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Regio- and stereoselective synthesis of (*E*)-1-bromo-2-iodoalkenes through iodobromination of internal alkynes

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ABSTRACT

One-step synthesis of (*E*)-1-bromo-2-iodoalkenes from internal alkynes through IBr addition is described. The IBr was generated in situ from commercially available TMSBr and NIS. This simple protocol enables highly efficient regio- and stereoselective iodobromination of the triple bond on a gram scale in *anti*-mode, and provides a potentially diverse scaffold for preparation of differentially all-carbon tetrasubstituted olefins.

1. Introduction

Tetrasubstituted olefins bearing four different carbon-linked groups have played an important role in organic chemistry,[1] because of their ability to serve as pharmaceuticals,[2] bioactive molecules,[3] and potentially therapeutic compounds.[4] They have also been found as substructure in organic material science, for example, molecular switches,[5] optical devices,[6] and macromolecular architecture.[7] Moreover, the olefins have been employed as key building blocks for producing adjacent chiral-carbon centers through face-selective addition reactions.[8] Despite the utility of the differentially all-carbon tetrasubstituted alkenes, their synthetic availability remains a challenge owing to difficulty in geometrically defined olefin synthesis. The endocyclic version having distinct geometry are somewhat achievable by way of several protocols, for example, carbonyl olefination,[9] elimination reaction,[10] olefin metathesis,[11] and cycloaddition.[12] However, for the single formation of acyclic version, those protocols encounter problem of low stereochemical control. Even the carbometallation, a most widely used for preparation of polysubstituted alkenes,[13] requires a directing group to control the stereoselectivity, which has limited utilities for unsymmetrically internal alkyne substrates. This drawback causes poor generality concerning substrate tolerance, metal option, and a diversity of products on the reaction.[14]

Given these limitations of typical procedures, methods employing differentially substituted olefin templates have turned out to be potent strategy for synthesis of tetrasubstituted olefins bearing four different carbon-linked groups.[1] Two outstanding achievements were reported by Ferreira in 2013[15] and Ogilvie in 2006[16] (Scheme 1). Ferreira group developed *trans*-selective halosilylation of unsymmetrical alkynes, and the halosilylated template was transformed into the acyclic olefins. Ogilvie group found the *trans*-selective iodochlorination, and the resultant template was derived to the cross-coupling adducts. Noteworthy is that both strategies adopt simple metal-free access to the templates and the single isomeric templates warrant the geometry of the tetrasubstituted olefins. As other template approaches, carbolithiation of trifluoromethyl enolethers,[17] and successive cross-coupling of vinyl-2-pyrimidilsulfide precursors,[18] copper-catalyzed carbotrifluation of unsymmetrical alkynes,[19] were performed. However, one of the most straightforward ways shown in Scheme 2 is still difficult: an addition reaction of molecular hetero-dihalogen such as IBr to the alkynes gives four possible iodobrominated templates, and lack of the auxiliary groups for stereo-control results in formidable mixtures of products and low yields.[20a,b] Moreover, iodination is frequently more difficult than bromination and chlorination, because the reaction proceeds slowly and is often reversible under standard conditions.[20c,d,e] Actually, even metal-assisted and ionic liquid-promoted iodination-protocols were limited to narrow scope of substrate generality and reaction efficacy.[20f,g,h]

On the other hand, we recently reported regio- and stereoselective iodobromination of ynamides for synthesis of (*E*)-1-

