NaI.[8] By optimizing the solvent, reaction temperature and amount of the reagents, the conditions shown in eqn (1) were found to be suitable, successfully leading to the production of 2,5-diphenyl-2-oxazoline (**1**) without the formation of an *N*-benzoylaziridine. When the effect of other representative iodinating agents, such as iodine, *N*-iodosuccinimide (NIS) and bis(pyridine)iodine tetrafluoroborate (IPy_2BF_4),[10] on the reaction was investigated under the same conditions, iodine and IPy_2BF_4 did not give the desired oxazoline, and the yield of **1** was rather low (28%) in the case of NIS. In a study of the role of *t*-BuOX halogen atoms in the reaction, when *t*-BuOCl was used, a small amount of *N*-(2-chloro-2-phenylethyl)benzamide was produced.[11] When the reaction was conducted with a combination of *t*-BuOCl and NaBr, oxazoline **1** was obtained in 16% yield without the formation of the adduct, as in the case when only *t*-BuOCl was used. These results show that *t*-BuOI represents an ideal reagent for the direct synthesis of oxazolines. Although the reaction was conducted in the dark, as a precaution, the efficiency of the aziridination[8] using *t*-BuOI in interior light was found to bear comparison with results in the dark.

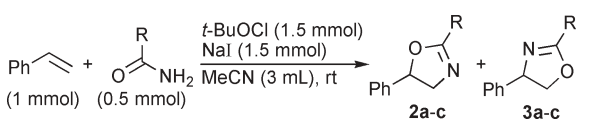


(1)

Some other amides were examined for their potential for oxazoline synthesis from styrene (Table 1). The reaction of styrene with *para*-methoxybenzamide using *t*-BuOI under the above conditions afforded oxazoline **2a** in 37% yield. An electron-deficient amide, *para*-nitrobenzamide, was found to be reactive, giving oxazoline **2b** in 67% yield along with the regioisomer **3b** in 11% yield, which are readily separable by silica gel chromatography. Although the efficiency needs to be improved, an aliphatic amide also functioned as a component of an oxazoline.

Since *para*-nitrobenzamide was found to act as a good component for the synthesis of oxazolines, some unfunctionalized olefins were subjected to the reaction using the amides and *t*-BuOI (Table 2). α-Methylstyrene was smoothly converted to oxazoline **2d** as one regioisomer by the reaction with *para*-nitrobenzamide. When *trans*-β-methylstyrene was employed, two regioisomers were produced in 72% yield, while the reaction gave *trans*-oxazolines

Table 1 Oxazoline synthesis from styrene with amide derivatives



R	Time/h	Yield (%)	**2** : **3**	Recovery of amide (%)
p-$MeOC_6H_4$	5	37	100 : 0	63
p-$NO_2C_6H_4$	12	78	86 : 14	21
n-Bu	5	28	86 : 14	53

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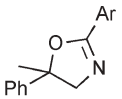
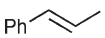
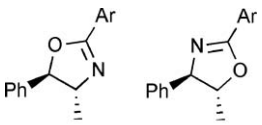
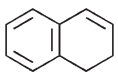
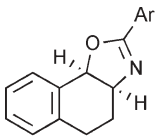
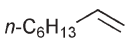
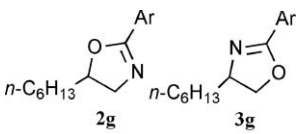
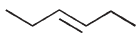
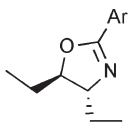
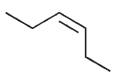
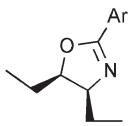
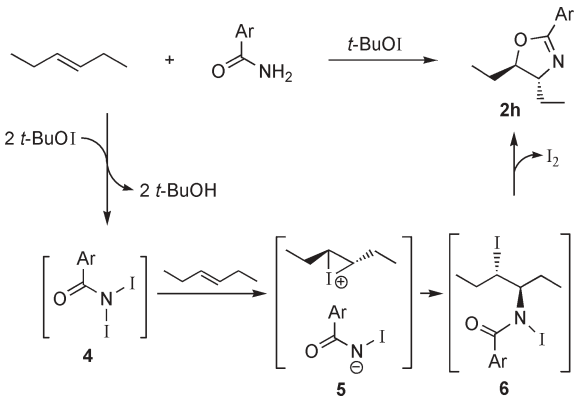
† Electronic supplementary information (ESI) available: Procedure of synthesis and experimental data of oxazolines. See DOI: 10.1039/b706572h

Table 2 Synthesis of oxazolines from olefins with *para*-nitrobenzamide[a]

Olefin	Time/h	Yield (%)	Product [ratio]
	5	79	 **2d**
	12	72	 **2e** **3e** **[90 : 10]**
	12	55	 **2f**
	24	50	 **2g** **3g** **[70 : 30]**
	96	71	 **2h**
	96	68	 **2i**

[a] Reaction conditions: olefin (1 mmol), *para*-nitrobenzamide ($ArCONH_2$, 0.5 mmol), *t*-BuOCl (1.5 mmol), NaI (1.5 mmol), MeCN (3 mL), rt.

exclusively with retention of the stereochemistry of the starting olefin. The reaction of 1,2-dihydronaphthalene with *para*-nitrobenzamide proceeded to afford the corresponding oxazoline **2f** as the sole product. Mono and disubstituted aliphatic olefins were also applicable to the reaction and, in the reactions of *trans*- and *cis*-3-hexene, complete stereoselectivity was observed, indicating that a cyclic iodonium intermediate might be involved in the reaction path. From another synthetic viewpoint, the present method can be regarded as an aminohydroxylation of olefins, because oxazolines are easily converted to the corresponding β-aminoalcohols.[5b,12]



Scheme 1 A plausible reaction pathway.

Our proposed pathway for the synthesis of oxazolines is shown in Scheme 1, using 3-hexene as the specific case. Two equivalents of *t*-BuOI, generated *in situ*, initially react with the amide, not the olefin, to give diiodinated amide **4**. This occurs because a Lewis acid or UV light is known[9b] to be required for olefins to react with *t*-BuOI. When benzamide in CD_3CN was treated with *t*-BuOCl and NaI, the ^1H NMR spectrum showed a signal corresponding to the active hydrogens on the amide nitrogen that smoothly disappeared and a signal corresponding to the *tert*-butyl group of *t*-BuOH that appeared within one hour.[13] From the NMR study, the generation of **4**[14] might be suggested but there is no clear evidence at present. The active species **4** might function as an iodonium source, which reacts with 3-hexene to generate the cyclic iodonium intermediate **5**, followed by the addition of the counter amide anion, yielding adduct **6**.

In fact, after the reaction of *para*-nitrobenzamide with *t*-BuOI, the addition of *trans*-3-hexene led to the production of oxazoline **2h** in almost the same yield (70% by ^1H NMR) as the reaction shown in Table 2. More recently, Corey's group reported an elegant haloamidation of olefins using *N*-bromoacetamide and a Lewis acid catalyst.[15] Although the nitrogen source in the reaction is the solvent, CH_3CN, iodoamides formed by the addition of CH_3CN to the iodonium intermediate **5** were not observed in our case.

In summary, a simple synthetic method is described for the direct formation of oxazolines from unfunctionalized olefins and readily accessible amides. In addition, the utility of *t*-BuOI, besides aziridination,[8] could be demonstrated for the unprecedented ring construction of oxazolines. Although the efficiency needs to be improved to be a more practical transformation, and toleration toward functional groups should be addressed, this is the first example of the synthesis of valuable oxazolines. Further applications of *t*-BuOI in other transformations are currently under investigation.

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