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Iodobenzene-Catalyzed Intramolecular Oxidative Cyclization Reactions of δ-Alkynyl β-Ketoesters

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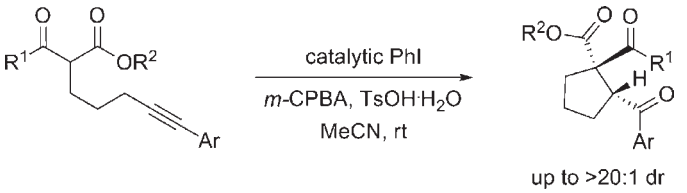
ABSTRACT



Iodobenzene is shown to catalyze the 5-*exo-dig* cyclization of δ-alkynyl β-ketoesters under oxidative conditions that generate hypervalent iodine species in situ. The cyclopentane products contain adjacent quaternary and tertiary stereocenters which are generated with excellent diastereoselectivity.

The catalytic activation of alkynes to nucleophilic addition by π-acidic metal complexes has received considerable attention from the synthetic community;[1] however there are almost no examples of such activation by organocatalysts.[2] Molecular iodine has been shown to activate alkynes to nucleophilic attack, but stoichiometric quantities of iodine are required in these cases.[3] Stoichiometric quantities of hypervalent iodine reagents are also known to activate alkynes to nucleophilic attack by heteroatoms.[4] Considering the low cost, as well as the ease of use and handling, of hypervalent iodine species compared to noble metals, the development of novel reactions utilizing these compounds is of increasing interest to synthetic chemists.[5] Notably, over the past few years, reports have appeared demonstrating the use of hypervalent iodine compounds prepared in situ from aryliodides and used as catalysts in various oxidation reactions.[6]

Considering that molecular iodine and hypervalent iodine mediated cyclization reactions bear similarities to gold catalysis, we reasoned that 5-*exo-dig* cyclizations onto alkynes, promoted by iodine(III) species, to generate carbon−carbon bonds should be feasible. To this end, we prepared alkyne **1a** and surveyed hypervalent iodine reagents as mediators for intramolecular cyclization. Upon stirring with $PhI(OAc)_2$ (PIDA) or $PhI(OCOCF_3)_2$ (PIFA) in acetonitrile at room temperature, or at reflux with PIFA, no reaction took place (Table 1, entries 1 and 2). Stirring with Koser's reagent (PhI(OH)OTs) returned ∼95% of **1a**, but some unidentifiable products (at that point) were evident in the ^{1}H NMR spectrum (entry 3). At this stage, we decided to generate the hypervalent iodine species in situ from iodobenzene with *p*-toluenesulfonic acid and *m*-chloroperbenzoic acid, and we were delighted to find that

(1) For an excellent review, see: Furstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449.

(2) Miyamoto, K.; Sei, Y.; Yamaguchi, K.; Ochiai, M. *J. Am. Chem. Soc.* **2009**, *131*, 1382–1383.

(3) For a selected example, see: Bi, H.-P.; Guo, L.-N.; Duan, X.-H.; Gou, F.-R.; Huang, S.-H.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2007**, *9*, 397–400.

(4) (a) Pardo, L. M.; Tellitu, I.; Domínguez, E. *Synthesis* **2010**, 971–978. (b) Tellitu, I.; Serna, S.; Herrero, M. T.; Moreno, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2007**, *72*, 1526–1529.

(5) For reviews on hypervalent iodine chemistry, see: (a) Zhdankin, V. V. *J. Org. Chem.* **2011**, *76*, 1185–1197. (b) Zhdankin, V. V. *Arkivoc* **2009**, 1–62. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299–5358. (d) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656–3665. (e) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354–362. (f) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523–2584. (g) Koser, G. F. *Aldrichimica Acta* **2001**, *34*, 89–102. (h) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123–1178.

(6) (a) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086–2099. (b) Dohi, T.; Kita, Y. *Chem. Commun.* **2009**, 2073–2085. (c) Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem.* **2008**, 4229–4239. (d) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402–4404.