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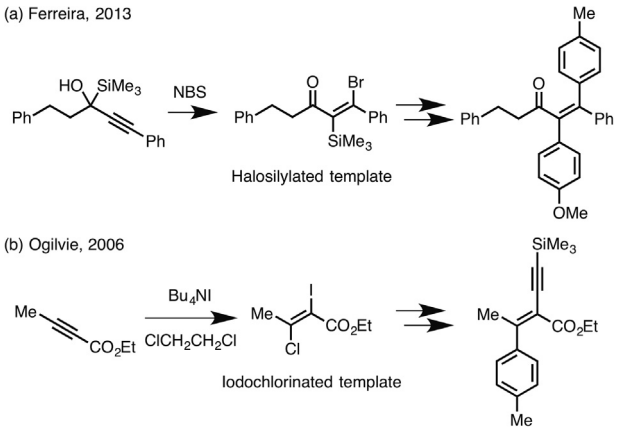
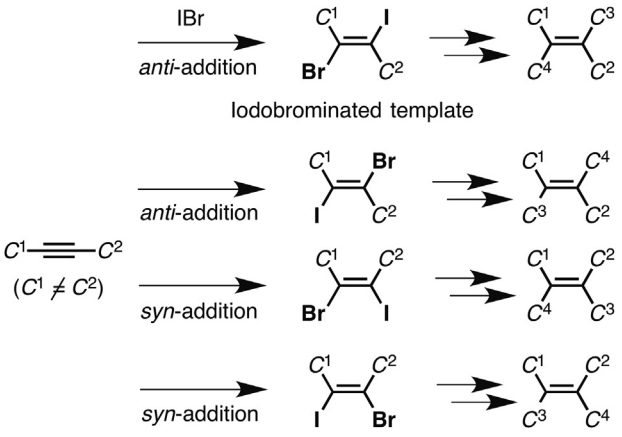


Scheme 1. Differentially substituted olefin template strategy.



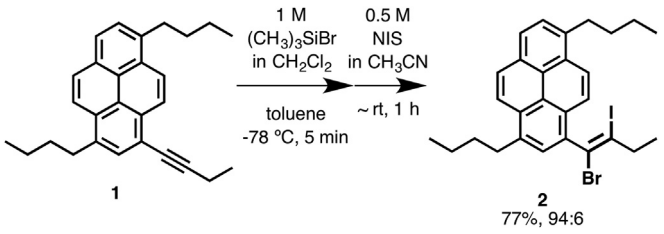
Scheme 2. Iodobromination of internal alkynes for dihalogen templates, and the access to tetrasubstituted olefins bearing four different carbon-linked groups.

bromo-2-iodo-enamides in gram-scale using in situ generated IBr.[21] The IBr was generated from mixing of 1 M bromotrimethylsilane (TMSBr) in CH_2Cl_2 and 0.5 M *N*-iodosuccinimide (NIS) in acetonitrile, and added to ynamides with high regio- and stereoselectivity: the single isomeric adducts were formed as good candidates for multi-substituted olefins.

In this paper, we present a synthesis of vicinal bromoiodoalkenes from internal alkynes in a highly regio- and stereoselective manner, which would favor one of four possible pathways in Scheme 2. The in situ generated IBr underwent the addition reaction to conventional aliphatic alkynes having no heteroatoms for control, although commercially available IBr didn't work well even when used in diethyl ether solution.[21] The reaction completed in 1 h under mild condition, and was readily amenable to gram-scale. Thus, the method provides a general entry for (*E*)-1-bromo-2-iodoalkenes that can be a diverse scaffold for differentially all-carbon tetrasubstituted olefins.

2. Results and discussion

Initially, we commenced our investigations with the reactions previously reported for the TMSBr/NIS combination-mediated iodobromination (Scheme 3).[21] The mixture of **1** and TMSBr (1 M) in CH_2Cl_2 was stirred at −78 °C for 5 min,[22] then NIS (0.5 M) in acetonitrile was added, and the reaction was conducted at room temperature. The starting **1** disappeared right after addition of NIS, and virtually single spot was observed on TLC monitoring. Fortunately, for the crude mixture, ^{1}H NMR spectroscopic analysis revealed a 94:6 isomeric ratio. Workup and purification with



Scheme 3. Regio- and stereoselective iodobromination of **1** to synthesize **2**.

column chromatography gave corresponding IBr adduct **2** of 443 mg in 77% yields with the almost same 94:6 ratio. The molecular structure of **2** was determined by crystallographic analysis as shown in Fig. 1,[23] disclosing its stereochemistry as a (*E*)-1-bromo-2-iodovinyl adduct.

