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PhI(OCOCF$_3$)$_2$-Mediated Construction of a 2-Spiropseudoindoxyl Skeleton via Cascade Annulation of 2-Sulfonamido-*N*-phenylpropiolamide Derivatives

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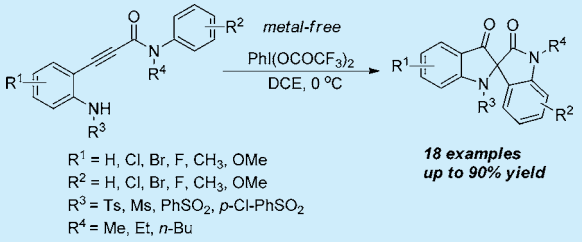
Supporting Information

ABSTRACT: A cascade annulation of 2-sulfonamido-*N*-phenylpropiolamide derivatives leading to the construction of the 2-spiropseudoindoxyl skeleton was realized under mild conditions with phenyliodine(III) bis(trifluoroacetate) (PIFA) as the sole oxidant. This metal-free spirocyclization process is suggested to encompass a sequential C(sp^2)−C(sp) and C(sp^2)−N bond formation with the concomitant introduction of a carbonyl oxygen.



Over the past decades, cascade reactions,[1] during which several bonds are formed in one single process, have received much attention. In contrast to classical multistep sequences, in most cascade reactions, it is not possible to isolate intermediates or change the reaction conditions. For this reason, this type of reactionis highly efficient. Furthermore, such reactions are often highly regio- or/and stereoselective. After much research effort, cascade annulation has become a useful synthetic strategy for constructing spiro polycyclic rings.[2] However, most ring-constructing reactions so far established involve transition-metal reagents such as organopalladium.[3] There is still a demand for methodology research in formulating novel cascade annulation reactions that are adapted for metal-free conditions.[4]

The spiropseudoindoxyl skeleton, one of the key heterocyclic structures, is abundant in many indole alkaloids.[5] It has been found that many potent antiviral agents that exhibit promising anticancer properties[6] or potent opioid agonistic activities in guinea pig ileum and in mouse vas deferens[7] are alkaloids bearing a spiropseudoindoxyl core. The biological significance and the complexity of the structure of the core have aroused great interest among both synthetic and medicinal chemists for developing feasible and efficient synthetic routes for the assembly of this class of compounds.

A literature survey showed that a handful of synthetic methods have been reported for the construction of 2-spiropseudoindoxyls thus far.[8−11] The majority of the existing methods rely on the oxidative rearrangement of the corresponding indole derivatives.[8] Examples include (i) coupling of *N*-(*p*-toluenesulfonyl)-2-aminobenzaldehyde derivatives with N-substituted maleimides using (RhCp*Cl$_2$)$_2$ as a catalyst through oxidative functionalization of the formyl C−H bond;[9] (ii) tandem oxidation of a carbon−hydrogen bond in the acyclic precursor substrates in the presence of a combination of iodobenzene diacetate (PIDA) and tetrabutylammonium iodide;[10] (iii) spiro products converted from diarylacetylene through hypervalent iodine-mediated cascade annulations upon treatment with a combination of PIDA and BF$_3$·Et$_2$;[11] and (iv) selective annulation at the C2 position in a 3-phenoxyalkynylindole substrate bearing an electron-withdrawing group.[12] Other reported methods include using phenylpropiolamides and diarylacetylenes as the starting substrates. As illustrated in Scheme 1, regioselective Au(III)-catalyzed cycloisomerization of *o*-nitrophenylpropiolamides, followed by an intramolecular dipolar cycloaddition, could result in the formation of new tetracyclic pseudoindoxyls, which were further hydrogenated to form the 2-spiropseudoindoxyls (Scheme 1, a).[13] The treatment of propargylamine derivatives with the gold complex gave the requisite isoxazolidine derivatives via a cycloisomerization−cycloaddition cascade reaction (Scheme 1, b).[14] In our previous work,[15] we discovered a hypervalent iodine-mediated cascade annulation reaction in realizing the construction of a series of 2-spiropseudoindoxyl compounds via two successive oxidative C−N bond formations (Scheme 1, c). Although these methods succeeded in affording the corresponding 2-spiropseudoindoxyl compounds, development of new methods for the synthesis of additional spiropseudoindoxyl derivatives that may contain novel functionality and/or substituent(s) is still in demand.

