First hypervalent iodine(III)-catalyzed C–N bond forming reaction: catalytic spirocyclization of amides to *N*-fused spirolactams

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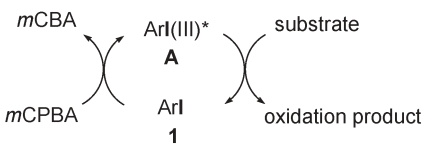
A protic solvent, 2,2,2-trifluoroethanol (CF_3CH_2OH), was successfully introduced into hypervalent iodine(III)-involved catalytic cycles as an effective solvent, and the first iodoarene-catalyzed intramolecular carbon–nitrogen bond forming reaction was achieved under strong acid-free and mild conditions.

Over the last decade, hypervalent iodine(III) reagents having a wide array of reactivities have increased in importance as a safe alternative to toxic heavy-metal oxidizers such as Pb(IV), Tl(III) and Hg(II), for performing a variety of organic transformations.[1] Conventional use of hypervalent iodine(III) reagents is usually restricted to a stoichiometric process, though it might be possible to perform the reactions in a catalytic manner under electrochemical conditions.[2] Recently, the concept of catalytic utilization of hypervalent iodine(III) reagents has been extended to other synthetically important classes of transformations such as carbon–oxygen[3–6] and even carbon–carbon bond forming reactions[3] by use of stoichiometric chemical terminal cooxidants, *m*-chloroperbenzoic acid (*m*CPBA) (Scheme 1) or *N*-bromosuccinimide (NBS).

These pioneering studies surely open up a new opportunity for hypervalent iodine chemistry and pave the way for broader application of the reagents as organocatalysts in organic synthesis in line with recent demands for ecologically conscious chemical processes.[7] However, in these cases, strong acidic conditions ($NEt_3{\cdot}nHF$,[2] CF_3CO_2H,[3] $BF_3{\cdot}Et_2O$[3,4] and *p*-TsOH[5]) are needed to achieve high turnover number (TON) and turnover frequency (TOF) of the reactions, which might be one of major faults of the present catalytic systems limiting the scope of the catalytic strategy.

Recently, in our effort toward extension of the catalytic strategy, we have found that a highly polar and poorly nucleophilic solvent, 2,2,2-trifluoroethanol (TFE),[8,9] acts like the acids, and remarkably enhanced the rate of 4-iodotoluene (**1**)-catalyzed spirocyclization reaction.[3] Thus, we consider that use of TFE might lead to extension of the catalytic concept to other bond forming reactions. Herein, we would like to report the first iodoarene-catalyzed carbon–nitrogen bond forming reaction to give *N*-fused spirolactams applying a TFE medium (Scheme 2).



Scheme 1 A catalytic cycle involving transformation of iodoarene **1** to hypervalent iodine(III) intermediates in the presence of *m*CPBA.

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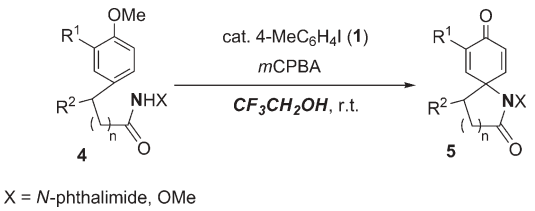


Scheme 2 The first iodoarene-catalyzed C–N bond forming reaction.

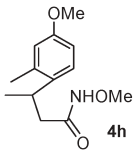
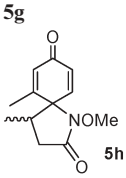
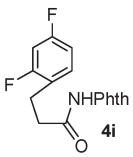
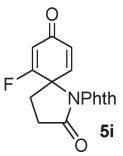
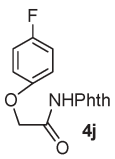
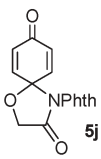
Having been inspired by the recent broad applications of stoichiometric reactions involving nitrenium ion in the synthesis of natural products and biologically active compounds,[9c,10] we selected the intramolecular cyclization reaction of 3-(4-methoxyphenyl)-*N*-(1,3-dioxoisoindolin-2-yl)propanamide **4a** as the target for C–N bond formation (Table 1). A main disadvantage of the stoichiometric reactions is the requirement of excess phenyliodine bis(trifluoroacetate) (PIFA) or its strong acid derivatives (~3 equiv.) Therefore, a catalytic alternative is of great interest.[11] Thus, we started our survey under catalytic conditions using a 10 mol% amount of **1** and 1.5 equiv. of *m*CPBA, as a terminal oxidant, in TFE, and fortunately, an efficient catalytic reaction was observed with 83% yield of five-membered ring spirodienone lactam **5a** and 8.3 times of TON (entry 1). Consequently, the influence of the loading of **1** in the catalytic reaction was then examined. The highest TON reached was 28 times at 2.5 mol% loading of the catalyst in TFE after 12 hours of stirring (entry 3). Replacement of TFE with the more polar and acidic 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) showed a decrease of TON (entry 4). In the reaction, neither an electron-donating nor -withdrawing group in the aromatic ring of the iodoarene is

