Video Article

Chemoselective Preparation of 1-Iodoalkynes, 1,2-Diiodoalkenes, and 1,1,2-Triiodoalkenes Based on the Oxidative Iodination of Terminal Alkynes

Youzhi Li*[1], Daya Huang*[1], Ju Huang[1], Yan Liu[1], Keiji Maruoka[1,2]

[1]School of Chemical Engineering and Light Industry, Guangdong University of Technology

[2]Department of Chemistry, Graduate School of Science, Kyoto University

*These authors contributed equally

Correspondence to: Yan Liu at yanliu@gdut.edu.cn, Keiji Maruoka at maruoka@kuchem.kyoto-u.ac.jp

URL: https://www.jove.com/video/58063
DOI: doi:10.3791/58063

Keywords: Chemistry, Issue 139, Chemoselective, synthesis, iodination, alkynes, 1-iodoalkynes, 1, 2-diiodoalkenes, 1, 1, 2-triiodoalkenes, hypervalent-iodine reagent

Date Published: 9/12/2018

Citation: Li, Y., Huang, D., Huang, J., Liu, Y., Maruoka, K. Chemoselective Preparation of 1-Iodoalkynes, 1,2-Diiodoalkenes, and 1,1,2-Triiodoalkenes Based on the Oxidative Iodination of Terminal Alkynes. *J. Vis. Exp.* (139), e58063, doi:10.3791/58063 (2018).

Abstract

We present the chemoselective synthesis of 1-(iodoethynyl)-4-methylbenzene, 1-(1,2-diiodovinyl)-4-methylbenzene, and 1-methyl-4-(1,2,2-triiodovinyl)benzene as representative examples for the practical chemoselective preparation of 1-iodoalkynes, 1,2-diiodoalkenes, and 1,1,2-triiodoalkenes from the chemoselective iodination of terminal alkynes mediated by hypervalent-iodine reagents. The chemoselectivity was confirmed by using *p*-tolylethyne as a model substrate to screen a variety of iodine sources and/or the hypervalent-iodine reagents. A combination of tetrabutylammonium iodide (TBAI) and (diacetoxyiodo)benzene (PIDA) selectively generates 1-iodoalkynes, while a combination of KI and PIDA generates 1,2-diiodoalkenes. A one-pot synthesis based on both TBAI-PIDA and KI-PIDA yields the corresponding 1,1,2-triiodoalkenes. These protocols were subsequently applied to the synthesis of synthetically important aromatic and aliphatic 1-iodoalkynes, 1,2-diiodoalkenes, and 1,1,2-triiodoalkenes, which were obtained in good yield with excellent chemoselectivity.

Video Link

The video component of this article can be found at https://www.jove.com/video/58063/

Introduction

Iodoalkynes and iodoalkenes are widely used important precursors and building blocks in organic synthesis[1,2,3,4], biologically active substances, and useful in the synthesis of materials and complex molecules given the ease of converting the C-I bond[5,6,7,8]. In recent years, the oxidative iodination of terminal alkynes has attracted more attention to the synthesis of iodoalkyne and iodoalkene derivatives. So far, efficient methods that use metal catalysts[9,10,11,12], hypervalent-iodonium catalysts[13,14], an anodic oxidation system[15], ionic liquid systems[16], KI (or I_2)-oxidant combinations[17,18,19,20], ultrasound[21], phase-transfer catalysts[22], *N*-iodosuccinimide[9,22,23,24,25], *n*-BuLi[26,27,28,29,30,31], Grignard reagents[32], and morpholine catalysts[17,33,24,35] have been developed for the iodination of alkynes. Recently, we have reported a practical and chemoselective protocol for the synthesis of 1-iodoalkynes, 1,2-diiodoalkenes, and 1,1,2-triiodoalkenes[36]. The features of this method are green and practical: (1) the toxicity of hypervalent-iodine catalysts as oxidative functionalization reagents is low compared to other conventional heavy-metal-based oxidants[37,38,39,40,41,42], and (2) TBAI and/or KI are used as iodine sources. In addition, our system affords excellent selectivity under mild conditions. The chemoselective synthesis of 1-iodoalkynes, 1,2-diiodoalkenes, and 1,1,2-triiodoalkenes requires precise control over various factors, including the composition, the oxidant, the iodine source, and the solvent. Among these, the iodine source is the most important factor for the chemoselectivity of the reaction. After the screening of several types and loadings of the iodine source as well as the solvents, three methods were identified and established. Firstly, TBAI as an iodine source in combination with PIDA (TBAI-PIDA) is selective for the synthesis of 1-iodoalkynes. Alternatively, 1,2-diiodoalkenes are efficiently obtained using a KI-PIDA system. Both methods afford the corresponding products in high yield and high chemoselectivity. The corresponding tri-iodinationproducts, *i.e.*, 1,1,2-triiodoalkenes, were obtained in good yield from the one-pot synthesis that combine the TBAI-PIDA and KI-PIDA systems[36].

Here, we will demonstrate how the chemoselectivity for the iodination of terminal alkynes can be steered from 1-iodoalkynes to 1,2-diiodoalkenes and to 1,1,2-triiodoalkenes under similar reaction conditions, highlighting the precise control that can be exerted by judiciously choosing oxidant, iodine source, and solvent. For the development of this new synthetic technique, *p*-tolylethyne was used as a model substrate. Although the following protocols focus on the synthesis of 1-(iodoethynyl)-4-methylbenzene, (*E*)-1-(1,2-diiodovinyl)-4-methylbenzene, and 1-methyl-4-(1,2,2-triiodovinyl)benzene, these compounds are representative for 1-iodoalkynes, 1,2-diiodoalkenes, and 1,1,2-triiodoalkenes, respectively, *i.e.*, the protocols are broad in scope, and the same techniques can be applied to the chemoselective iodination of aromatic and aliphatic terminal alkynes[36].

Reagents employed in the chemoselective iodination of terminal alkynes and small deviations from the techniques described result in dramatic differences with respect to the target products. For instance, changing of iodine source from TBAI to KI and changing of solvent from CH_3CN to a

CH_3CN-H_2O has a dramatic impact on the chemoselectivity of the iodination. The detailed protocol aims at helping new practitioners in the field with the chemoselective iodination of terminal alkynes to avoid many common pitfalls during the synthesis of 1-iodoalkynes, 1,2-diiodoalkenes, and 1,1,2-triiodoalkenes.