During the past decade, hypervalent iodine reagents,[16] a class of efficient and easy-to-handle, nonmetallic oxidants with low toxicity, have been extensively employed in organic synthesis.

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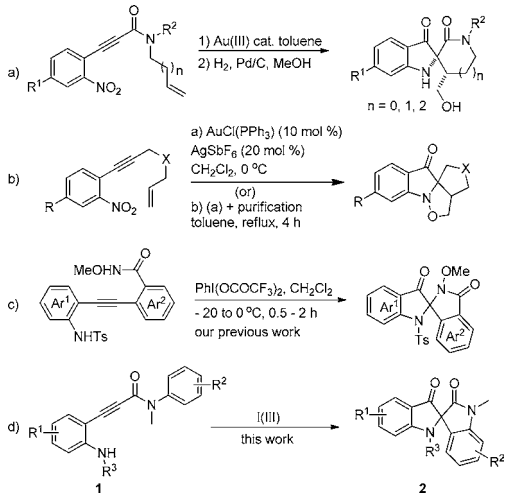
Scheme 1. Synthetic Strategies for the Construction of the 2-Spiropseudoindoxyl Skeleton

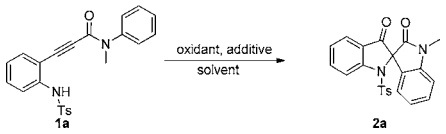


Although hypervalent iodine reagents have been widely utilized in the synthesis of various heterocyclic compounds,[17,18] application of hypervalent iodine reagents in the formation of spiroheterocycles through cascade annulation reactions is less well established. Inspired by the results from our previous work (Scheme 1, c), we set out to investigate the possibility of forming a novel class of 2-spiropseudoindoxyls **2** through an oxidative cascade annulation reaction of the corresponding 2-amino-benzyne derivatives **1** (Scheme 1, d).

We began our investigation by choosing compound **1a**, a relatively easily prepared product from commercially available propargylic acid and *N*-methylaniline in a straightforward three-step process,[19] as the model substrate. However, when **1a** was treated with PIDA (1.2 equiv) in DCM, DMF, or THF, the reaction delivered no desired product; the higher reaction temperature did not alter the negative result at all (Table 1, entries 1−3). To our delight, when 0.1 equiv of $BF_3{\cdot}Et_2O$ was introduced, the reaction of **1a** with 2.2 equiv of PIDA in DCE afforded the desired compound **2a** in 41% yield (Table 1,entry 4).[20,21] When PIDA was replaced with the more potent oxidant PIFA, the reaction gave a slightly improved yield (60%, Table 1, entry 5). Switching to other solvents such as THF, DMF, CH_3CN, and Ac_2O gave no better yield (Table 1, entries 6−9). However, addition of 0.1 equiv of $BF_3{\cdot}Et_2O$ was found to very slightly raise the yield to 50% (Table 1, entry 10). Further studies involving many trials of various combinations of the reaction condition parameters led us to discover that the highest yield was achieved when the temperature was lowered to 0 °C in DCE with PIFA as oxidant (Table 1, entry 11). Addition of $BF_3{\cdot}Et_2O$ (0.1 equiv) only lowered the yield (Table 1, entries 12 and 14). Reactions at even lower temperatures not only prolonged the reaction time but at the same time lowered the yield (Table 1, entry 13). Another commonly applied hypervalent iodine(III) reagent, i.e., PhIO, was tested but failed to afford the desired product (Table 1, entry 15).

The second part of our investigation was on the scope and substituent tolerance of the newly developed method. A series of 2-sulfonamido-*N*-phenylpropiolamide derivatives were successfully prepared under the optimized conditions (see the Supporting Information for details). Results listed in Scheme 2 showed that the desired products were all obtained in moderate to good yields. Taking the substituents on the nitrogen atom

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	solvent	temp (°C)	time (h)	yield[b] (%)
1	PIDA	DCM	rt to 80	24	NR[c]
2	PIDA	DMF	rt to 120	24	NR[c]
3	PIDA	THF	rt to 65	24	NR[c]
4[e]	PIDA	DCE	rt	4	41
5	PIFA	DCE	rt	2	60
6	PIFA	THF	rt to 65	24	NR[c]
7	PIFA	DMF	rt to120	24	NR[c]
8	PIFA	MeCN	rt	7	53
9	PIFA	Ac_2O	rt	3	48
10[e]	PIFA	DCE	rt	2	50
11	**PIFA**	**DCE**	**0**	**5**	**76**
12[e]	PIFA	DCE	0	5	65
13	PIFA	DCE	−20	20	39
14[e]	PIFA	DCE	−20	20	34
15	PhIO	DCE	rt	24	NR

