Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Efficient asymmetric synthesis of spiro-2(3*H*)-furanones via phase-transfer-catalyzed alkynylation

Xiangfei Wu, Seiji Shirakawa and Keiji Maruoka*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Efficient asymmetric synthesis of spiro-2(3*H*)-furanones was achieved via phase-transfer-catalyzed highly enantioselective alkynylation of cyclic β-keto esters with hypervalent iodine reagents.

Introduction

The development of efficient asymmetric methods for the synthesis of chiral spirocyclic compounds has attracted much attention in recent years,[1] because such structures are found in many important biologically active natural products.[2] Among these spirocyclic compounds, chiral spirolactones are one of the most important targets in synthetic organic chemistry.[2f] Although several examples of asymmetric synthesis of spirolactones have recently been reported,[3] efficient methods for the enantioselective synthesis of spiro-2(3*H*)-furanones possessing an all-carbon quaternary center are still very limited,[4] despite the importance of these compounds in natural product chemistry and medicinal chemistry (Fig. 1).[5] In this context, we are interested in the development of efficient asymmetric synthesis of spiro-2(3*H*)-furanones.

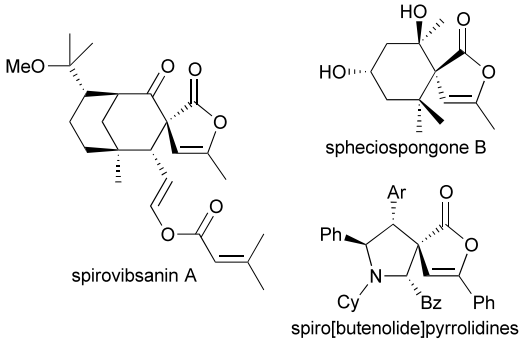
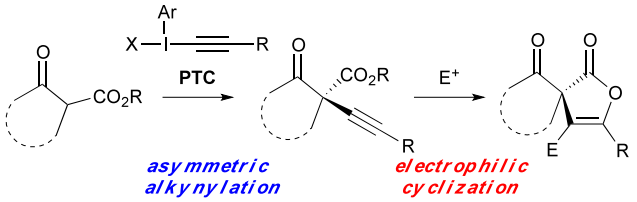


Fig. 1 Natural products and biologically active compounds possessing the spiro-2(3*H*)-furanone structure.

Our key strategy for the enantioselective synthesis of spiro-2(3*H*)-furanones involves asymmetric alkynylation of cyclic β-keto esters with hypervalent iodine reagents[6] under phase-transfer conditions (Scheme 1).[7–9] Subsequent intramolecular electrophilic cyclization of the alkynylation product gave a spiro-2(3*H*)-furanone.[10,11] Herein we report an efficient, highly enantioselective synthesis of spiro-2(3*H*)-furanones via phase-transfer-catalyzed alkynylation of cyclic β-keto esters with alkynylbenziodoxoles.

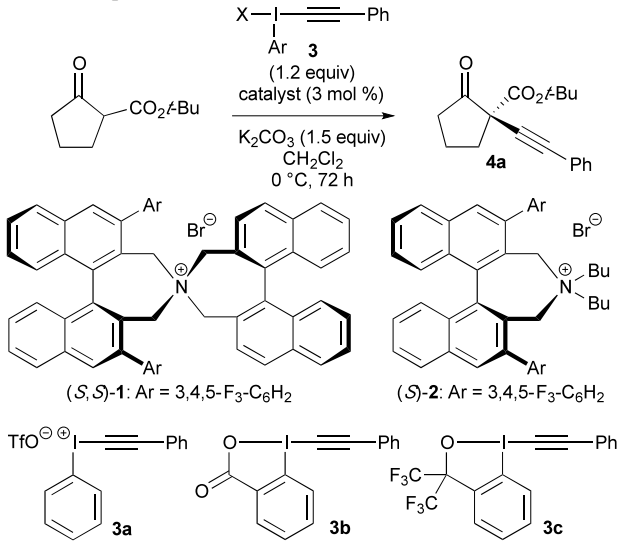


Scheme 1 Synthetic strategy.