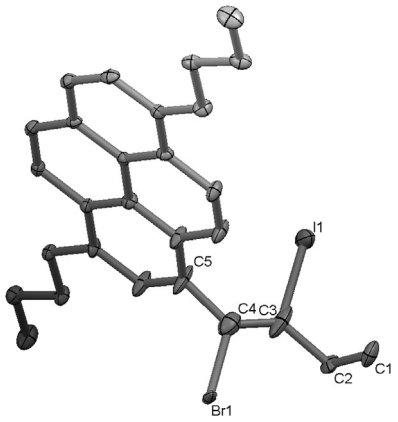
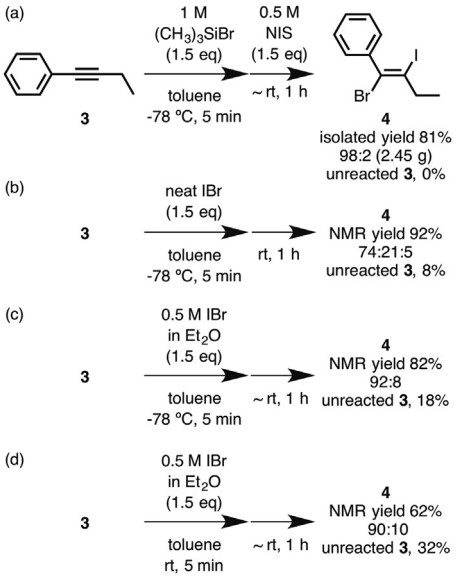


Fig. 1. ORTEP drawing of **2** with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): C(2)–C(3)=1.507, C(3)–I(1)=2.168, C(3)–C(4)=1.267, C(4)–Br(1)=1.905, C(4)–C(5)=1.501.

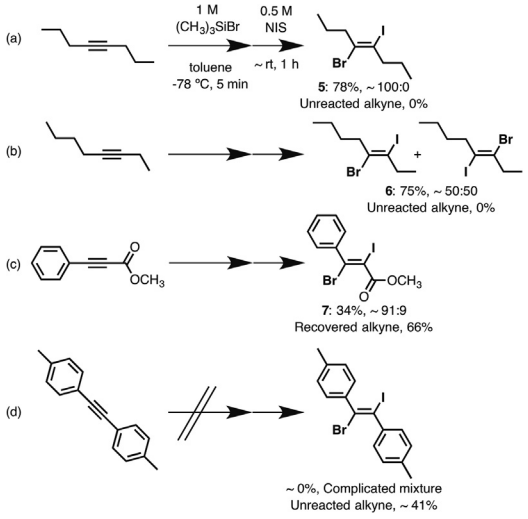
To clarify the reactivity of triple bonds with IBr, a simple of 1-phenyl-1-butyne **3** was tested (Scheme 4). For a, the in situ IBr successfully completed the addition reaction, providing 2.45 g of **4** in 81% yield with a 98:2 isomeric ratio. On the other hand, for b, commercially available IBr (neat sample)[24] resulted in a 74:21:5 isomeric ratio through possible three reaction path. For c, IBr in diethyl ether improved the ratio and lowered the yield compared with those of b. For d, when IBr in diethyl ether acted at room temperature, tremendous amounts of unreacted **3** were observed. Unfortunately, for b–d, R_f values of **3** and **4** on TLC analyzing were too close to separate them in pure forms. Thus, the in situ IBr proved to be more practical than the bulk: **4** with a 98:2 ratio has the potential to assemble different carbon-linked groups into the double bond accurately.