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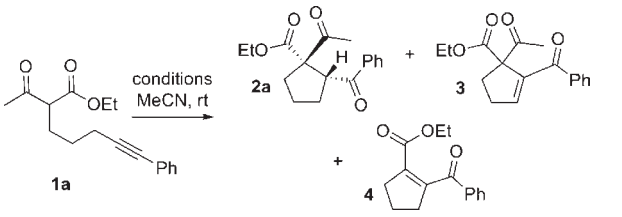
Table 1. Cyclization Optimization Studies



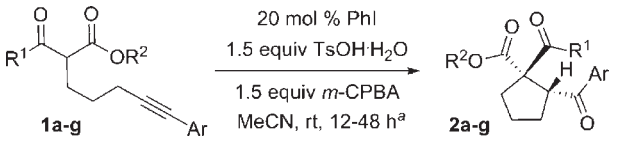
entry	conditions	conversion (%)	% **2a**:**3**:**4**[a]
1	1.5 equiv $PhI(OAc)_2$	0	
2[b]	1.5 equiv $PhI(OCOCF_3)_2$	0	
3	1 equiv PhI(OH)OTs	<5	
4	10 mol % PhI, 3 equiv TsOH H_2O, 3 equiv *m*-CPBA, 24 h	100	17:17:67
5	50 mol % PhI, 1.5 equiv TsOH H_2O, 1.5 equiv *m*-CPBA, 24 h	89	85:0:15
6	20 mol % PhI, 1.1 equiv TsOH H_2O, 1.1 equiv *m*-CPBA, 24 h	45	86:0:14
7	20 mol % PhI, 1.2 equiv TsOH H_2O, 2 equiv *m*-CPBA, 24 h	84	73:7:20
8	20 mol % PhI, 1 equiv TsOH H_2O, 3 equiv *m*-CPBA, 24 h	100	32:21:48
9	20 mol % PhI, 20 equiv H_2O, 2 equiv *m*-CPBA, 24 h	<5	
10	1.5 equiv TsOH H_20, 1.5 equiv *m*-CPBA, 24 h	0	

[a] Determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Reaction run at room temperature and at reflux.

cyclization occurred using these conditions. Three products were isolated and were identified as cyclopentane **2a** and cyclopentenes **3** and **4**. *Notably, this is only the second example of the organocatalytic activation of alkynes to nucleophilic attack* that the authors are aware of.[2,7] The ratio of these three products was found to be dependent on the relative quantities of the catalyst, the oxidant, and the acid used. With 3 equiv of acid and oxidant with 10 mol % catalyst, cyclopentene **4** was the major product (entry 4). By increasing the amount of catalyst and reducing the number of equivalents of acid and oxidant, the major product became cyclopentane **2a** (entry 5). By reducing the relative amounts of catalyst, oxidant, and acid further, the preference for formation of cyclopentane **2a** was still favored but conversion was low (entry 6). Conversion could be increased by adding more oxidant; however cyclopentene **3** started to be formed at the expense of cyclopentane **2a** (entries 7 and 8). Running the reaction without the acid or iodobenzene resulted in no reaction (entries 9 and 10).

Cyclopentane **2a** was formed diastereoselectively, with a 14:1 dr, and in good yield. The identity of the major diastereomer was determined by a NOESY NMR experiment.[8] With these results in hand, we synthesized derivatives of compound **1a** and subjected them to the oxidative cyclization reaction conditions (Table 2). The methyl and isopropyl ester derivatives of ethyl ester **1a** were cyclized, and the former resulted in a slightly diminished yield whereas the latter only provided 37% yield (entries 1 and 3 vs 2). More importantly, the presence of the isopropyl ester reduced the diastereomeric ratio from 14:1 to 5:1. The increased steric bulk of the isopropyl ester is presumed to make the cyclization event more difficult and reduce the facial selectivity. The success of the cyclization reaction was also found to be dependent on the alkyne substituent, with alkyl substituted benzene derivatives cyclizing in low yield but with superior diastereoselectivity (>20:1 dr) (entries 4 and 5). However, the *p*-chlorobenzene substrate cyclized in a superior 88% yield with 14:1 dr (entry 6). A substrate with an ethyl ketone substituent cyclized in a diminished yield and diastereoselectivity (entry 7). Substrates bearing *p*-nitrophenyl or *p*-methoxyphenyl substituted alkynes cyclized in only trace amounts. The reason for this is unknown.

Table 2. Iodobenzene Catalyzed Cyclization Reactions



entry	R^1	R^2	Ar	product	yield (%)[b]	dr[c]
1	Me	Me	Ph	**2b**	54	14:1
2	Me	Et	Ph	**2a**	61	14:1
3	Me	*i*-Pr	Ph	**2c**	37	5:1
4	Me	Me	*p*-*t*-BuC_6H_4	**2d**	25	>20:1
5	Me	Me	*p*-*n*-BuC_6H_4	**2e**	20	>20:1
6	Me	Me	*p*-ClC_6H_4	**2f**	88	14:1
7	Et	Et	Ph	**2g**	21	10:1

[a] Reaction completion indicated by solid precipitation. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of crude reaction mixture.