Results and discussion

We first examined the asymmetric alkynylation of 2-oxocyclopentanecarboxylate with hypervalent iodine reagents **3** under the influence of binaphthyl-modified chiral quaternary ammonium salts (*S*,*S*)-**1**[12] and (*S*)-**2**[13] as reliable phase-transfer catalysts (Table 1). Although related asymmetric alkynylations have already been reported by Waser,[8b] enantioselectivity of the products was moderate at best (<79% ee) and the scope of alkynylation reagents was limited to trialkylsilylacetylene derivatives. To improve the enantioselectivity of the reaction, we investigated the effect of several hypervalent iodine reagents **3**. When the asymmetric alkynylation was performed with iodonium salt **3a**, alkynylation product **4a** was obtained in good yields with no asymmetric inductions (entries 1 and 2). The reactions with alkynylbenziodoxolone reagent **3b** gave product **4a** in moderate to good yields with low enantioselectivities (11–26% ee, entries 3 and 4). These results are in agreement with previous observations on the importance of employing cyclic hypervalent iodine reagents for asymmetric induction.[8b,c,14] Based on these observations, we next examined the alkynylation with alkynylbenziodoxole **3c**. Although the reaction using catalyst (*S*,*S*)-**1** was very sluggish (entry 5), catalyst (*S*)-**2** promoted the alkynylation with reagent **3c** to give alkynylation product **4a** in good yield with good enantioselectivity (83% ee, entry 6). Changing the solvent to toluene improved the enantioselectivity and **4a** was obtained with high enantioselectivity (94% ee, entry 7), representing the first example of highly enantioselective alkynylation reported to date using hypervalent iodine reagent.

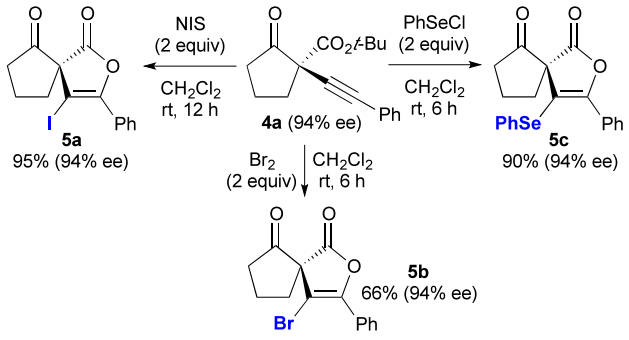
Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	3	Yield[b] (%)	ee[c] (%)
1	(*S*,*S*)-**1**	**3a**	82	0
2	(*S*)-**2**	**3a**	85	0
3	(*S*,*S*)-**1**	**3b**	56	26
4	(*S*)-**2**	**3b**	88	11
5	(*S*,*S*)-**1**	**3c**	trace	–
6	(*S*)-**2**	**3c**	78	83
7[d]	(*S*)-**2**	**3c**	76	94

[a] Reaction conditions: *tert*-Butyl 2-oxocyclopentanecarboxylate (0.025 mmol), **3** (0.030 mmol), and K_2CO_3 (0.038 mmol) in the presence of catalyst (3 mol %) in dichloromethane (2 mL) at 0 °C for 72 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Toluene was used as solvent.

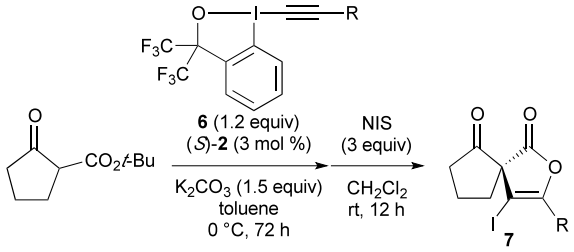
The obtained alkynylation product **4a** was readily cyclized by treatment with appropriate electrophiles to give spiro-2(3*H*)-furanones **5** (Scheme 2).[11,15] For example, treatment of **4a** with *N*-iodosuccinimide or bromine in dichloromethane at room temperature for 6–12 h gave the corresponding halogenated spiro-2(3*H*)-furanones **5a** and **5b** in good to high yields without any loss of stereoinformation. Furthermore, phenylselenyl chloride could be employed to the cyclization to give spiro-2(3*H*)-furanone **5c** in high yield.



Scheme 2 Electrophilic cyclization of alkynylation product **4a**.