As summarized in Scheme 5, screening of substituents bonded to the triple bond was conducted on the in situ IBr-mediated iodobromination. For a, a symmetrical alkyne of 4-octyne undertook smooth halogenation to yield **5** in 78% as a single isomer; however, for b, unsymmetrical 3-octyne resulted in mixtures with a 50:50 isomeric ratio. For c,[25] **7** was successfully isolated in 34% yield with a 91:9 isomeric ratio although unreacted methyl 3-phenylpropiolate was recovered in 66%.[26] For d, mysteriously, 1,2-di-*p*-tolylethyne ended up in complicated mixtures including 41% of unreacted starting alkyne and no desired adduct: neither did 1,2-diphenylethyne.[27] These mean alkyl substituents is necessary for completing the reaction and 1-aryl-2-alkylethyne is relatively good substrate for outputting high regioselectivity.

With a workable protocol in hand, we studied the substrate scope for the iodobromination of 1-aryl-2-alkylethyne (Table 1).



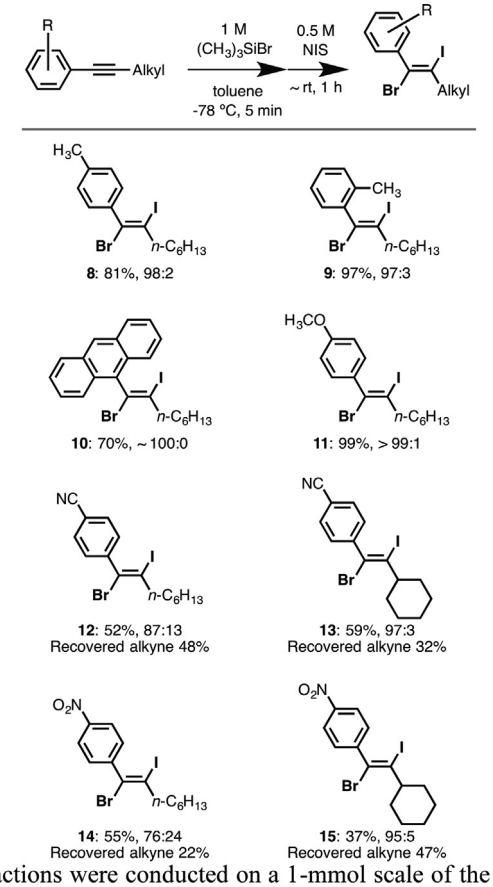
Scheme 4. Iodobromination of 1-phenyl-1-butyne with the in situ and commercially available IBr.



Scheme 5. Screening of substituents bonded to the triple bonds.

The long C_6H_{13}-chained **8** was given with a high 98:2 isomeric ratio in 81% yield. The sterically encumbered **9** with *ortho*-tolyl group and **10** with 9-anthryl group was smoothly yielded in 97% with a 97:3 isomeric ratio and 70% as a single isomer, respectively. For **11**, the attachment of the electron-donating methoxy group was no problem for obtaining the well-defined alkene geometry. On the other hand, unfortunately, syntheses of nitrile **12** and **13**, and nitro **14** and **15** were accompanied by numerous amounts of the starting alkynes. Laborious purification by silica-gel column chromatography isolated the IBr adducts from the starting alkynes in 37–59% yields. Interestingly, there was difference in isomeric ratios between the cyclohexyl and normal-hexyl compounds: 97:3 of **13** and 95:5 of **15** were achieved as more effective ratios compared to 87:13 of **12** and 76:24 of **14**. This indicates that anionic Br would recognize the difference of bulkiness between the cyclohexyl and normal hexyl group, and the following addition of Br to the triple bonds preferentially occurred at the carbon bonded to aromatic rings. Thus, minor isomers in this reaction system would be (*E*)-form of regio-isomers, in which the position of Br interchanges with that of I on major products.

Table 1
Substrate scope[a]

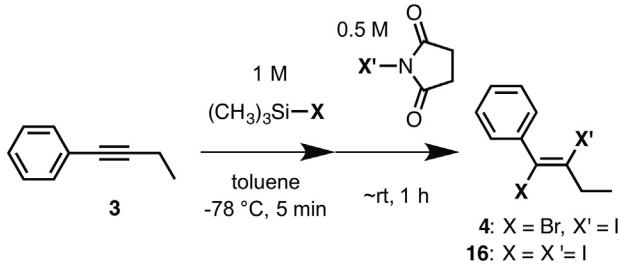


[a] Reactions were conducted on a 1-mmol scale of the alkynes, and yields are for isolated compounds. The isomeric ratios were determined by ^{1}H NMR spectra.