[a]Reaction conditions: all reactions were carried out with **1a** (0.5 mmol) and oxidant (1.1 mmol) in dried solvent (25 mL) unless otherwise stated. [b]Isolated yield. [c]NR = no reaction. [e]$BF_3{\cdot}Et_2O$ (0.1 equiv) was added.

(R^3) for example, we found that not only the tosyl group (Scheme 2, **2a**) but also methanesulfonyl (Scheme 2, **2b**), phenylsulfonyl (Scheme 2, **2c**), and *p*-chlorophenylsulfonyl substituents (Scheme 2, **2d**) could be well tolerated. Moreover, the method could also be extended to substrates with the two aryl moieties each bearing an electron-donating (methyl and methoxy) or electron-withdrawing (halogens) substituent (Scheme 2, **2e−p**). It should be mentioned that the *ortho*-substituted substrates, regardless the electronic nature of the substituent, also proceeded to give the desired product (Scheme 2, **2j**). Finally, the scope of the R^4 substituent was also investigated.[22] The results showed that for substrate with R^4 being either ethyl or *n*-butyl the reaction resulted in the formation of product **2q** or **2r** in moderate yields, respectively. However, the reaction of the substrate with R^4 as a benzyl group led to a complex mixture with no desired spirocyclized product being detected. it should also be noted that the substrate containing R^1 as *p*-methoxy gave a complex mixture and therefore failed to afford the desired product under the optimized conditions (not shown).

Compound **2o** was successfully characterized via X-ray crystallography (Figure 1).

Control experiments were carried out to further elucidate the reaction mechanism (Scheme 3). According to Searcey's work,[23] there is a possibility that substrate **1a** might undergo catalytic indolization in the presence of TFA to form the indole intermediate **A**. In order to verify this, we conducted the experiments of substrate **1a** with TFA (0.1−1.5 mol) in the absence of PIDA. The results showed that no reaction occurred under the conditions, which might indicate that no indole intermediate **A** was formed during the PIFA-mediated spirocyclization process. Since both the aniline and tosylamide moieties might interact with the electrophilic hypervalent iodine reagent, we carried out control experiments involving treatment of diarylacetylene **B** and phenylpropiolamide derivatives **E** separately with the oxidant. First the reaction of diarylacetylene **B**

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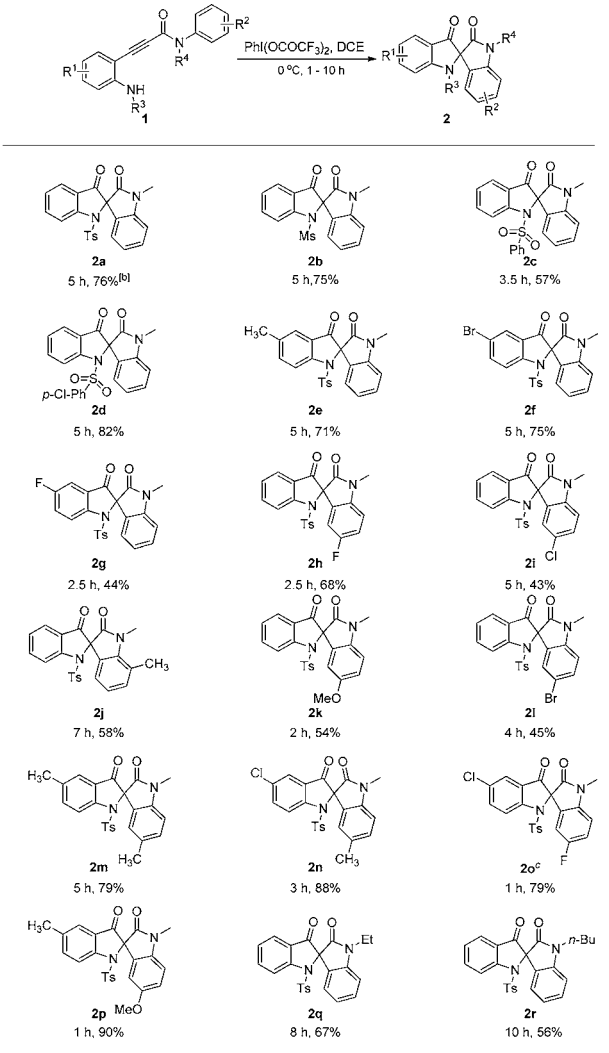
Scheme 2. PIFA-Mediated Synthesis of 2-Spiropseudoindoxyl Derivatives from 2-Sulfonamido-*N*-phenylpropiolamides[a]