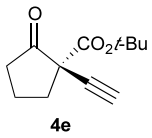
With an efficient synthetic route to chiral spiro-2(3*H*)-furanones in hand, we further explored the substrate generality of the enantioselective alkynylation of 2-oxocyclopentanecarboxylate with various alkynylbenoziodoxoles **6** (Table 2). In this study, it was found that alkynylaton product of type **4**, without isolation, could be treated with *N*-iodosuccinimide to give spiro-2(3*H*)-furanones **7** directly, thereby further improving the efficiency of this transformation. The reactions with arylacetylene derivatives **6** (R = Ar) that contain various aromatic and heteroaromatic groups gave the corresponding spiro-2(3*H*)-furanones **5a** and **7a**–**c** in moderate overall yields with high enantioselectivities (90–95% ee, entries 1–4). Unfortunately, the reaction with methylacetylene substituted iodine reagent **6d** did not afford the target product (entry 5). Trimethylsilylacetylene derivative **6e** was also employed in this reaction. Although the second cyclization step did not proceed, the acetylation product **4e** was obtained with high enantioselectivity (93% ee, entry 6).

Table 2 Efficient asymmetric synthesis of spiro-2(3*H*)-furanones **7**[a]



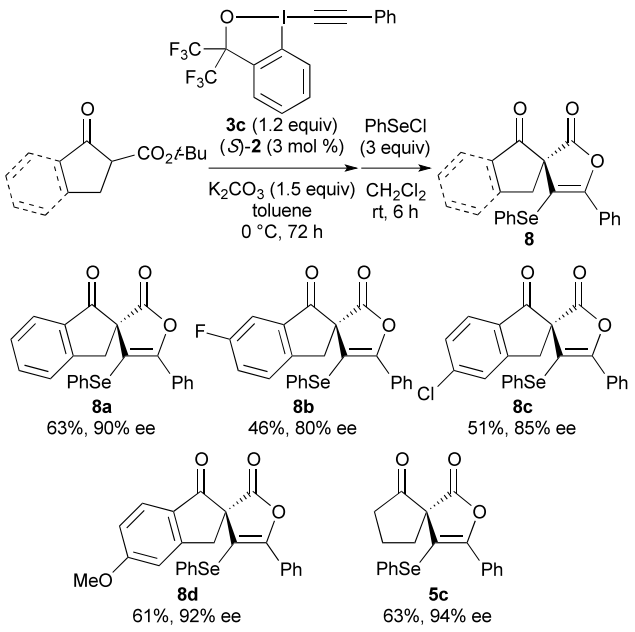
Entry	R of reagent **6**	Yield[b] (%)	ee[c] (%)
1	Ph (**3c**)	60 (**5a**)	94
2	4-MeO-C_6H_4 (**6a**)	63 (**7a**)	95
3	4-F-C_6H_4 (**6b**)	41 (**7b**)	90
4[d]	2-thienyl (**6c**)	53 (**7c**)	93
5	Me (**6d**)	~0 (**7d**)	–
6[e]	Me_3Si (**6e**)	80 (**4e**)[f]	93

[a] Reaction conditions: 1st step; *tert*-Butyl 2-oxocyclopentanecarboxylate (0.025 mmol), **3c** or **6** (0.030 mmol), and K_2CO_3 (0.038 mmol) in the presence of catalyst (3 mol %) in toluene (2 mL) at 0 °C for 72 h. 2nd step; crude alkynylation compound **4**, *N*-iodosuccinimide (0.075 mmol) in dichloromethane (1 mL) at room temperature for 12 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] Reaction time for 2nd step = 24 h. [e] KF (1.5 equiv) was used instead of K_2CO_3. [f] 2nd cyclization step did not proceed. Yield corresponds to alkynylation product **4e**.

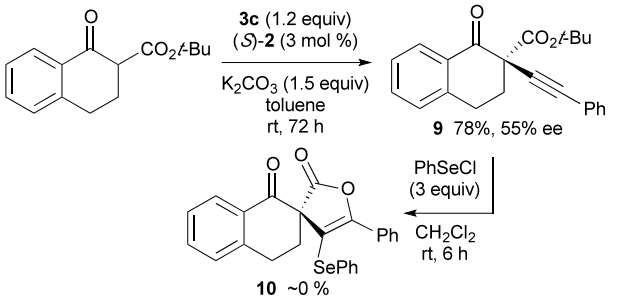


Other cyclic β-keto esters were also examined for the asymmetric synthesis of spiro-2(3*H*)-furanones **8** (Scheme 3). Various 1-oxo-2-indanecarboxylates could be employed for this reaction to give spirocyclic compounds **8a**–**d** in good to high enantioselectivities (80–92% ee). The reaction with 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate were also examined (Scheme 4). Although asymmetric alkynylation with **3c** was promoted by catalyst (*S*)-**2** to give product **9** with

moderate enantioselectivity (55% ee), the second cyclization was not successful. The absolute configuration of the products was determined by X-ray diffraction analysis of **8a** (Fig. 2).[16,17]



Scheme 3 Efficient asymmetric synthesis of spiro-2(3*H*)-furanones **8**.