Different patterns of *N*-halosuccinimide/halotrimethylsilane were tested on 1-phenyl-1-butyne, and the results are summarized in Table 2. Interestingly, entry 2 shows a 76% yield and an 87:13 ratio of **4**, which is similar to the record resulting from entry 4 of an 81% yield and a 98:2 ratio. This means both combination of TMSI/NBS and TMSBr/NIS generate in situ IBr, which differ in degree but not in kind, and each in situ IBr has intrinsically similar reactivity to commercial IBr used in Scheme b–d. The generative efficiency of IBr charged with δ^+ of I and δ^- of Br was better compatibility with entry 4 than entry 2. The use of TMSI and NIS at entry 1 didn't consume all the starting **3**, and afforded **16** in 26% yield as a single isomer. For entries 3 and 7, TMSI/NCS and TMSCl/NIS gave only **16** in low yields, in which the chloride atom was not installed. For entries 5, 6, 8, and 9, the starting **3** disappeared on TLC monitoring; however, the resultant crude products formed from messy unknown side-products. Thus, practically, a worthwhile selective-halogenation is observed only in the combination of TMSBr/NIS. The product distribution seems to be affected by the polarized iodide, that is, readily produced by NIS compared to TMSI. The polarized I with δ^+ would activate the alkyne to form triangle iodonium cation, and the triangle cation undertook an addition reaction of anionic bromide at the benzylic carbon in *anti*-mode. For NBS and NCS, the alkyne activation by cationic bromide and chloride is more difficult than NIS, and the reagents didn't have control of the halogenation reaction.

To establish the utility of the vicinal iodobrominated adduct as a differentially substituted olefin template, the IBr-adduct **4** was subjected to conventional transformations using palladium-

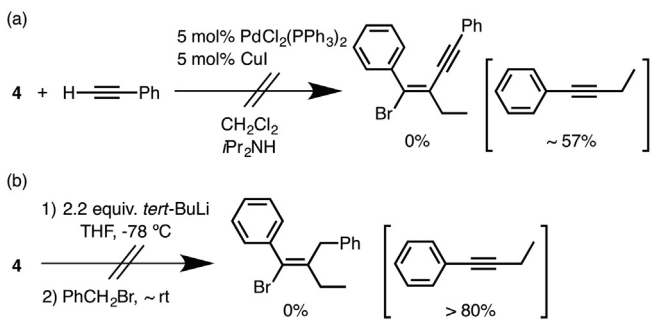
Table 2
Screening of halogen sources[a]



Entry	X/X′	Product	Yield [%][b]	Isomeric ratio	Recovered **3** [%]
1	I/I	**16**	26 (40[c])	~100:0	60
2	I/Br	**4**	76	87:13	19[c]
3	I/Cl	**16**	24	~100:0	32[c]
4	Br/I	**4**	81	98:2	0
5[d]	Br/Br	—	—	—	0
6[d]	Br/Cl	—	—	—	0
7	Cl/I	**16**	30[c]	~100:0	11[c]
8[d]	Cl/Br	—	—	—	0
9[d]	Cl/Cl	—	—	—	0

[a] Reaction conditions: **3** (130 mg, 1 mmol), toluene (4 mL), TMSX (1 M) in dichloromethane, NX′S (0.5 M) in acetonitrile.
[b] Isolated yields.
[c] NMR yields.
[d] Although the starting **3** disappeared on TLC, complex mixtures were produced in the crude state.