Protocol

1. Synthesis of 1-(Iodoethynyl)-4-Methylbenzene (2, 1-Iodoalkynes)

1. Add 133 mg (0.36 mmol) of TBAI and 3 mL of CH_3CN to a reaction tube that contains a magnetic stirring bar, which is open to air. Then, add 38 μL (0.3 mmol) of *p*-tolylethyne to the mixture using a microsyringe.
2. Add 96.6 mg (0.3 mmol) of PIDA to the vigorously stirred reaction mixture in 10 portions over a period of 20 min using a spatula.
3. Stir the reaction mixture at room temperature for 3 h.
4. Pour the resulting mixture into a separatory funnel that contains 30 mL of water, and quench with aqueous $Na_2S_2O_3$ (10%, 0.5 mL). Extract the aqueous layer three times with 10 mL of ethyl acetate.
5. Wash the combined organic layers with 10 mL of saturated brine and dry over anhydrous sodium sulfate (0.5 g).
6. Filter off the sodium sulfate using a Buchner funnel, and concentrate the filtrate under reduced pressure to obtain the crude product.
7. Purify the crude product by column chromatography on silica gel using hexane as the eluent; the pure product, 1-(iodoethynyl)-4-methylbenzene, is obtained as a light yellow liquid (71.9 mg, 99% yield; R_f = 0.79).
8. Analyze the product by ^1H and ^{13}C NMR spectroscopy, and high-performance liquid chromatography (HPLC).

2. Synthesis of (*E*)-1-(1,2-Diiodovinyl)-4-Methylbenzene (3, 1,2-Diiodoalkenes)

1. Add 124.5 mg (0.75 mmol) of KI and 1 mL of CH_3CN to a reaction tube that contains a magnetic stirring bar, which is open to air. Then, add 38 μL (0.3 mmol) of *p*-tolylethyne and 3 mL of H_2O to the mixture via a microsyringe.
2. Add 96.6 mg (0.3 mmol) of PIDA to the vigorously stirred reaction mixture in 10 portions over a period of 20 min using a spatula.
3. Stir the reaction mixture at room temperature for 24 h.
4. Pour the resulting mixture into a separatory funnel that contains 30 mL of water, quench with aqueous $Na_2S_2O_3$ (10%, 1 mL), and extract the aqueous layer three times with 10 mL of ethyl acetate.
5. Wash the combined organic layers with 10 mL of brine and dry over anhydrous sodium sulfate (0.5 g).
6. Filter off the sodium sulfate using a Buchner funnel, and concentrate the filtrate under reduced pressure to obtain the crude product.
7. Purify the crude product by column chromatography on silica gel using hexane as the eluent. The pure product, (*E*)-1-(1,2-diiodovinyl)-4-methylbenzene, is obtained as a light yellow liquid (111.9 mg, 98% yield; R_f = 0.84).
8. Analyze the product by ^1H and ^{13}C NMR spectroscopy as well as HPLC.

3. Synthesis of 1-Methyl-4-(1,2,2-Triiodovinyl)benzene (4, 1,1,2-Triiodoalkenes)

1. Add 133 mg (0.36 mmol) of TBAI and 1 mL of CH_3CN to a reaction tube that contains a stirring bar, which is open to air. Then, add 38 μL (0.3 mmol) of *p*-tolylethyne using a microsyringe.
2. Add 96.6 mg (0.3 mmol) of PIDA to the vigorously stirred reaction mixture in 10 portions over a period of 20 min using a spatula. Stir the reaction mixture for 3 h at room temperature.
3. Add 124.5 mg (0.75 mmol) of KI in 3 mL of H_2O to the reaction mixture.
4. Add 193.2 mg (0.6 mmol) of PIDA to the reaction mixture in 10 portions over a period of 20 min using a spatula. Stir the reaction mixture for another 3 h at room temperature.
5. Add another 124.5 mg (0.75 mmol) of KI in 3 mL of H_2O and 1 mL of CH_3CN to the reaction mixture.
6. Add another 193.2 mg (0.6 mmol) of PIDA to the reaction mixture in 10 portions over a period of 20 min using a spatula. Stir the reaction mixture for another 12 h at room temperature.
7. Pour the resulting mixture into a separatory funnel that contains 30 mL of water, quench with aqueous $Na_2S_2O_3$ (10%, 2 mL), and extract the aqueous layer three times with 10 mL of ethyl acetate.
8. Wash the combined organic layers with 10 mL of brine and dry over anhydrous sodium sulfate (0.5 g).
9. Filter off the sodium sulfate using a Buchner funnel, and concentrate the filtrate under reduced pressure to obtain the crude product.
10. Purify the crude product by column chromatography on silica gel using hexane to get the pure product, 1-methyl-4-(1, 2, 2-triiodovinyl)benzene, as a yellow liquid (138.4 mg, 93% yield; R_f = 0.79).
11. Analyze the product by ^1H and ^{13}C NMR spectroscopy as well as HPLC.

4. Determination of the Selectivity for the Mono-, Di-, or Tri-iodination of Terminal Alkynes by HPLC

Note: The selectivity for the mono-, di-, tri-iodination of the alkynes was determined by HPLC. HPLC was performed on an instrument using a 5 μm, 4.6 mm × 150 mm column, CH_3CN/H_2O = 75/25 (v/v) as the solvent, a flow rate of 1.0 mL/min, and a detector wavelength of λ = 254 nm.

1. Preparation of the external standard solution for HPLC
    1. Precisely weigh out **2** (1-(iodoethynyl)-4-methylbenzene; 9.58 mg, 39.58×10^{-3} mmol), **3** ((*E*)-1-(1,2-diiodovinyl)-4-methylbenzene; 19.29 mg, 52.14×10^{-3} mmol), and **4** (1-methyl-4-(1,2,2-triiodovinyl)benzene; 11.10 mg, 22.38×10^{-3} mmol).
    2. Mix and dissolve these three compounds in 1 mL of CH_3CN and dilute the stock solution 100 times before performing the HPLC separation.
    3. Determine the peak area ratio (%) of each product on HPLC chromatogram.

4. Calculate the ratio of the molar absorptivity of each compound according to the following formula:
   $\varepsilon_2 : \varepsilon_3 : \varepsilon_4 = A_2/n_2 : A_3/n_3 : A_4/n_4$
   where ε is the molar absorptivity, A the peak area, and n the molar weight.

2. Calculate the chemoselectivity according to the following formula:
   $n_2 : n_3 : n_4 = A_2/\varepsilon_2 : A_3/\varepsilon_3 : A_4/\varepsilon_4$

Representative Results

The chemoselective synthesis of 1-iodoalkynes, 1,2-diiodoalkenes, and 1,1,2-triiodoalkenes based on the oxidative iodination of *p*-tolylethyne is summarized in **Figure 1**. All reactions were exposed to air. All compounds in this study were characterized by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and HPLC to access the structure of the product and the selectivity of the reaction, as well as to explore the purity. The obtained products are stable upon storage at 4 °C in a refrigerator for four months, *i.e.*, significant changes in HPLC and ^{1}H NMR data were not detected. Key data for representative compounds are described in this section.