Scheme 4 Asymmetric alkynylation of 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate.

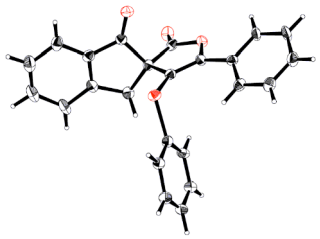


Fig. 2 X-ray crystal structure of **8a**.

Conclusions

In summary, we have successfully developed an efficient, highly enantioselective synthesis of spiro-2(3*H*)-furanones via phase-transfer-catalyzed alkynylation of cyclic β-keto esters with alkynylbenziodoxoles. Further studies will be directed toward expansion of the reaction scope.

Experimental

General procedure for asymmetric alkynylation of 2-oxocyclopentanecarboxylate (Table 1)

To a solution of 2-oxocyclopentanecarboxylate (0.025 mmol), iodine reagent **3** (0.030 mmol), and chiral phase-transfer catalyst (*S*,*S*)-**1** or (*S*)-**2** (3 mol %) in dichloromethane or toluene (2 mL) was added K_2CO_3 (0.038 mmol) at 0 °C. The reaction mixture was vigorously stirred for 72 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 5 mL). The combined extracts were dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography or preparative thin layer chromatography on silica gel (ethyl acetate/hexane/dichloromethane as eluent) to give alkynylation product **4**.

General procedure for cyclization of alkynylation product 4a (Scheme 2)

A solution of *N*-iodosuccinimide, bromine, or phenylselenyl chloride (0.030 mmol) in dichloromethane (1 mL) was added dropwise to a solution of the alkynylated compound **4a** (0.015 mmol) in dichloromethane (1 mL) at room temperature. The reaction mixture was stirred for 6–12 h at room temperature. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (NIS and Br_2) or $NaHCO_3$ (PhSeCl) and extracted with dichloromethane (3 × 5 mL). The combined extracts were dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography or preparative thin layer chromatography on silica gel (ethyl acetate/hexane/dichloromethane as eluent) to give cyclization product **5**.

General procedure for efficient asymmetric synthesis of spiro compounds 7 and 8 (Table 2, Scheme 3)

To a solution of β-keto ester (0.025 mmol), iodine reagent **3c** or **6** (0.030 mmol), and chiral phase-transfer catalyst (*S*)-**2** (3 mol %) in toluene (2 mL) was added K_2CO_3 (0.038 mmol) at 0 °C. The reaction mixture was vigorously stirred for 72 h at 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 5 mL). The combined extracts were dried over Na_2SO_4, and concentrated. The residue was dissolved in dichloromethane (1 mL), and to this solution was added a solution of *N*-iodosuccinimide or phenylselenyl chloride (0.075 mmol) in dichloromethane (1 mL) at room temperature. The reaction mixture was stirred for 6–12 h at room temperature. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (NIS) or $NaHCO_3$ (PhSeCl) and extracted with dichloromethane (3 × 5 mL). The combined extracts were dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography or preparative thin layer chromatography on silica gel (ethyl acetate/hexane/dichloromethane as eluent) to give cyclization product **7** or **8**.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research from JSPS and MEXT (Japan). X.W. thanks the financial support from China Scholarship Council.

Notes and references

Laboratory of Synthetic Organic Chemistry and Special Laboratory of Organocatalytic Chemistry, Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto, 606-8502, Japan. Fax: +81-75-753-4041; Tel: +81-75-753-4041; E-mail: maruoka@kuchem.kyoto-u.ac.jp

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1. For reviews on asymmetric synthesis of spirocyclic compounds, see: (a) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3003; (b) M. Wilsdorf and H.-U. Reissig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3003; (c) G. S. Singh and Z. Y. Desta, *Chem. Rev.*, 2012, **112**, 6104; (d) A. K. Franz, N. V. Hanhan and N. R. Ball-Jones, *ACS Catal.*, 2013, **3**, 540.

