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Iodoarene-Catalyzed Cyclizations of Unsaturated Amides

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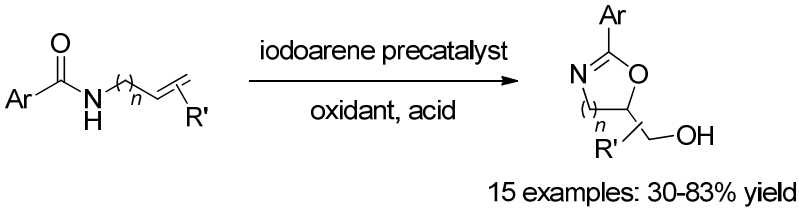
Supporting Information Placeholder



ABSTRACT: The cyclization of *N*-alkenylamides catalyzed by iodoarenes under oxidative conditions is presented. Five-, six- and seven-membered rings with a range of substitutions can be prepared by this route. Preliminary data from the use of chiral iodoarenes as precatalysts show that enantiocontrol is feasible.

Research in hypervalent iodine chemistry has gained considerable momentum in recent years.[1] In particular, the emergence of catalytic and enantioselective processes with iodine(III) species is starting to make these competitive with metal-catalysis.[2] Recent examples include the catalytic enantioselective spirolactonization of phenols,[3] dioxygenation of styrenes,[4] and intramolecular C-H/C-H cross-coupling.[5] This ability to effect "metal-like" synthetic transformations without the toxicity, supply or cost issues of transition metal salts is attractive.

We have previously developed catalytic methods using *in-situ* generated hypervalent iodine species and have reported the oxidative cyclization of δ-alkynyl β-ketoesters[6] and the enantioselective oxidative cyclization of δ-ketoacids.[7] We wished to extend this catalytic concept to the formation of useful heterocycles such as oxazolines and dihydrooxazines. Oxazolines are common structural motifs found in natural products with notable biological activities, e.g. the leupyrrins, active against fungi and eukaryotic cells,[8] and the bistratamides, which possess anticancer properties (Figure 1).[9] Dihydrooxazines are useful synthetic intermediates in organic synthesis[10] and derivatives possessing fungicidal activity have also been reported.[11]

In this Communication, we disclose our results on the catalytic cyclization of unsaturated amides to give oxazolines, dihydrooxazines and larger ring analogs. At the beginning of our study, Moon and Harned published the stoichiometric hypervalent iodine mediated cyclization of *N*-allylamides (Scheme 1).[12] Their report was limited to five membered ring formation, the use of terminal alkenes and the products described were all racemic. Herein, we reveal catalytic conditions for the cyclization and expand the scope of the process to include other ring sizes and more substituted alkenes. In addition, we have achieved enantiocontrol in this cyclization using chiral iodoarenes.

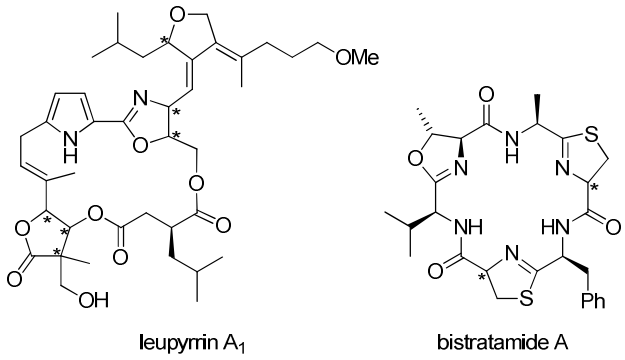
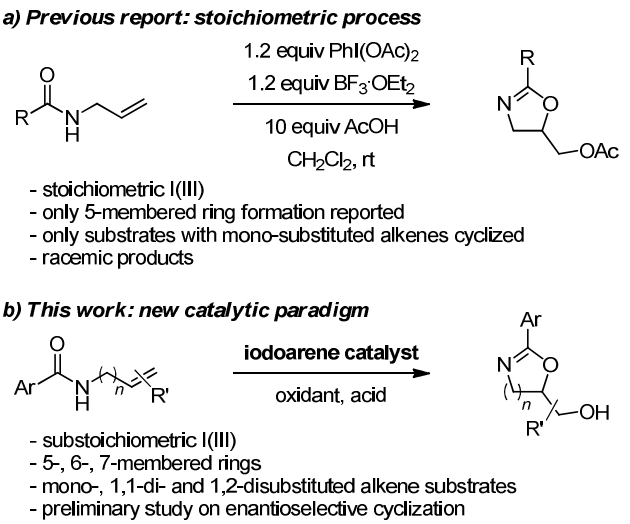


Figure 1. Examples of natural products containing oxazolines.