[a]All reactions were carried out at 0 °C with **1** (0.5 mmol) and PIFA (1.1 mmol) in DCE (25 mL) under stirring. [b]Isolated yields were given. [c]The structure of **2o** was confirmed by X-ray crystallography.

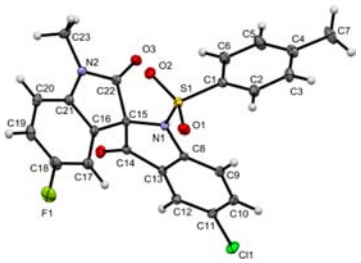
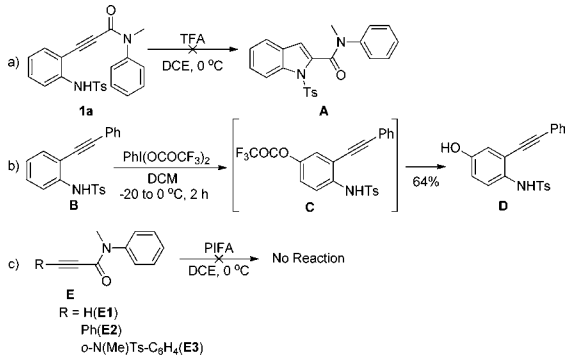


Figure 1. X-ray crystal structure of **2o**.

with PIFA under the described conditions led to the isolation of functionalized product **D** in 64% yield.[15] This result indicates two points: (a) the tosylamide moiety was reactive and (b) no cyclized product was formed without the phenylpropiolamide moiety. The various compounds **E** were further synthesized and subjected to the standard conditions. Unfortunately, no desired products were obtained under the standard conditions, which might be because (c) phenylpropiolamide is stable enough to be

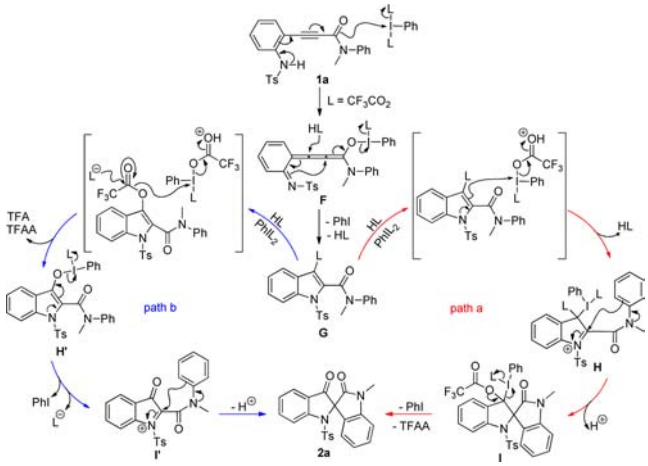
Scheme 3. Control Experiments



unreactive under the conditions and (d) the N-unprotected tosylamide moiety is necessary for the transformation.[24] Based on the above results, we tentatively conclude that both the tosylamide and the phenylpropiolamide moieties are necessary in substrates **1** for the reaction to occur.

According to these control experimental results as well as our previous studies,[25,11] we propose two plausible mechanistic pathways for this newly discovered PIFA-mediated tandem oxidation reaction (Scheme 4). First, substrate **1a** reacts with

Scheme 4. Proposed Mechanistic Pathways



PIFA to give the O−I intermediate **F**.[11] Then nucleophilic attack of the released trifluoroacetate anion onto the allene carbon center in **F** initiates an indolization process, affording intermediate **G** accompanied by the loss of one molecule of iodobenzene and trifluoroacetic acid. Then intermediate **G** undergoes two separate pathways to give the desired product **2a**. In path a, oxidation of **G** at the C3 position of the indole moiety by PIFA affords the key C−I intermediate **H** with the loss of one molecule of trifluoroacetic acid. Next, intermediate **H** goes through an intramolecular annulation with the subsequent deprotonation to give intermediate **I**, which is converted to the final product **2a** via reductive elimination and the subsequent detrifluoracetylation process. In path b, intermediate **G** reacts with PIFA, assisted by the released trifluoroacetate anion, to give the O−I intermediate **I′** by losing one molecule of trifluoroacetic acid and trifluoroacetic anhydride. Intermediate **I′** is eventually converted the title product **2a** after a series of redox O−I bond cleavage, spirocyclization, and aromatization processes.