The structure of 1-(iodoethynyl)-4-methylbenzene (**2**, 1-iodoalkynes) was determined by comparing its NMR data with reference data. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, J = 8.0 Hz, 2 H), 7.11 (d, J = 8.0 Hz, 2 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1, 132.2, 129.0, 120.4, 94.3, 21.6, 5.1. The key proton signal for the terminal alkyne (3.0 ppm) disappears and the observation of a signal at 5.1 ppm in the ^{13}C NMR spectrum confirms the mono-iodination of *p*-tolylethyne (**Figure 2**), consistent with reported NMR data[43]. HPLC analysis: C18 (5 μm, 4.6 mm × 150 mm), CH_3CN/H_2O = 75/25 (v/v), flow rate = 1.0 mL/min^{-1}, λ = 254 nm, retention time: 6.2 min (**Figure 7**).

The structure of (*E*)-1-(1,2-diiodovinyl)-4-methylbenzene (**3**, 1,2-diiodoalkenes) was determined by comparing its NMR data with reference data. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 8.0 Hz, 2 H), 7.22 (s, 1 H), 7.15 (d, J = 8.0 Hz, 2 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 139.0, 129.0, 128.4, 96.6, 80.1, 21.4. The key proton signal in the olefin at 7.2 ppm confirms the di-iodination of *p*-tolylethyne, and ^{13}C NMR spectrum shows the corresponding olefin carbon atoms at 96.6 ppm and 80.1 ppm, respectively (**Figure 3**). The NMR data are consistent with previously reported values, in which **3** was determined as the *E* type[18]. HPLC analysis: C18 (5 μm, 4.6 mm × 150 mm), CH_3CN/H_2O = 75/25 (v/v), flow rate = 1.0 mL/min^{-1}, λ = 254 nm, retention time: 10.6 min (**Figure 8**).

The structure of 1-methyl-4-(1,2,2-triiodovinyl)benzene (**4**, 1,1,2-triiodoalkene) was determined by NMR, high-resolution mass spectrometry (HRMS), and HPLC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16 (s, 4 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 138.9, 129.3, 127.4, 112.9, 22.2, 21.5 (**Figure 4**); HRMS (EI) calcd for $C_9H_7I_3$: 495.7682 ($[M]^+$); found: 495.7672 (**Figure 5**); HPLC analysis: C18 (5 μm, 4.6 mm × 150 mm), CH_3CN/H_2O = 75/25 (v/v), flow rate = 1.0 mL/min^{-1}, λ = 254 nm, retention time: 11.5 min (**Figure 9**).

The chemoselectivity of the iodination was determined by HPLC. The HPLC performance of **2**, **3**, and **4** as external standards is shown in **Figure 6**. The molar ratio of **2**, **3**, and **4** as external standards is 39.58 : 52.14 : 22.38. The peak area ratio (%) in the HPLC chromatogram of **2:3:4** is 49.801% : 30.762% : 19.436% (**Figure 6**). Accordingly, the ratio of molar absorptivity is ε_2: ε_3: ε_4= 2.131 : 1 : 1.472.

The TBAI-PIDA system selectively affords **2** (**2:3:4=** 100:0:0; **Figure 7**), while the KI-PIDA system selectively furnishes **3**(**2:3:4=** 0.8:98.8:0.4; **Figure 8**). Combined in one-pot, the TBAI-PIDA and KI-PIDA systems efficiently yield **4** as a major product (**2:3:4=** 3.7:3.2:93.1; **Figure 9**).

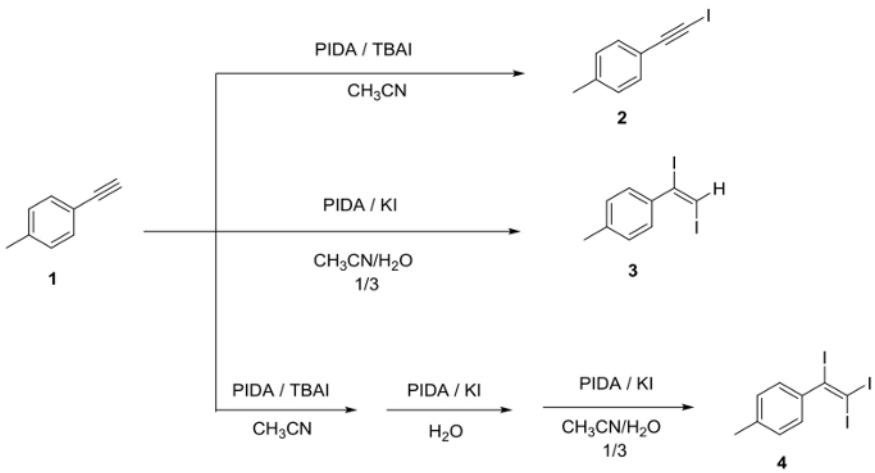


Figure 1. Chemoselective mono-, di- and tri-iodination of alkynes. *p*-Tolylethyne was used as a model substrate. Please click here to view a larger version of this figure.

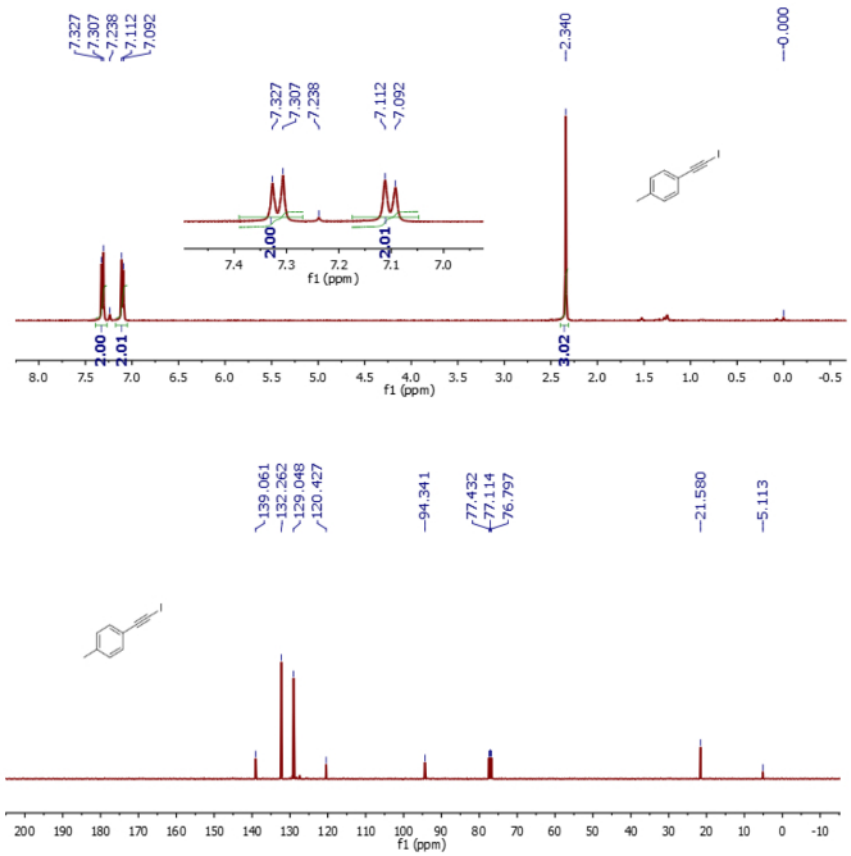


Figure 2. ^{1}H NMR and ^{13}C NMR spectra of 2. This figure has been reproduced from ref. 36 with permission. Please click here to view a larger version of this figure.