Two plausible mechanisms are proposed for this cyclization (Figure 1). Both involve oxidation of the iodobenzene to a phenyliodine(III) species, which then either coordinates to the alkyne of the substrate (pathway A) or forms a ketoester α-I(III) species (pathway B). The former can then undergo intramolecular cyclization to form a cyclopentane ring and vinyliodine(III) moiety **5**. The latter can undergo alkyne insertion to generate **5**. This species loses iodobenzene, thus regenerating the catalyst, and producing a vinylic carbocation. This is trapped by water, and the resulting enol tautomerizes to the observed tricarbonyl compound.

The α-tosyloxylation of β-ketoesters is a facile process with Koser's reagent and with the reaction conditions utilized for the present cyclization.[9] However, the α-tosyloxylation of the cyclization substrates in this paper does

(7) For an example of an iodobenzene catalyzed oxidation of iodide to iodate(I) and subsequent iodate(I) mediated iodolactonisation of alkynes, see: Liu, H.; Tan, C.-H. *Tetrahedron Lett.* **2007**, *48*, 8220–8222.

(8) See the Supporting Information for a copy of the NOESY spectrum.

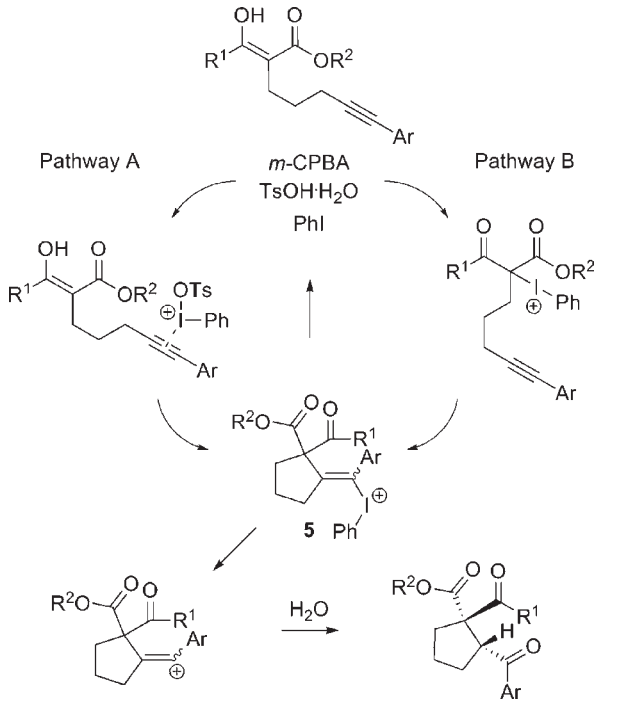


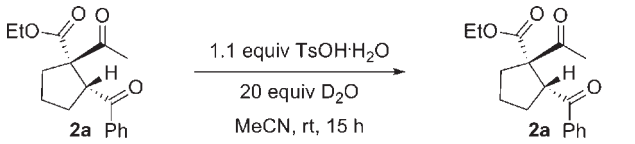
Figure 1. Proposed catalytic cycle for cyclopentane formation.

not occur under either of these conditions. If reaction pathway B were operative the formation of α-tosyloxylation side products would be expected. Their absence suggests that reaction pathway A is more likely.

Notably, these cyclopentane products contain adjacent quaternary and tertiary stereocenters and one diastereomer is formed preferentially. This selectivity could be due to initial formation of a mixture of diastereomers which equilibrate to the thermodynamically more stable one under the acidic reaction conditions, or the observed diastereomer is formed selectively. We reasoned that if equilibration is occurring then stirring the compound in D_2O under acidic conditions similar to those in the cyclization reaction should lead to deuterium incorporation. In the event, no deuterium incorporation was evident after 15 h and **2a** was returned quantitatively (Scheme 1). It is postulated that the hindered system pushes the phenyl ketone out of the plane such that the proton is perpendicular to the carbonyl π^* orbital and enolization cannot occur. Thus, suggesting that the enol is protonated diastereoselectively and the kinetic product is formed.