In summary, we have developed a metal-free approach for construction of a series of diversely functionalized 2-

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spiropseudoindoxyl compounds from 2-sulfonamido-*N*-phenylpropiolamide derivatives by using hypervalent iodine reagent as the sole oxidant. The spirocyclization process involves an iodine(III)-mediated cascade C(sp^2)−C(sp) and C(sp^2)−N formation with the introduction of a carbonyl group from the hypervalent iodine reagent. Further studies are still in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00058.

Experimental procedures, characterization data for all new compounds, NMR spectra, and X-ray data for **2o** (PDF)
X-ray data for **2o** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Selected reviews for "cascade" reactions: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (c) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (d) Parsons, P. J.; Penkett, C. S.; Shell, A. *Chem. Rev.* **1996**, *96*, 195. (e) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (f) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (g) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (h) Eilbracht, P.; Barfacker, L.; Buss, C.; Hollmann, C.; Kitsos-Rzychon, B. E.; Kranemann, C. L.; Rische, T.; Roggenbuck, R.; Schmidt, A. *Chem. Rev.* **1999**, *99*, 3329. (i) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (j) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442. (k) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47. (l) Tietze, L. F.; Bachmann, J.; Wichmann, J.; Burkhardt, O. *Synthesis* **1994**, *1994*, 1185. (m) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304. (n) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390.

(2) (a) Mothe, S. R.; Novianti, M. L.; Ayers, B. J.; Chan, P. W. H. *Org. Lett.* **2014**, *16*, 4110. (b) Bencivenni, G.; Wu, L. Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M. P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200.

(3) Reviews on Pd-catalyzed cascade reactions: (a) Negishi, E.; Copéret, C.; Ma, S.; Liou, S. Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (b) Heumann, A.; Reglier, M. *Tetrahedron* **1996**, *52*, 9289. (c) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65. (d) Zou, T.; Zhang, X.-G.; Li, J.-H.; Deng, C.-L.; Tang, R.-Y. *Adv. Synth. Catal.* **2012**, *354*, 889.

(4) For selected examples of iodine(III)-mediated cascade reactions, see: (a) Manna, S.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 7324; *Angew. Chem.* **2014**, *126*, 7452. (b) Tang, S.; Peng, P.; Pi, S. F.; Liang, Y.; Wang, N. X.; Li, J. H. *Org. Lett.* **2008**, *10*, 1179. (c) Kim, H. J.; Cho, S. H.; Chang, S. *Org. Lett.* **2012**, *14*, 1424. (d) Wang, J.; Yuan, Y.; Xiong, R.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2012**, *14*, 2210. (e) Mendelsohn, B. A.; Lee, S.; Kim, S.; Teyssier, F.; Aulakh, V. S.; Ciufolini, M. A. *Org. Lett.* **2009**, *11*, 1539.

(5) (a) Kim, J.; Schneekloth, J. S.; Sorensen, E. J. *Chem. Sci.* **2012**, *3*, 2849. (b) Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1947**, *30*, 2081. (c) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904.

(6) (a) Kyei, A. S.; Tchabanenko, K.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 8931.

(7) Takayama, H.; Ishikawa, H.; Kurihara, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L. T.; Watanabe, K.; Murayama, T.; Horie, S. *J. Med. Chem.* **2002**, *45*, 1949.

(8) (a) Stoermer, D.; Heathcock, C. *J. Org. Chem.* **1993**, *58*, 564. (b) Finch, N.; Gemenden, C. W.; Hsu, I. H.-C.; Kerr, A.; Sim, G. A.; Taylor, W. I. *J. Am. Chem. Soc.* **1965**, *87*, 2229. (c) O'Rell, D. D.; Lee, F. G. H.; Boekelheide, V. *J. Am. Chem. Soc.* **1972**, *94*, 3205. (d) Stahl, R.; Borschberg, H.-J. *Helv. Chim. Acta* **1994**, *77*, 1331. (e) Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786.