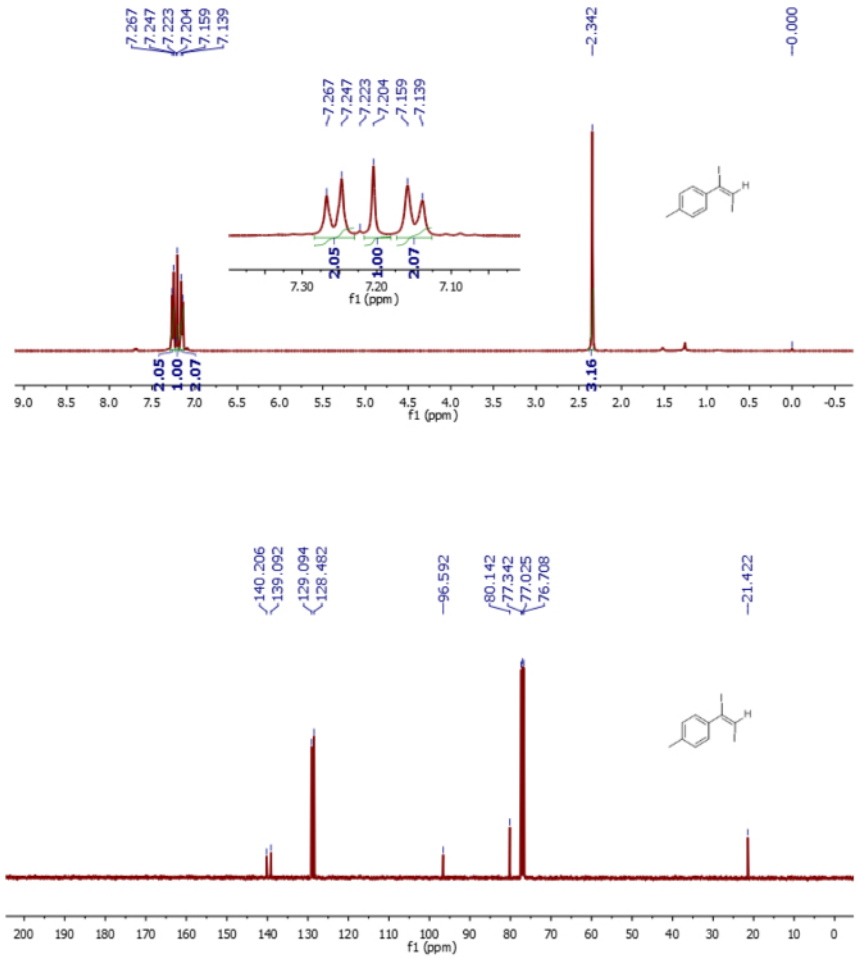


Figure 3. ^{1}H NMR and ^{13}C NMR spectra of 3. This figure has been reproduced from ref. 36 with permission. Please click here to view a larger version of this figure.

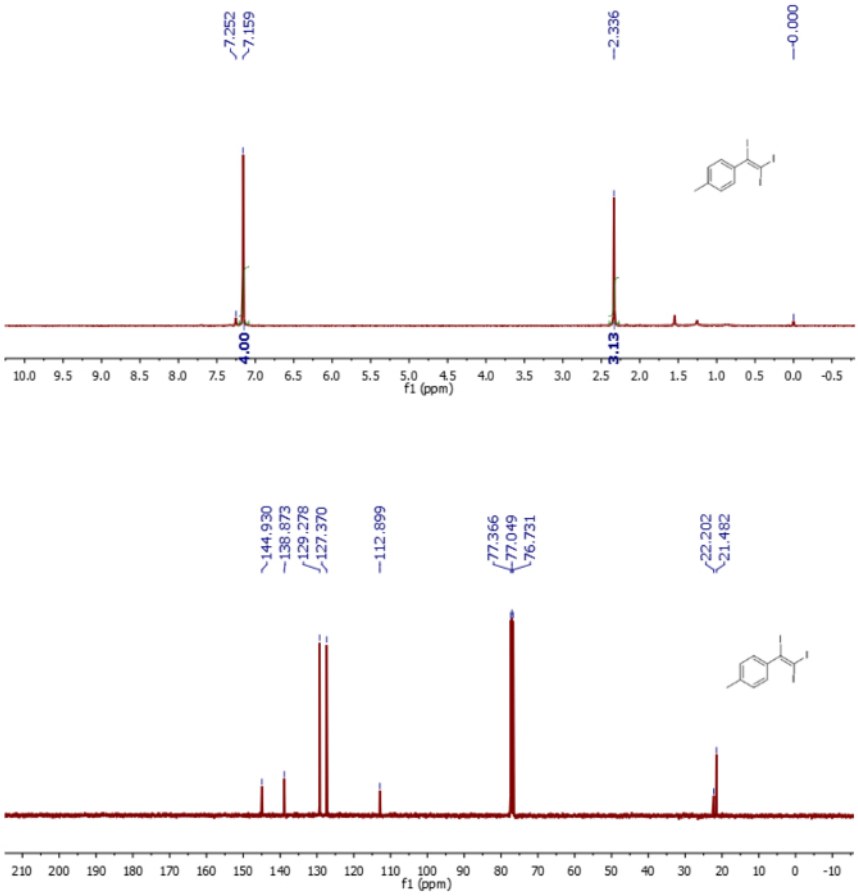


Figure 4. ^{1}H NMR and ^{13}C NMR spectra of 4. This figure has been reproduced from ref. 36 with permission. Please click here to view a larger version of this figure.