There are few examples in the literature of iodoarene-catalyzed reactions involving alkenes.[4,13] One issue with these processes is the potential for undesired oxidation of the olefin in preference to the iodoarene especially as common oxidants for the conversion of iodoarenes into the active iodine(III) species include peracids.

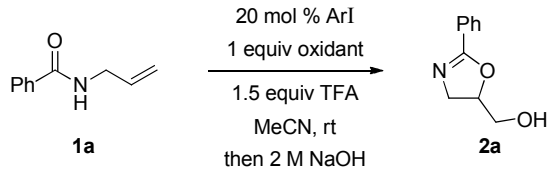
Scheme 1. Cyclization of *N*-alkenylamides by iodine(III) species.



We began our investigation with *N*-allylbenzamide **1a** and used reaction conditions similar to that used by us in previous reports, namely iodobenzene as the precatalyst with an oxidant, *m*-CPBA, an acid, TFA, and a solvent, acetonitrile, at room temperature (Table 1, entry 1). Unfortunately, these conditions led to no conversion of the starting material; not even epoxidation of the alkene occurred. However, changing the oxidant to Selectfluor led to a small amount of the desired product **2a** being formed (entry 2). Importantly, a basic workup of the reaction mixture was required in order to isolate the product. Changing the iodoarene catalyst led to surprising variations in yield: 2-iodoanisole led to a 62% yield (entry 3), whereas 3-iodoanisole, 4-iodoanisole and 5-iodo-*m*-xylene provided low yields of isoxazoline (entries 4, 5 and 6). We have demonstrated previously that the presence of a 2-methoxy substituent stabilizes aryliodine(III) species.[14] Guilbault and Legault demonstrated that the steric hindrance caused by the introduction of a methyl group ortho to the iodine atom in iodoarene precatalysts led to drastic rate enhancements in the α-tosyloxylation of ketones.[15] Using 2-iodoanisole as catalyst, the oxidant was varied, however the use of *m*-CPBA and Oxone both led to no conversion (entries 7 and 8). Finally, running the reaction without the 2-iodoanisole, but with the Selectfluor, led to complete recovery of the starting amide showing that the iodoarene is necessary for this process to proceed (entry 9).

With the optimized cyclization reaction conditions in hand, we next studied the scope of this process (Scheme 2). A variety of arylamides were successfully cyclized including electron rich and electron poor examples to provide the corresponding oxazolidinones **2a**-**2e** in good yields. Subjecting acetamide **1f** to the reaction conditions led to a mixture of products and **2f** could not be isolated in pure form. Furan oxazoline **2g** was isolated in 79% yield and **2h** was isolated as a ~1:1 mixture of diastereomers in 74% combined yield. The cyclization of amides **1i**-**1m** was investigated next and we were pleased to find that the six membered rings **2i**-**2m** formed in good yields. However, two equivalents of Selectfluor were generally required for complete conversion to occur in these cases. In addition, the seven membered ring **2n** was successfully formed in 30% yield. However, the eight membered ring **2o** was not formed. In theory, **2n** or **2o** could cyclize to the corresponding pyrrolidine or piperidine but neither of these was observed.

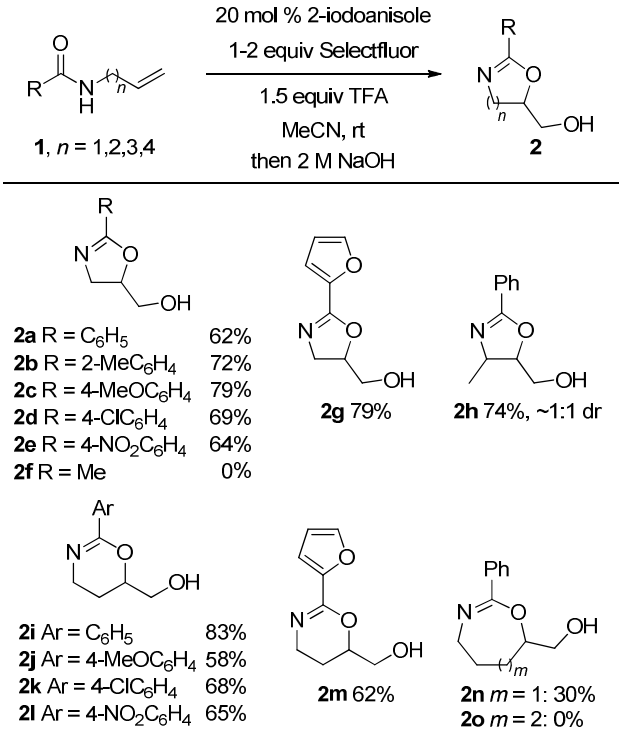
Table 1. Investigation of reaction conditions