2. For reviews on biologically active natural products including spirocyclic structure, see: (a) J. E. Aho, P. M. Pihko and T. K. Rissa, *Chem. Rev.*, 2005, **105**, 4406; (b) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748; (c) S. Beaumont, E. A. Ilardi, N. D. C. Tappin and A. Zakarian, *Eur. J. Org. Chem.*, 2010, 5743; (d) J. Sperry, Z. E. Wilson, D. C. K. Rathwell and M. A. Brimble, *Nat. Prod. Rep.*, 2010, **27**, 1117; (e) Y.-S. Cai, Y.-W. Guo and K. Krohn, *Nat. Prod. Rep.*, 2010, **27**, 1840; (f) A. Bartoli, F. Rodier, L. Commeiras, J.-L. Parrain and G. Chouraqui, *Nat. Prod. Rep.*, 2011, **28**, 763.

3. (a) K. Tsuchikama, Y. Kuwata and T. Shibata, *J. Am. Chem. Soc.*, 2006, **128**, 13686; (b) M. N. Paddon-Row, L. C. H. Kwan, A. C. Willis and M. S. Sherburn, *Angew. Chem., Int. Ed.*, 2008, **47**, 7013; (c) M. Uyanik, T. Yasui and K. Ishihara, *Angew. Chem., Int. Ed.*, 2010, **49**, 2175; (d) S. Sternativo, A. Calandriello, F. Costantino, L. Testaferri, M. Tiecco and F. Marini, *Angew. Chem., Int. Ed.*, 2011, **50**, 9382; (e) C. Cassani, X. Tian, E. C. Escudero-Adán and P. Melchiorre, *Chem. Commun.*, 2011, **47**, 233; (f) Q.-H. Deng, H. Wadepohl and L. H. Gade, *J. Am. Chem. Soc.*, 2012, **134**, 2946; (g) X. Li, C. Yang, J.-L. Jin, X.-S. Xue and J.-P. Cheng, *Chem.–Asian J.*, 2013, **8**, 997; (h) T. Dohi, N. Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama and Y. Kita, *J. Am. Chem. Soc.*, 2013, **135**, 4558; (i) K. Liu, H.-L. Teng, L. Yao, H.-Y. Tao and C.-J. Wang, *Org. Lett.*, 2013, **15**, 2250; (j) J. Zheng, L. Lin, Y. Kuang, J. Zhao, X. Liu and X. Feng, *Chem. Commun.*, 2014, **50**, 994.

4. (a) T. Cao, J. Deitch, E. C. Linton and M. C. Kozlowski, *Angew. Chem., Int. Ed.*, 2012, **51**, 2448; (b) T. Cao, E. C. Linton, J. Deitch, S. Berritt and M. C. Kozlowski, *J. Org. Chem.*, 2012, **77**, 11034.

5. (a) M. Kubo, T. Fujii, H. Hioki, M. Tanaka, K. Kawazu and Y. Fukuyama, *Tetrahedron Lett.*, 2001, **42**, 1081; (b) A. Amal Raj, R. Raghunathan, M. R. SrideviKumari and N. Raman, *Bioorg. Med. Chem.*, 2003, **11**, 407; (c) D. Liu, M.-J. Xu, L.-J. Wu, Z.-W. Deng and W.-H. Lin, *J. Asian Nat. Prod. Res.*, 2009, **11**, 811.

6. For reviews on hypervalent iodine reagents, see: (a) P. J. Stang, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 274; (b) V. V. Zhdankin and P. J. Stang, *Tetrahedron*, 1998, **54**, 10927; (c) J. P. Brand, D. Fernández González, S. Nicolai and J. Waser, *Chem. Commun.*, 2011, **47**, 102; (d) E. A. Merritt and B. Olefsson, *Synthesis*, 2011, 517; (e) D. Fernández González, F. Benfatti and J. Waser, *ChemCatChem*, 2012, **4**, 955; (f) M. Brown, U. Farid and T. Wirth, *Syntlett*, 2013, **24**, 424; (g) A. Parra and S. Reboredo, *Chem.–Eur. J.*, 2013, **19**, 17244.