Product **3** was initially envisaged to be generated by an iodine(III) mediated/catalyzed oxidation of **2a**. Whereas compound **4** was thought to arise from a *m*-CPBA mediated Baeyer–Villager oxidation of **2a** followed by elimination of acetic acid. However, attempts to convert **2a** into **3**

Scheme 1. Deuterium Incorporation via Tautomerization?



and/or **4** directly have been unsuccessful suggesting that some intermediate structure follows three separate reaction pathways to generate **2a**, **3**, or **4**. Accordingly, intermediate **5** could potentially undergo Baeyer–Villager oxidation followed by the loss of iodobenzene and then acetic acid to generate alkene **4** (Figure 2). Alternatively, intermediate **5** could be converted into cyclopentene **3** by a similar mechanism to that reported for the IBX-mediated oxidation of carbonyl compounds to α,β-unsaturated carbonyl systems by Nicolaou.[10] Namely, the addition of excess oxidant oxidizes the I(III) to an I(V) species which undergoes a single electron transfer from the alkene to the iodine center. Deprotonation and elimination of an I(III) species generates cyclopentene **3**.

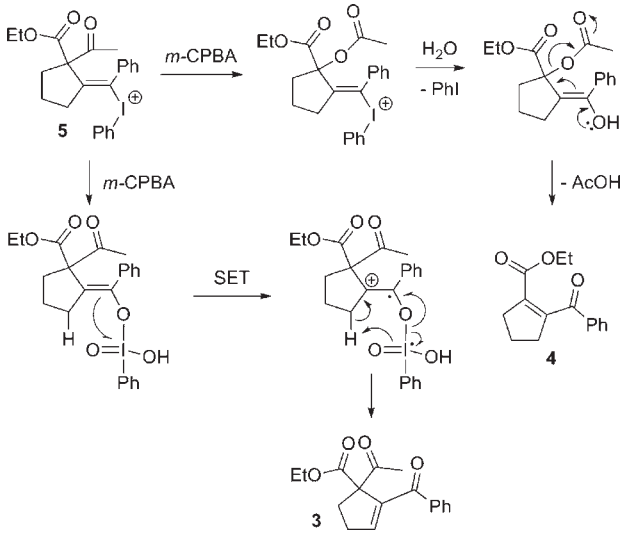


Figure 2. Plausible mechanisms for the formation of alkenes **3** and **4**.

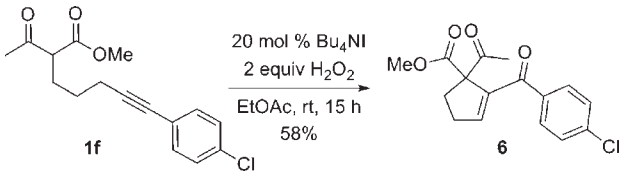
We have also found that if alkyne **1f** is treated with 20 mol % tetrabutylammonium iodide and 2 equiv of aqueous hydrogen peroxide solution in ethyl acetate at room temperature, cyclization to the previously minor product becomes dominant (Scheme 2).[11] However, this reaction must proceed through a different mechanistic pathway

(9) (a) Altermann, S. M.; Richardson, R. D.; Page, T. K.; Schmidt, R. K.; Holland, E.; Mohammed, U.; Paradine, S. M.; French, A. N.; Richter, C.; Bahar, A. M.; Witulski, B.; Wirth, T. *Eur. J. Org. Chem.* **2008**, 5315–5328. (b) Wirth, T.; Hirt, U. H. *Tetrahedron: Asymmetry* **1997**, *8*, 23–26. (c) Moriarty, R. M.; Vaid, R. K.; Koser, G. F. *Synlett* **1990**, 365–383.

(10) (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596–7597.

(11) For a recent example of ammonium (hypo)iodite catalysis, see: Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science* **2010**, *328*, 1376–1379.

Scheme 2. Tetrabutylammonium Iodide Catalyzed Cyclization



to the iodobenzene catalyzed transformation. Preliminary studies have shown that KOI can also mediate this cyclization.[12]

(12) KOI can be generated in situ by mixing KOH with iodine in methanol: Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329–4332.

In conclusion, the diastereoselective intramolecular cyclization of δ-alkynyl β-ketoesters has been catalyzed by iodobenzene under oxidative conditions. This transformation demonstrates the rare concept of alkyne activation by an organocatalyst, which has previously been the sole domain of π-acidic metal complexes. Ongoing work is directed toward gaining a greater understanding of the mechanism of this reaction and expanding the scope of this methodology.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. Copies of ^{1}H, ^{13}C, and NOESY spectra. This material is available free of charge via the Internet at http://pubs.acs.org.