catalyzed cross-coupling[28] and lithium–halogen exchange reactions[29] (Scheme 6). Straightforwardly, the iodine-selective conversion was aimed; however, unfortunately, trials were unworkable. Although the consumption of the starting **4** was observed on palladium-mediated reaction conditions, many unknown by-products were generated along with 1-phenyl-1-butyne. In particular, for Scheme 6a, Sonogashira reaction strangely put back **4** to numerous 57% of 1-phenyl-1-butyne.[30,31] For Scheme 6b, the employment of *tert*-BuLi also resulted in 80% conversion of **4** into 1-phenyl-1-butyne. The Ferreira's template of (*E*)-1-silyl-2-iodoalkenes, and the Ogilvie's template of (*E*)-1-chloro-2-iodoalkenes, they have big difference in reactivity between Si and I, or Cl and I, and so would be successfully lead to the cross-coupling adducts. In our case, the reactivity between Br and I has close analogy, and the palladium catalyzed-protocols are as yet unworkable on the selective approach. In addition, the weak bonding of C–I and C–Br in (*E*)-1-bromo-2-iodoalkenes seems to be readily cleavable, giving the corresponding alkyne. Thus, a general method for utilizing the (*E*)-1-bromo-2-iodoalkenes as a differentially substituted olefin template is strongly desired, and development of the method is focused in our group. On the other hand, from the viewpoint of vinyl halides, halo-olefins have been found as substructures in bioactive natural products and pharmaceutically interesting compounds.[32] So, the bis-halogenated olefins in this paper might be worth constructing bioactive compounds and potential therapeutics.



Scheme 6. Attempt at reacting on iodide-site of **4**.

3. Conclusion

In summary, a convenient and practical route to (*E*)-1-bromo-2-iodoalkenes from the simple internal alkynes in remarkable yields with notable regio- and stereoselectivity was described. The significant key was an exact addition of the in situ generated IBr to the triple bond: the IBr produced from TMSBr and NIS was more effective than commercially bulk IBr. Attempts at employing nine combinations of TMSX/NX′S revealed the eight entries except TMSBr/NIS were substantially unworkable: the underlying clue would be attributable to a well-matching pair of anionic Br from TMSBr and cationic iodide from NIS. Although the C=C double bond appended to iodide and bromide is an excellent candidate as a differentially substituted olefin template, we don't yet find a procedure for preparation of all-carbon tetrasubstituted alkenes. Application of this iodobromination-methodology to synthesizing differentially all-carbon tetrasubstituted olefins such as (*Z*)-tamoxifen analogues is ongoing and will be reported in due course.

4. Experimental section

4.1. General

All reactions sensitive to air or moisture were carried out under an argon atmosphere and anhydrous conditions unless otherwise noted. Dry solvents were purchased and used without further purification and dehydration. All reagents were purchased and used without further purification. Analytical thin layer chromatography was carried out on Merck silica 60F_{254}. Column chromatography was carried out with silica gel 60N (Kanto Chemical Co.). HRMS were reported on the basis of TOF (time of flight)-MS, and EB (double-focusing)-MS. ^{1}H and ^{13}C NMR spectra were recorded with a 5 mm QNP probe at 400 MHz and 100 MHz, respectively. Chemical shifts are reported relative to residual solvent signals [^{1}H NMR: $CHCl_3$ (7.26 ppm); ^{13}C NMR: $CDCl_3$ (77.0 ppm)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

4.2. Preparation of 1 M halotrimethylsilane (TMSX) stock solution in dichloromethane

TMSBr (3.5 g) was added to dry dichloromethane (20 mL), TMSI (5 g) was added to dry dichloromethane (25 mL), and TMSCl (2.6 g) was added to dry dichloromethane (21 mL); each was used as a 1 M TMSX solution for our experimental usage. The reactivity of the freshly prepared TMSX solution was maintained at least for two weeks. However, in the case of 1 M toluene solution of TMSX, unfortunately, complete decomposition by ^{1}H NMR was spectroscopy was observed only in 24 h.