7. For recent reviews on asymmetric phase-transfer catalysis, see: (a) M. J. O'Donnell, *Aldrichimica Acta*, 2001, **34**, 3; (b) K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013; (c) M. J. O'Donnell, *Acc. Chem. Res.*, 2004, **37**, 506; (d) B. Lygo and B. I. Andrews, *Acc. Chem. Res.*, 2004, **37**, 518; (e) J. Vachon and J. Lacour, *Chimia*, 2006, **60**, 266; (f) T. Ooi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2007, **46**, 4222; (g) T. Ooi and K. Maruoka, *Aldrichimica Acta*, 2007, **40**, 77; (h) T. Hashimoto and K. Maruoka, *Chem. Rev.*, 2007, **107**, 5656; (i) K. Maruoka, *Org. Process Res. Dev.* 2008, **12**, 679; (j) S.-s. Jew and H.-g. Park, *Chem. Commun.*, 2009, 7090; (k) K. Maruoka, *Chem. Rec.*, 2010, **10**, 254; (l) S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 4312.

8. (a) D. Fernández González, J. P. Brand and J. Waser, *Chem.–Eur. J.*, 2010, **16**, 9457; (b) D. Fernández González, J. P. Brand, R. Mondière and J. Waser, *Adv. Synth. Catal.*, 2013, **355**, 1631; (c) M. Kamlar, P. Putaj and J. Veselý, *Tetrahedron Lett.*, 2013, **54**, 2097; see also: (d) M. Ochiai, M. Kunishima, Y. Nagao, K. Fuji, M. Shiro and E. Fujita, *J. Am. Chem. Soc.*, 1986, **108**, 8281; (e) M. Ochiai, T. Ito, Y. Takaoka, Y. Masaki, M. Kunishima, S. Tani and Y. Nagao, *J. Chem. Soc., Chem. Commun.*, 1990, 118; (f) M. D. Bachi, N. Bar-Ner, C. M. Crittell, P. J. Stang and B. L. Williamson, *J. Org. Chem.*, 1991, **56**, 3912.

9. For asymmetric alkynylation of β-keto esters with acetylenic ketones and esters under phase-transfer conditions, see: T. B. Poulsen, L. Bernardi, J. Alemán, J. Overgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 441.

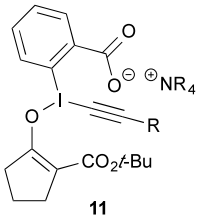
10. For reviews on lactonization, see: (a) M. D. Dowle and D. I. Davies, *Chem. Soc. Rev.*, 1979, **8**, 171; (b) S. Ranganathan, K. M. Muraleedharan, N. K. Vaish and N. Jayaraman, *Tetrahedron*, 2004, **60**, 5273; (c) S. A. Snyder, D. S. Treitler and A. P. Brucks, *Aldrichimica Acta*, 2011, **44**, 27; (d) C. K. Tan, L. Zhou and Y.-Y. Yeung, *Synlett*, 2011, 1335; (e) J. M. J. Nolsøe and T. V. Hansen, *Eur. J. Org. Chem.*, 2014, DOI: 10.1002/ejoc.201301400.

11. Z. W. Just and R. C. Larock, *J. Org. Chem.*, 2008, **73**, 2662.

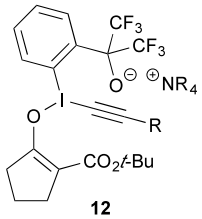
12. (a) T. Ooi, M. Takeuchi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2000, **122**, 5228. (b) T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 5139.

13. (a) M. Kitamura, S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 1549; (b) M. Kitamura, S. Shirakawa, Y. Arimura, X. Wang and K. Maruoka, *Chem.–Asian J.*, 2008, **3**, 1702.

14. Based on our observations about importance of cyclic structure in hypervalent iodine reagents, and the report by Waser,[8b] plausible structures (**11** and **12**) for the intermediate of these reactions were proposed as shown in below.



11



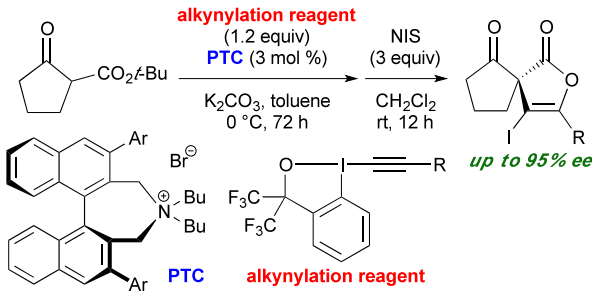
12

15. Reaction mechanism of the electrophilic cyclization was discussed in ref. 11.

16. The crystal structure of **8a** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 986764). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.

17. The alkynylations with acyclic β-keto esters proceeded very sluggishly.

Graphical Abstract



Efficient asymmetric synthesis of spiro-2(3*H*)-furanones was achieved via chiral phase-transfer-catalyzed alkynylation.