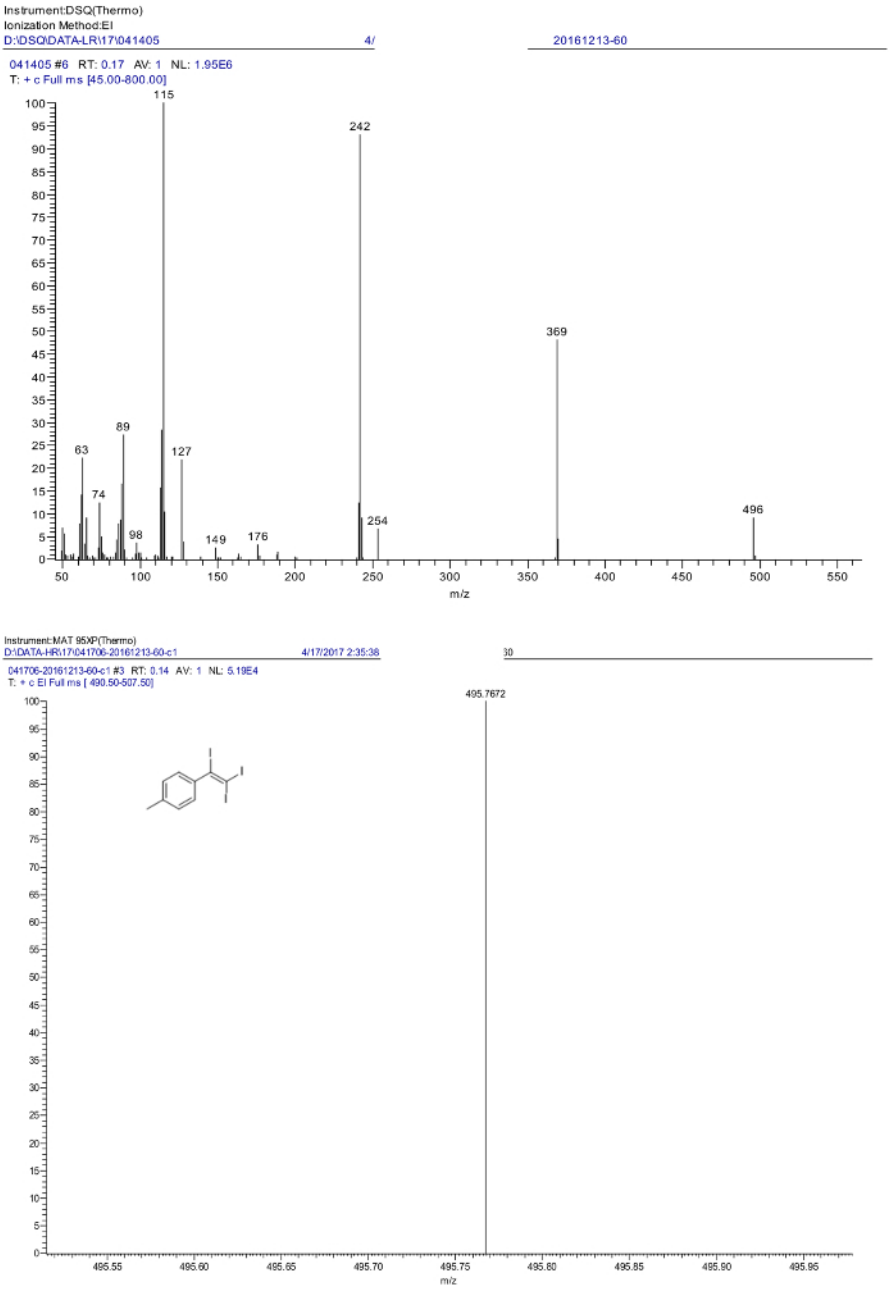
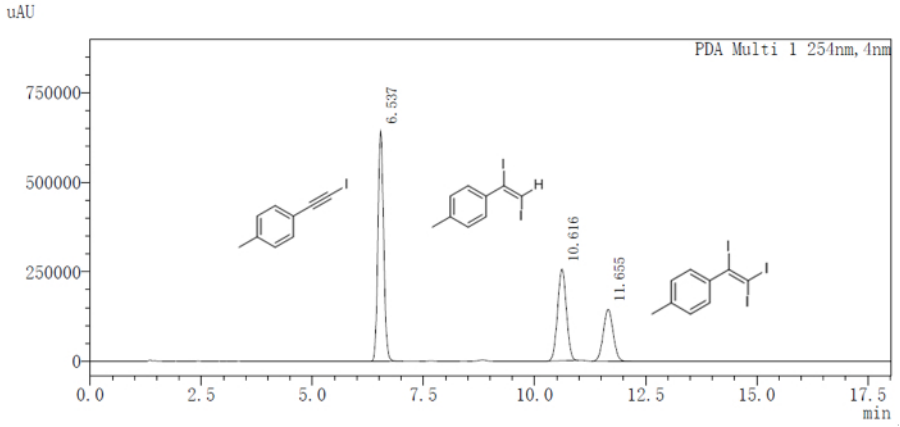


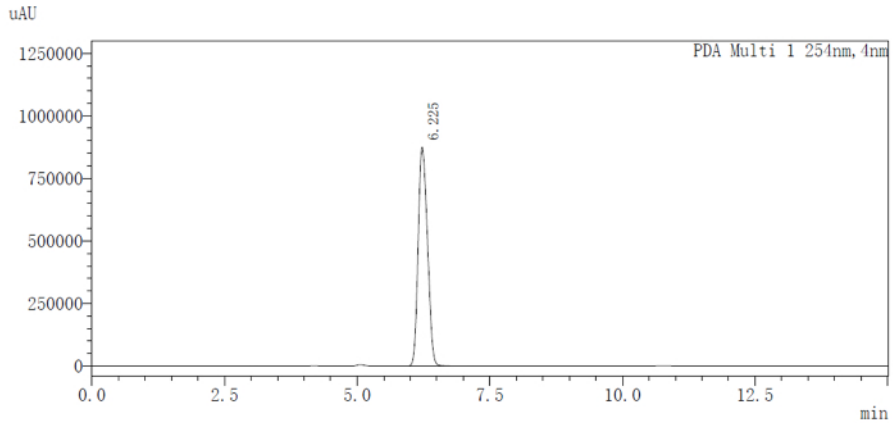
Figure 5. HRMS spectra of 4. This figure has been reproduced from ref. 36 with permission. Please click here to view a larger version of this figure.