(9) Zhang, T.; Qi, Z.; Zhang, X.; Wu, L.; Li, X. *Chem. - Eur. J.* **2014**, *20*, 3283.

(10) Sun, Y.; Gan, J.; Fan, R. *Adv. Synth. Catal.* **2011**, *353*, 1735.

(11) Zhang, X.; Hou, W.; Zhang-Negrerie, D.; Zhao, K.; Du, Y. *Org. Lett.* **2015**, *17*, 5252.

(12) Zhang, Y. Q.; Zhu, D. Y.; Jiao, Z. W.; Li, B. S.; Zhang, F. M.; Tu, Y. Q.; Bi, Z. *Org. Lett.* **2011**, *13*, 3458.

(13) Marien, N.; Brigou, B.; Pinter, B.; De Proft, F.; Verniest, G. *Org. Lett.* **2015**, *17*, 270.

(14) Suneel Kumar, C. V.; Ramana, C. V. *Org. Lett.* **2014**, *16*, 4766.

(15) Zhang, X.; Yang, C.; Zhang-Negrerie, D.; Du, Y. *Chem. - Eur. J.* **2015**, *21*, 5193.

(16) For selected reviews on hypervalent iodine reagents, see: (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523. (b) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (c) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111. (d) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656; *Angew. Chem.* **2005**, *117*, 3722. (e) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (f) Richardson, R. D.; Wirth, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4402; *Angew. Chem.* **2006**, *118*, 4510. (g) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (h) Brand, J. P.; Gonzalez, D. F.; Nicolai, S.; Waser, J. *Chem. Commun.* **2011**, *47*, 102. (i) Quideau, S.; Wirth, T. *Tetrahedron* **2010**, *66*, 5737. (j) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328.

(17) (a) Correa, A.; Herrero, M. T.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron* **2003**, *59*, 7103. (b) Kikugawa, Y.; Nagashima, A.; Sakamoto, T.; Miyazawa, E.; Shiiya, M. *J. Org. Chem.* **2003**, *68*, 6739. (c) Wardrop, D. J.; Basak, A. *Org. Lett.* **2001**, *3*, 1053.

(18) (a) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartín, R. *J. Org. Chem.* **2006**, *71*, 3501. (b) Wang, K.; Fu, X.; Liu, J.; Liang, Y.; Dong, D. *Org. Lett.* **2009**, *11*, 1015.

(19) (a) Tang, J. S.; Guo, C. C. *Synthesis* **2015**, *47*, 108. (b) Zhou, M. B.; Wei, W. T.; Xie, Y. X.; Lei, Y.; Li, J. H. *J. Org. Chem.* **2010**, *75*, 5635. (c) Li, S.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 2387.

(20) We also tried other Lewis acids including TMSOTf, $AlCl_3$, $FeCl_3$, and $ZnCl_2$. However, none of them is effective for this transformation.

(21) For selected examples describing the application of $BF_3{\cdot}Et_2O$ in activating PIDA, see: (a) Yuan, J.; Zhang, Q.; Yu, M.; Huang, P.; Zhang, R.; Dong, D. *Org. Lett.* **2015**, *17*, 5012. (b) Zheng, Y.; Li, X.; Ren, C.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *J. Org. Chem.* **2012**, *77*, 10353.

(22) Our attempt to expand the substrate scope of R^4 by including groups of cyclohexyl, isopropyl, and phenyl was not successful due to Sonogashira cross-coupling reaction between the corresponding propiolamides and *o*-iodoaniline, which impeded the formation of the desired substrates.

(23) Stephenson, M. J.; Howell, L. A.; O'Connell, M. A.; Fox, K. R.; Adcock, C.; Kingston, J.; Sheldrake, H.; Pors, K.; Collingwood, S. P.; Searcey, M. *J. Org. Chem.* **2015**, *80*, 9454.

(24) We have carried out the reaction of *N*-H (**E4**) and acyl (**E5**) (R^3) substituted substrates. However, no desired product was obtained in each case (complex mixture formed).

(25) (a) Yang, C.; Zhang, X.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *J. Org. Chem.* **2015**, *80*, 5320.

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