entry	ArI	oxidant	yield (%)[a]
1	iodobenzene	*m*-CPBA	0
2	iodobenzene	Selectfluor	6
3	2-iodoanisole	Selectfluor	62
4	3-iodoanisole	Selectfluor	9
5	4-iodoanisole	Selectfluor	10
6	5-iodo-*m*-xylene	Selectfluor	13
7	2-iodoanisole	*m*-CPBA	0
8	2-iodoanisole	Oxone	0
9	-	Selectfluor	0

[a] Yields of isolated compounds. Selectfluor: 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate).

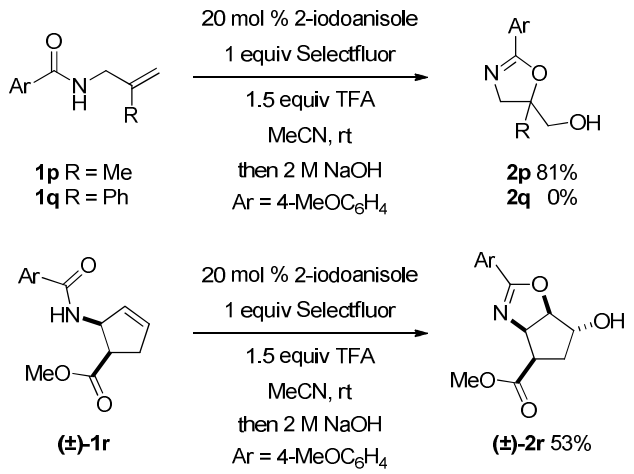
Scheme 2. Scope of cyclization of mono-substituted alkenes



With a desire to increase the scope of the cyclization further, 1,1-disubstituted alkenes **1p** and **1q** were subjected to the reaction conditions (Scheme 3). Methyl derivative **2p** was formed in 81% yield whereas the phenyl derivative **2q** was not isolated. In the latter case, complete conversion of the starting material was observed but several unidentified products were formed

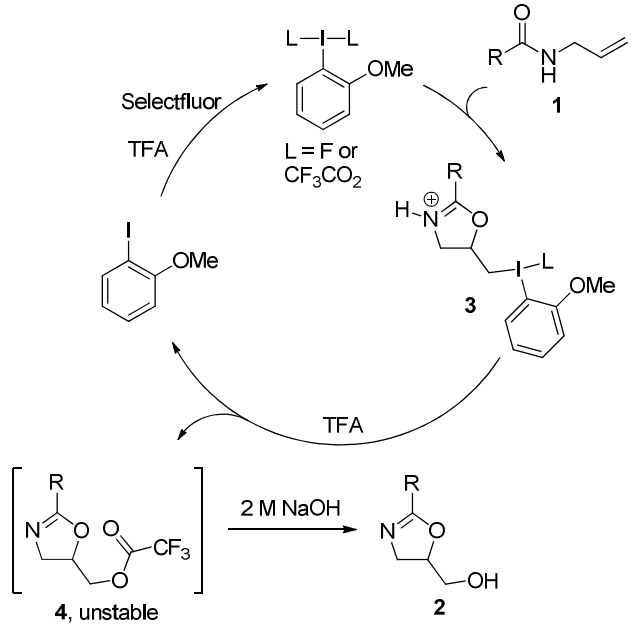
which could not be separated. *Cis*-1,2-Disubstituted alkene **1r** cyclized to the bicycle **2r** in 56% yield as one diastereomer. No sign of the other diastereomer was detectable by NMR analysis of the crude reaction mixture. Attempts to cyclize a trisubstituted alkene were unsuccessful as undesired background alkene addition processes occurred.

Scheme 3. Scope of cyclization of di-substituted alkenes



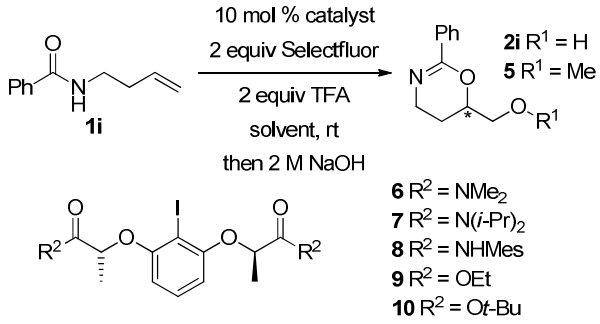
The mechanism of this cyclization is proposed to involve oxidation of the iodoarene to the iodine(III) species which activates the alkene to intramolecular attack by the amide oxygen to generate intermediate **3** (Scheme 4). Nucleophilic addition of TFA, or its conjugate base, breaks the alkyl carbon-iodine bond in **3**, which regenerates the iodoarene catalyst and releases the cyclized product **4**. This compound **4** cannot be isolated as it is unstable, but it is believed to be the trifluoroacetate. Nonetheless, treatment of this with 2 M NaOH solution provides the stable alcohol **2**.