4.3. General procedure of (*E*)-3-(1-bromo-2-iodobut-1-en-1-yl)-1,6-dibutylpyrene 2, for Scheme 3

Under an argon atmosphere, to a solution of **1** (366 mg, 1.0 mmol) in anhydrous toluene (4 mL) at −78 °C was added TMSBr (1.5 mL of 1 M in dichloromethane) dropwise over 5 min, and the mixture was stirred for 5 min. Then, NIS (337 mg, 1.5 mmol) in acetonitrile was slowly added over 5 min, and the cooling-bath was removed to warm to room temperature. After additional stirring for 1 h, the reaction was quenched at 0 °C with saturated aqueous sodium thiosulfate, and stirred for 10 min, and warmed to ambient temperature. The aqueous phase was extracted with toluene (15 mL×3), and the combined organic phases were washed with brine (30 mL), and then dried with sodium sulfate, and concentrated to give 589 mg of crude products. Purification by silica gel

column chromatography (eluent: hexane) afforded 443 mg of **2** in 77% yield as a yellow solid material. Analytical data are listed in the section below.

*4.3.1. 3-(But-1-yn-1-yl)-1,6-dibutylpyrene (**1**).*[33,34] 68% yield (730 mg); a yellow solid; mp: 94.5–95.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.57 (d, *J*=9.4 Hz, 1H), 8.29 (d, *J*=9.4 Hz, 1H), 8.17 (d, *J*=9.2 Hz, 1H), 8.07 (d, *J*=9.2 Hz, 1H), 8.03 (d, *J*=9.4 Hz, 1H), 7.95 (s, 1H), 7.85 (d, *J*=9.4 Hz, 1H), 3.34 (t, *J*=7.8 Hz, 2H), 3.28 (t, *J*=7.8 Hz, 2H), 2.67 (q, *J*=7.5 Hz, 2H), 1.88–1.79 (m, 4H), 1.54–1.48 (m, 4H), 1.42 (t, *J*=7.5 Hz, 3H), 1.00 (t, *J*=7.4 Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 137.7, 136.6, 130.9, 130.6, 129.9, 129.1, 129.0, 127.9, 127.6, 125.7 (two peaks are overlapped), 125.5, 125.1, 123.4, 122.6, 118.3, 97.3, 79.6, 34.3, 34.1, 33.7, 33.5, 23.2, 23.1, 14.6, 14.4 (two peaks are overlapped), 14.0 ppm; MS (FAB) *m*/*z*: 366 (M^+); IR (neat): 3043, 2954, 2926, 2854, 2219, 1602, 1498, 1462 cm^{-1}; Anal. Calcd for $C_{28}H_{30}$: C, 91.75; H, 8.25. Found: C, 91.74; H, 8.32.

*4.3.2. (E)-3-(1-Bromo-2-iodobut-1-en-1-yl)-1,6-dibutylpyrene (**2**).* 77% yield (94:6, 215 mg); a yellow solid; mp: 109.7–110.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.34 (d, *J*=9.4 Hz, 1H), 8.21 (d, *J*=9.2 Hz, 1H), 8.12–8.07 (m, 3H), 7.86 (d, *J*=9.4 Hz, 1H), 7.72 (s, 1H), 3.41–3.26 (m, 4H), 3.14 (dq, *J*=7.3, 7.3 Hz, 1H), 3.02 (dq, *J*=7.3, 7.3 Hz, 1H), 1.85 (tt, *J*=7.6, 7.6 Hz, 2H), 1.84 (tt, *J*=7.6, 7.6 Hz, 2H), 1.56–1.46 (m, 4H), 1.37 (t, *J*=7.3 Hz, 3H), 1.01 (t, *J*=7.3 Hz, 3H), 1.00 (t, *J*=7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 138.1, 137.7, 137.3, 129.9 (two peaks are overlapped), 129.1, 128.3, 128.1, 127.9, 126.1, 126.0, 125.9, 125.4, 124.2, 123.9, 122.7, 116.8, 107.1, 39.3, 34.4, 34.0, 33.8, 33.7, 23.3, 23.1, 14.4, 14.3, 13.6 ppm; MS (FAB) *m*/*z*: 572 (M^+); IR (neat): 3044, 2948, 2925, 2852, 1603, 1499, 1463, 1368 cm^{-1}; Anal. Calcd for $C_{28}H_{30}BrI$: C, 58.66; H, 5.27. Found: C, 58.53; H, 5.40.