PDA Ch1 254 nm

Peak#	Ret. Time	Area	Height	Area%	Conc.
1	6.537	5735334	642226	49.801	
2	10.616	3542736	256501	30.762	
3	11.655	2238390	144721	19.436	
Total		11516461	1043447	100	

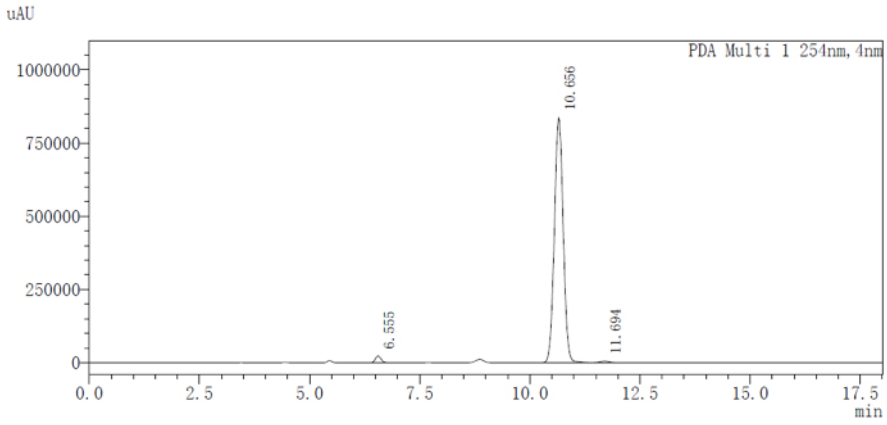
Figure 6. HPLC spectrum of a mixture of 2, 3, and 4 mixture as external standards (**2**: 9.58 mg; **3**: 19.29 mg; **4**: 11.10 mg). This figure has been reproduced from ref. 36 with permission. Please click here to view a larger version of this figure.



PDA Ch1 254 nm

Peak#	Ret. Time	Area	Height	Area%	Conc.
1	6.225	10666806	874559	100	
Total		10666806	874559	100	

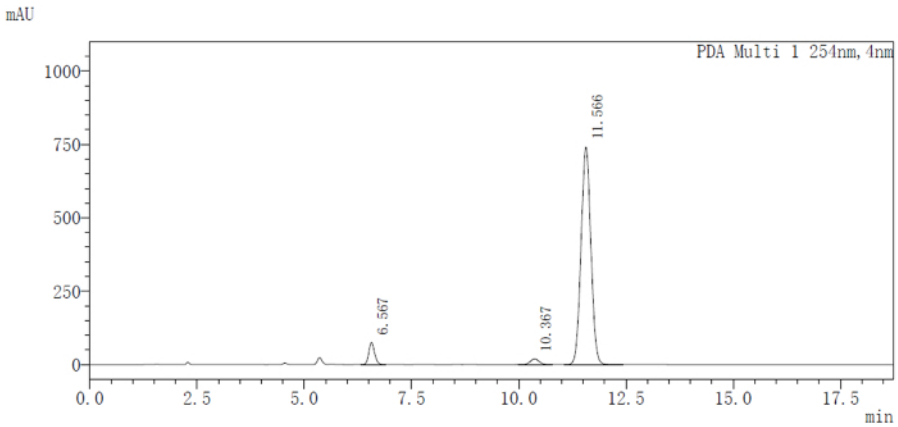
Figure 7. HPLC spectrum of 2, synthesized using the TBAI-PIDA system. This figure has been reproduced from ref. 36 with permission. Please click here to view a larger version of this figure.



PDA Ch1 254 nm

Peak#	Ret. Time	Area	Height	Area%	Conc.
1	6.555	207092	22880	1.734	
2	10.656	11672424	835942	97.725	
3	11.694	64630	4411	0.541	
Total		11944145	863233	100	

Figure 8. HPLC spectrum of 3, synthesized using the KI-PIDA system. This figure has been reproduced from ref. 36 with permission. Please click here to view a larger version of this figure.



PDA Ch1 254 nm

Peak#	Ret. Time	Area	Height	Area%	Conc.
1	6.567	707523	75389	5.542	
2	10.367	276206	19645	2.163	
3	11.566	11782974	740836	92.295	
Total		12766703	835870	100	

Figure 9. HPLC spectrum of 3, synthesized using a combination of the TBAI-PIDA and KI-PIDA systems in one pot. This figure has been reproduced from ref. 36 with permission. Please click here to view a larger version of this figure.

Discussion

1-Iodoalkynes, 1,2-diiodoalkenes, and 1,1,2-triiodoalkenes can be chemoselectively synthesized using hypervalent-iodine reagents as efficient mediators for oxidative iodination(s). The most critical factors of these chemoselective iodination protocols are the nature and loading of the iodine source, as well as the solvent. For example, 1-iodoalkyne **2** was obtained as the major product (52% yield) when TBAI (2.5 equiv loading) was selected as the iodine source in combination with MeOH as the solvent (**2:3:4=** 90:5:5). When changing the iodine source to KI, such a selectivity was not observed, whereas using NH_4I resulted in the predominant formation of 1,2-diiodoalkene **3**. The details of the optimization of the reaction conditions are documented elsewhere[36] (**Table 1**).

Several attempts were made to identify the optimal conditions for the formation of 1-iodoalkynes[36]. Firstly, the TBAB loading greatly affects the selectivity towards 1-iodoalkyne **2**. Lowering the TBAB loading from 2.5 to 1.2 equiv favors the formation of **2**. Secondly, the nature of the solvent strongly influences the formation of 1-iodoalkyne **2** in terms of selectivity and yield. For example, CH_3CN, Et_2O, THF, and DCM favor the

synthesis of **2** in terms of yield (excellent) and selectivity (absolute). DMF and toluene afford **2** in good yield, albeit with slightly lower selectivity. Notably, 1-iodoalkynes are most efficiently generated by treating the terminal alkyne (1.0 equiv) at room temperature for 2−24 h with PIDA (1.0 equiv) and TBAI (1.2 equiv) in CH_3CN, THF, or Et_2O.

Changing the solvent to a CH_3CN-H_2O mixture dramatically enhances the chemoselectivity towards 1,2-diiodoalkene **3**, when using KI as the iodine source. Optimal reaction conditions for the preparation of 1,2-diiodoalkenes were established as follows: treating the terminal alkyne (1.0 equiv) at room temperature for 2−24 h with PIDA (1.0 equiv) and KI (2.5 equiv) in MeCN-H_2O (1:3)[36].

A practical one-pot synthesis of 1,1,2-triiodoalkene **4** can be realized by combining the two aforementioned methods. Typically, terminal 4-ethynytoluene (1.0 equiv), PIDA (1.0 equiv), and TBAI (1.2 equiv) were stirred for 3 h at room temperature, followed by adding PIDA and an aqueous KI solution. Under these reaction conditions, 4-ethynytoluene was fully consumed; however, only 44% transformation was observed when 1.0 equiv of PIDA was using in the second step. Extending the reaction time did not increase the transformation. Therefore, the loading of PIDA (2.0 equiv) was increased in the second step to accelerate this transformation, leading to the formation of **4** in 88% yield as a major product. Interestingly, with an additional portion of PIDA and KI, a further increase of the yield of **4** (93%) was observed. Therefore, the reaction conditions for the synthetic method of **4** were optimized. (i) The terminal alkyne (1.0 equiv) was mixed with PIDA (1.0 equiv) and TBAI (1.2 equiv) for 3 h at room temperature in MeCN; (ii) after the addition of H_2O, PIDA (2.0 equiv), and KI (2.5 equiv), the reaction mixture was stirred for another 3 h; (iii) with the addition of H_2O, PIDA (2.0 equiv), and KI (2.5 equiv), the reaction mixture was stirred for another 12 h[36].