Table 1 Survey of hypervalent iodine(III)-catalyzed spirolactam formation by **4a** ($R^1 = R^2 = H$, X = *N*-phthalimide)

Entry	Loading of **1** (mol%)	Additive[a]	Time (h)	Yield (%)[b]	TON (times)
1	10	none	2.5	83	8.3
2	5	none	4	80	16
3	2.5	none	12	70	28
4[c]	2.5	none	12	25	10
5[d]	2.5	none	12	38	15.2
6[e]	2.5	none	24	7	2.8
7	2.5	CF_3CO_2H	7	54	21.6
8	2.5	$BF_3{\cdot}Et_2O$	24	12	4.8

[a] In each case, 1 equiv. of additive was used. [b] Isolated yield of pure **5a**. [c] HFIP was used as a solvent. [d] 4-Iodoanisole (**2**) was used as a catalyst. [e] 2,4-Difluoroiodobenzene (**3**) was used instead of **1**.

Table 2 Scope of the substrate **4**

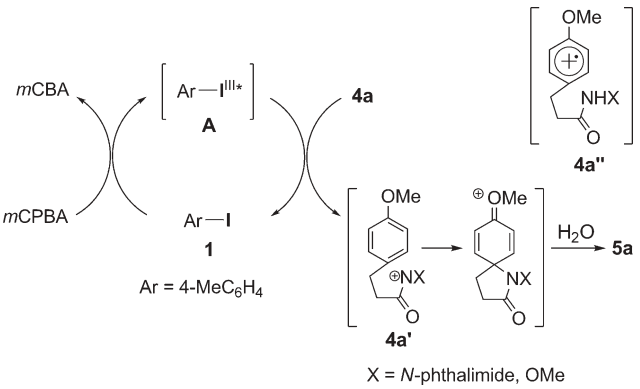
Entry[a]	Substrate (**4**) n	R^1	R^2	X	Lactam (**5**)	Time (h)	Yield (%)[b]
1	1	H	H	NPhth[c] (**4a**)	**5a**	2.5	83
2	1	Me	H	NPhth (**4b**)	**5b**	16	71
3	1	H	Me	NPhth (**4c**)	**5c**	7	75
4	1	H	H	OMe (**4d**)	**5d**	2.5	86
5	1	Ac	H	OMe (**4e**)	**5e**	7	53
6	0	H	H	OMe (**4f**)	**5f**	2	84
7	2	H	H	OMe (**4g**)	**5g**	11	64
8[d]	 **4h**				 **5h**	5	84[e]
9	 **4i**				 **5i**	2	89
10	 **4j**				 **5j**	24	79

[a] Reactions were performed in TFE at room temperature using 10 mol% of 4-iodotoluene (**1**). [b] Isolated yield. [c] NPhth = *N*-phthalimide. [d] 1 equiv. of CF_3CO_2H was added. [e] >97% de.

beneficial (entries 5 and 6), as the former destabilizes its iodine(III) states,[12] whereas the latter retards smooth generation of the iodine(III) species.[13] Reaction proceeded in the presence of trifluoroacetic acid, but the strong acid caused decomposition of the starting **4a** (entry 7), and $BF_3{\cdot}Et_2O$ harmed the catalytic reaction (entry 8). Other solvents such as dichloromethane, methanol, and acetonitrile were also employed with negative results.

To explore the generality and scope of the substrates in our catalytic procedure, we have examined several substrates.† As summarized in Table 2, propanamides **4b** and **4c** bearing both an alkyl group in the aromatic ring and the pendent side chain reacted smoothly to afford lactams **5b** and **5c** in high yields (entries 2 and 3). Easily accessible *N*-methoxy amide gave lactam **5d** in a similar manner (entry 4). In **4e**, Bayer–Villiger side products derived from the reaction at its aryl ketone moiety were not observed (entry 5). Aside from the five-membered ring lactams, four- and six-membered ring lactams **5f** and **5g** were obtained as sole isolable products (entries 6 and 7). Reaction of alkyl hydroxamate **4h** proceeded stereoselectively (>97% de) (entry 8).[10d] 4-Fluorophenyl propanamide derivatives are also usable in this catalytic reaction (entry 9).[9c] Acid-sensitive spirodienone *N*,*O*-acetal **5j** was successfully obtained from **4j** under the present strong acid-free catalytic conditions (entry 10).