Scheme 4. Postulated cyclization reaction mechanism



With an effective cyclization process in hand, we turned our attention to the use of chiral iodoarene precatalysts **6**-**10** in order to develop an enantioselective version of this process.[16] Using bisdimethylamide precatalyst **6** a very good yield of **2i** was obtained with moderate enantioselectivity of 82:18 er (Table 2, entry 1). Interestingly, the amount of precatalyst could be lowered to 10 mol % without a drop in yield, compared to the use of 2-iodoanisole. To determine the effect of temperature on the cyclization, the reaction was repeated at 50 °C and at -10 °C, however selectivity was lower in the former case and about the same in the latter (entries 2 and 3). Conducting the reaction with bistrifluoromethanesulfonamide instead of TFA led to lover yield and lower selectivity (entry 4). Using methanol as solvent instead of acetonitrile led to formation of methyl ether **5** in place of alcohol **2i**, but in low yield and with 63:37 er (entry 5). Using a 1:1 or 2:1 acetonitrile/methanol mixture as solvent led to separable mixtures of **2i** and **5** being formed (entries 6 and 7). The enantiomeric ratio of ether **5** was up to 81:19, equalling the highest obtained for **2i**. We then screened a few other related precatalysts **7**-**10** but did not see superior selectivity. With diisopropylamide precatalyst **7**, the conversion in MeCN was very low, however changing to a 1:2 mixture of MeCN and MeOH led to complete conversion to ether **6** with 75:25 er (entry 9). Mesityl amide **8** and ethers **9** and **10** led to moderate yields and enantioselectivites (entries 10-12). However, with the *t*-butyl ester precatalyst **10** the major enantiomers of products formed were opposite to the other precatalysts (entry 12).

Table 2. Preliminary chiral precatalyst screening

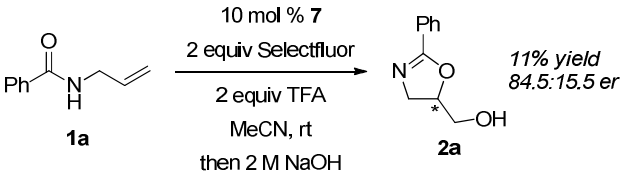


entry	cat.	solvent	2i: yield (%)[a]	er[b]	5: yield (%)[a]	er[b]
1	**6**	MeCN	86	82:18	0	-
2[c]	**6**	MeCN	75	67:33	0	-
3[d]	**6**	MeCN	10	79:21	0	-
4[e]	**6**	MeCN	11	63:37	0	-
5	**6**	MeOH	0	-	10	63:37
6	**6**	1: 1 MeCN/MeOH	37	71:29	28	76:24
7	**6**	1:2 MeCN/MeOH	51	76:24	34	81:19
8	**7**	MeCN	<5	n.d.	0	-
9	**7**	1:2 MeCN/MeOH	0	-	99	75:25
10	**8**	MeCN	53	75:25	0	-
11	**9**	MeCN	23	72:28	0	-
12	**10**	1:2 MeCN/MeOH	49	35:65	19	34:66

[a] Yields of isolated compounds. [b] Determined by chiral HPLC analysis. [c] Reaction performed at 50 °C. [d] Reaction performed at -10 °C. [e] Bistrifluoromethanesulfonamide used instead of TFA.

Cyclization of amide **1a** to generate isoxazoline **2a** was also performed using chiral precatalyst **7** and the product was generated in 84.5:15.5 er (Scheme 5).

Scheme 5. Enantioselective formation of isoxazoline 2a



In conclusion, the cyclization of unsaturated amides using catalytic quantities of iodoarenes has been developed. 2-Iodoanisole has proven to be a superior precatalyst than other iodoarenes tested in this process. In addition, chiral iodoarenes have been utilized to impart enantioselectivity, and levels of control up to 81:19 er have been achieved so far. Further work on related cyclizations, and efforts to improve observed enantioselectivities, is underway and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Characterization data and copies of ^{1}H and ^{13}C NMR spectra for novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

‡These authors contributed equally.

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