Herein, we have presented practical methods for the chemoselective preparation of 1-iodoalkynes, 1,2-diiodoalkenes, and 1,1,2-triiodoalkenes based on the hypervalent-iodine catalyzed iodination of terminal alkynes. These methods feature high chemoselectivity, good yield, low toxicity, mild reaction conditions, and broad scope. We expect that these new synthetic methods can be applied to the efficient and chemoselective synthesis of more iodoalkyne derivatives, materials, intermediates, and biologically active compounds.

Disclosures

The authors have nothing extraordinary to disclose.

Acknowledgements

This work was supported by the National Nature Science Foundation of China (21502023).

References

1. Sun, G. D., Wei, M. J., Luo, Z. H., Liu, Y. J., Chen, Z. J., Wang, Z. Q. An Alternative Scalable Process for the Synthesis of the Key Intermediate of Omarigliptin. *Organic Process Research & Development.* **20** (12), 2074-2079 (2016).
2. Wang, D., Chen, S., Chen, B. H. Green synthesis of 1,4-disubstituted 5-iodo-1,2,3-triazoles under neat conditions, and an efficient approach of construction of 1,4,5-trisubstituted 1,2,3-triazoles in one pot. *Tetrahedron Letters.* **55** (51), 7026-7028 (2014).
3. Chen, Z. W., Zeng, W., Jiang, H. F., Liu, L. X. Cu(II)-Catalyzed Synthesis of Naphthalene-1,3-diamine Derivatives from Haloalkynes and Amines. *Organic Letters.* **14** (21), 5385-5387 (2012).
4. Boutin, R. H., Rapoport, H. *α*-Amino acid derivatives as chiral educts for asymmetric products. Synthesis of sphingosine from *α'*-amino-*α,β*-ynones. *The Journal of Organic Chemistry.* **51** (26), 5320-5327 (1986).
5. Heravi, M. M., Asadi, S., Nazari, N., Lashkariani, B. M. Developments of Corey-Fuchs Reaction in Organic and Total Synthesis of Natural Products. *Current Organic Chemistry.* **19** (21), 2196-2219 (2015).
6. Vaidyanathan, G., McDougald, D., Koumarianou, E., Choi, J., Hens, M., Zalutsky, M. R. Synthesis and evaluation of 4-[^{18}F]fluoropropoxy-3-iodobenzylguanidine ([^{18}F]FPOIBG): A novel ^{18}F-labeled analogue of MIBG. *Nuclear Medicine and Biology.* **42** (8), 673-684 (2015).
7. Butini, S., Gemma, S., Brindisi, M., Borrelli, G., Lossani, A., Ponte, A. M., Torti, A., Maga, G., Marinelli, L., La Pietra, V., Fiorini, I., Lamponi, S., Campiani, G., Zisterer, D. M., Nathwani, S. M., Sartini, S., La Motta, C., Da Settimo, F., Novellino, E., Focher, F. Non-Nucleoside Inhibitors of Human Adenosine Kinase: Synthesis, Molecular Modeling, and Biological Studies. *Journal of Medicinal Chemistry.* **54** (5), 1401-1420 (2011).
8. Kabalka, G. W., Shoup, T. M., Daniel, G. B., Goodman, M. M. Synthesis and evaluation of a new series of 17 *α*-[^{123}I]iodovinyl estradiols. *Nuclear Medicine & Biology.* **27** (3), 279-287 (2000).
9. Lei, C. H., Jin, X. J., Zhou, J. R. Palladium-Catalyzed Alkynylation and Concomitant ortho Alkylation of Aryl Iodides. *ACS Catalysis.* **6**, 1635-1639 (2016).
10. Chen, W. W., Zhang, J. L., Wang, B., Zhao, Z. X., Wang, X. Y., Hu, Y. F. Tandem Synthesis of 3-Chloro-4-iodoisoxazoles from 1-Copper(I) Alkynes, Dichloroformaldoxime, and Molecular Iodine. *The Journal of Organic Chemistry.* **80** (4), 2413-2417 (2015).
11. Brotherton, W. S., Clark, R. J., Zhu, L. Synthesis of 5-Iodo-1,4-disubstituted-1,2,3-triazoles Mediated by in Situ Generated Copper(I) Catalyst and Electrophilic Triiodide Ion. *The Journal of Organic Chemistry.* **77** (15), 6443-6455 (2012).
12. Abe, H., Suzuki, H. Copper-Mediated Nucleophilic Displacement Reactions of 1-Haloalkynes. Halogen-Halogen Exchange and Sulfonylation. *Bulletin of the Chemical Society of Japan.* **72** (4), 787-798 (1999).
13. Yan, J., Li, J., Cheng, D. Novel and Efficient Synthesis of 1-Iodoalkynes. *Synlett.* **2007** (15), 2442-2444 (2007).
14. Ochiai, M., Uemura, K., Masaki, Y. *J. α-* versus *β*-Elimination of (*Z*)-(*α*-Halovinyl)iodonium Salts: Generation of *α*-Haloalkylidene Carbenes and Their Facile Intramolecular 1,2-Migration. *Journal of the American Chemical Society.* **115** (6), 2528-2529 (1993).
15. Nishiguchi, I., Kanbe, O., Itoh, K., Maekawa, H. Facile Iodination of Terminal Acetylenes by Anodic Oxidation in the Presence of NaI. *Cheminform.* **2000** (1), 89-91 (2000).
16. Nouzarian, M., Hosseinzadeh, R., Golchoubian, H. Ionic Liquid Iodinating Reagent for Mild and Efficient Iodination of Aromatic and Heteroaromatic Amines and Terminal Alkynes. *Synthetic Communications.* **43** (21), 2913-2925 (2013).