A plausible reaction mechanism of the present iodoarene-catalyzed C–N bond forming reaction is as follows (Scheme 3). First, iodoarene **1** generates the active hypervalent iodine(III) species **A** under the stated reaction conditions by the action of *m*CPBA, although synthesis of hypervalent iodine(III) compounds

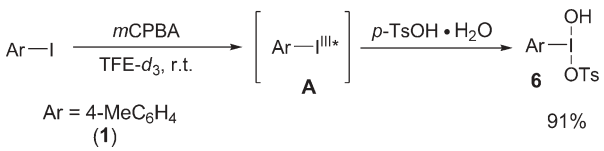


Scheme 3 A plausible reaction mechanism.

in TFE has never been reported. The iodine(III) species **A** assemble themselves to less reactive oligomers, and as a result are destined to be expelled from the catalytic cycle, if not using TFE or trifluoroacetic acid.[14,15] Next, generation of nitrenium ion **4a′** by the reaction of *in situ* **A** and **4a** completes the catalytic cycle with a concomitant liberation of iodoarene **1**. The fact that addition of phenyl ethers, *i.e.*, 4-ethylanisole, did not affect the reaction of **4a**, and successful transformation of electron-deficient aromatic compounds **4i** and **4j**, suggest the exclusive formation of nitrenium ion **4a′**, although formation of cation radical **4a″** induced by SET of the phenyl ether ring was also assumed.[8a,b] The resulting **4a′** undergoes cyclization and hydrolysis with or without the aid of TFE by water, which comes from commercial wet *m*CPBA, gives rise to the observed lactam product **5a**.

To confirm the presence of hypervalent iodine(III) species **A** during the catalytic cycle in TFE, we have conducted the following experiment (Scheme 4). In TFE-d_3, **1** (0.07 M) was dissolved with a slightly excess amount of *m*CPBA (1.5 equiv. relative to **1**) in the absence of propanamide **4**, and the mixture was then monitored by ^{1}H NMR. Indeed, the ^{1}H NMR measurement of the reaction mixture revealed that >99% of **1** was already consumed after 30 minutes[16] and a downfield shift in δ (ppm) of aromatic protons of **1** was observed; it suggests that effective conversion of **1** to hypervalent iodine species occurred under the conditions because hypervalent iodine groups possess a strong electron-withdrawing character and induce a downfield shift of the aromatic protons. Sequential addition of *p*-toluenesulfonic acid monohydrate to the resulting intermediate **A**, and stirring for an additional 2 hours, gave 4-[hydroxy(tosyloxy)iodo]toluene **6** in 91% yield as a white powder. This result clearly supports the formation of iodine(III) species during the catalytic cycle.

The existence of numerous known iodoarene compounds suggested a survey and utilization of an alternative useful catalytic precursor. Thus, we finally attempted to utilize the adamantane **7**[17a] (Fig. 1) as a recyclable catalyst. Accordingly, we tried the reaction of propanamide **4a** using 5 mol% of **7**. Although further



Scheme 4 Trapping of the catalytic species **A** in TFE by *p*-TsOH.

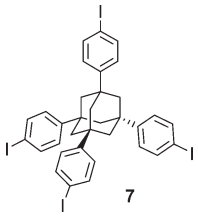


Fig. 1 Recyclable iodoarene **7** based on adamantane structure.

optimization is required, catalytic reaction was achieved in a TFE–dichloromethane system in this case and the desired lactam **5a** was obtained with a good isolated yield (5 h, 82%). After completion of the reaction, the remaining *m*CPBA was first removed by sequential treatment with saturated aq. $NaHCO_3$ and $Na_2S_2O_3{\cdot}5H_2O$. Here, catalysts **7** and lactam **5a** were present in the organic phase. As the catalyst was almost insoluble in methanol, it was simultaneously precipitated as a solid by replacement of the solvents with methanol, and was recoverable by simple filtration.[17] Lactam **5a** in the filtrate was purified by short column chromatography on silica-gel. The recovered **7** was stable under the catalytic conditions and reused repeatedly, hereby the use of the recyclable catalyst is bound to make the reaction practical.

In conclusion, we have established the catalytic spirolactam forming reaction induced by *in situ* generated hypervalent iodine(III) by the appropriate choice of the solvent, TFE. To the best of our knowledge, this is the first example of a successful iodoarene-catalyzed C–N bond forming reaction.

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Notes and references

† To a stirred solution of 4-iodotoluene **1** (10.9 mg, 0.05 mmol) and **4a** (162 mg, 0.5 mmol) in TFE (5 mL) was added *m*CPBA (185 mg, *ca.*70% purity, 0.75 mmol) at room temperature. After 2.5 hours, TFE was removed under reduced pressure. Aqueous saturated $NaHCO_3$, sodium thiosulfate, and AcOEt were sequentially added to the residue and then the mixture was stirred vigorously for 10 minutes. The organic layer was separated, and the aqueous layer was extracted with AcOEt. After evaporation, the residue was purified by column chromatography to give pure **5a**[9c] (128 mg, 83%).

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