17. Mader, S., Molinari, L., Rudolph, M., Rominger, F., Hashmi, A. S. K. Dual Gold-Catalyzed Head-to-Tail Coupling of Iodoalkynes. *Chemistry-A European Journal.* **21** (10), 3910-3913 (2015).
18. Jiang, Q., Wang, J. Y., Guo, C. C. $(NH_4)_2S_2O_8$-Mediated Diiodination of Alkynes with Iodide in Water: Stereospecific Synthesis of (*E*)-Diiodoalkenes. *Synthesis.* **47** (14), 2081-2087 (2015).
19. Madabhushi, S., Jillella, R., Mallu, K. K. R., Godala, K. R., Vangipuram, V. S. A new and efficient method for the synthesis of *α,α*-dihaloketones by oxyhalogenation of alkynes using oxone®-KX (X=Cl, Br, or I). *Tetrahedron Letters.* **54** (30), 3993-3996 (2013).
20. Reddy, K. R., Venkateshwar, M., Maheswari, C. U., Kumar, P. S. Mild and efficient oxy-iodination of alkynes and phenols with potassium iodide and *tert*-butyl hydroperoxide. *Tetrahedron Letters.* **51**(16), 2170-2173 (2010).
21. Stefani, H. A., Cella, R., Dorr, F. A., de Pereira, C. M. P., Gomes, F. P., Zeni, G. Ultrasound-assisted synthesis of functionalized arylacetylenes. *Tetrahedron Letters.* **46** (12), 2001-2003 (2005).
22. Naskar, D., Roy, S. 1-Haloalkynes from Propiolic Acids: A Novel Catalytic Halodecarboxylation Protocol. *The Journal of Organic Chemistry.* **64** (18), 6896-6897 (1999).
23. Gómez-Herrera, A., Nahra, F., Brill, M., Nolan, S. P., Cazin, C. S. J. Sequential Functionalization of Alkynes and Alkenes Catalyzed by Gold(I) and Palladium(II) *N*-Heterocyclic Carbene Complexes. *ChemCatChem.* **8** (21), 3381-3388 (2016).
24. Wang, B., Zhang, J. L., Wang, X. Y., Liu, N., Chen, W. W., Hu, Y. F. Tandem Reaction of 1-Copper(I) Alkynes for the Synthesis of 1,4,5-Trisubstituted 5-Chloro-1,2,3-triazoles. *The Journal of Organic Chemistry.* **78** (20), 10519-10523 (2013).
25. Li, M., Li, Y., Zhao, B., Liang, F., Jin, L. Facile and efficient synthesis of 1-haloalkynes via DBU-mediated reaction of terminal alkynes and *N*-haloimides under mild conditions. *RSC Advances.* **4** (57), 30046-30049 (2014).
26. Pérez, J. M., Crosbie, P., Lal, S., Díez-González, S. Copper (I)-Phosphinite Complexes in Click Cycloadditions: Three-Component Reactions and Preparation of 5-Iodotriazoles. *ChemCatChem.* **8** (13), 2222-2226 (2016).
27. Wilkins, L. C., Lawson, J. R., Wieneke, P., Rominger, F., Hashmi, A. S. K., Hansmann, M. M., Melen, R. L. The Propargyl Rearrangement to Functionalised Allyl-Boron and Borocation Compounds. *Chemistry-A European Journal.* **22** (41), 14618-14624 (2016).
28. Usanov, D. L., Yamamoto, H. Enantioselective Alkynylation of Aldehydes with 1-Haloalkynes Catalyzed by Tethered Bis(8-quinolinato) Chromium Complex. *Journal of the American Chemical Society.* **133** (5), 1286-1289 (2011).
29. Luithle, J. E. A., Pietruszka, J. Synthesis of Enantiomerically Pure cis-Cyclopropylboronic Esters. *European Journal of Organic Chemistry.* **2000** (14), 2557-2562 (2000).
30. Blackmore, I. J., Boa, A. N., Murray, E. J., Dennis, M., Woodward, S. A simple preparation of iodoarenes, iodoalkenes and iodoalkynes by reaction of organolithiums with 2,2,2-trifluoro-1-iodoethane. *Tetrahedron Letters.* **40** (36), 6671-6672 (1999).
31. Lee, G. C. M., Tobias, B., Holmes, J. M., Harcourt, D. A., Garst, M. E. A new synthesis of substituted fulvenes. *Journal of the American Chemical Society.* **112** (25), 9330-9336 (1990).
32. Rao, M. L. N., Periasamy, M. A Simple Convenient Method for the Synthesis of 1-Iodoalkynes. *Synthetic Communications.* **25** (15), 2295-2299 (1995).
33. Zeiler, A., Ziegler, M. J., Rudolph, M., Rominger, F., Hashmi, A. S. K. Adv. Scope and Limitations of the Intermolecular Furan-Yne Cyclization. *Advanced Synthesis & Catalysis.* **357** (7), 1507-1514 (2015).
34. Dumele, O., Wu, D. N., Trapp, N., Goroff, N., Diederich, F. Halogen Bonding of (Iodoethynyl)benzene Derivatives in Solution. *Organic Letters.* **16** (18), 4722-4725 (2014).
35. Hashmi, A. S. K., Dopp, R., Lothschutz, C., Rudolph, M., Riedel, D., Rominger, F. Scope and Limitations of Palladium-Catalyzed Cross-Coupling Reactions with Organogold Compounds. *Advanced Synthesis & Catalysis.* **352** (8), 1307-1314 (2010).
36. Liu, Y., Huang, D., Huang, J., Maruoka, K. Hypervalent Iodine Mediated Chemoselective Iodination of Alkynes. *The Journal of Organic Chemistry.* **82** (22), 11865-11871 (2017).
37. Wang, X., Studer, A. Iodine (III) Reagents in Radical Chemistry. *Accounts of Chemical Research.* **50** (7), 1712-1724 (2017).
38. Yoshimura, A., Zhdankin, V. V. Advances in Synthetic Applications of Hypervalent Iodine Compounds. *Chemical Reviews.* **116** (5), 3328-3435 (2016).
39. Charpentier, J., Fruh, N., Togni, A. Electrophilic Trifluoromethylation by Use of Hypervalent Iodine Reagents. *Chemical Reviews.* **115**(2), 650-682 (2015).
40. Zhdankin, V. V., Protasiewicz, J. D. Development of new hypervalent iodine reagents with improved properties and reactivity by redirecting secondary bonds at iodine center. *Coordination Chemistry Reviews.* **275** (16), 54-62 (2014).
41. Stang, P. J., Zhdankin, V. V. Organic Polyvalent Iodine Compounds. *Chemical Reviews.* **96** (3), 1123-1178 (1996).
42. Kohlhepp, S. V., Gulder, T. Hypervalent iodine(III) fluorinations of alkenes and diazo compounds: new opportunities in fluorination chemistry. *Chemical Society Reviews.* **45** (22), 6270-6288 (2016).
43. Hein, J. E., Tripp, J. C., Krasnova, L. B., Sharpless, K. B., Fokin, V. V. Copper(I)-Catalyzed Cycloaddition of Organic Azides and 1-Iodoalkynes. *Angewandte Chemie International Edition.* **48** (43), 8018-8021 (2009).