*4.3.3. (E)-(1-Bromo-2-iodobut-1-en-1-yl)benzene (**4**).* 81% yield (98:2, 2.45 g); a pale red oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.39–7.29 (m, 5H), 2.87 (q, *J*=7.4 Hz, 2H), 1.19 (t, *J*=7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 144.1, 129.4, 128.9, 128.6, 117.1, 103.9, 39.6, 13.3 ppm; MS (EI) *m*/*z*: 336 (M^+), 257 ($[M-Br]^+$); IR (neat): 3054, 2969, 2930, 2871, 1593, 1487, 1455, 1441 cm^{-1}; Anal. Calcd for $C_{10}H_{10}BrI$: C, 35.64; H, 2.99. Found: C, 35.66; H, 2.79; HRMS (DI) calcd for $C_{10}H_{10}BrI$: 335.9011, found 335.9029.

*4.3.4. (E)-4-Bromo-5-iodooct-4-ene (**5**).* 78% yield (~100:0, 246 mg); a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 2.07 (t, *J*=7.3 Hz, 2H), 2.68 (t, *J*=7.3 Hz, 2H), 1.63 (tq, *J*=7.3, 7.3 Hz, 2H), 1.58 (tq, *J*=7.3, 7.3 Hz, 2H), 0.96 (t, *J*=7.3 Hz, 3H), 0.94 (t, *J*=7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 130.0, 100.2, 47.8, 47.2, 22.0, 21.3, 13.3, 13.2 ppm; IR (neat): 2959, 2928, 2871, 1620, 1456, 1379, 1340, 862, 773, 742 cm^{-1}; MS (EI) *m*/*z*: 316 (M^+); Anal. Calcd for $C_8H_{14}BrI$: C, 30.31; H, 4.45. Found: C, 30.31; H, 4.35; HRMS (DI) Calcd for $C_8H_{14}BrI$: 315.9324, found 315.9336.

*4.3.5. (E)-4-Bromo-3-iodooct-3-ene, and (E)-3-bromo-4-iodooct-3-ene (**6**).* 75% yield (50:50, 238 mg); a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 2.76–2.64 (m, 4H), 1.60–1.48 (m, 2H), 1.41–1.30 (m, 2H), 1.12–1.04 (m, 3H), 0.96–0.92 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 124.1, 122.4, 101.3, 99.3, 45.8, 45.1, 40.2, 39.7, 30.7, 30.0, 22.0, 21.9, 14.4, 13.1, 12.5 ppm; MS (EI) *m*/*z*: 316 (M^+); IR (neat): 2956, 2927, 2871, 1622, 1455, 1431, 1080 cm^{-1}; HRMS (DI) calcd for $C_8H_{14}BrI$: 315.9324, found 315.9325.

*4.3.6. Methyl (E)-3-bromo-2-iodo-3-phenylacrylate (**7**).* 57% yield (90:10, 234 mg); a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.44–7.38 (m, 5H), 3.96 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 166.4, 140.8, 130.0, 128.9, 128.8, 123.4, 81.9, 53.7 ppm; MS (EI) *m*/*z*: 366 ($[MH]^+$), 287 ($[MH-Br]^+$); IR (neat): 2950, 1725, 1590, 1442, 1432, 1240, 1204 cm^{-1}; HRMS (DI) calcd for $C_{10}H_8BrIO_2$: 365.8752, found 365.8779.

*4.3.7. (E)-1-(1-Bromo-2-iodooct-1-en-1-yl)-4-methylbenzene (**8**).* 98% yield (~100:0, 200 mg); a pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.22 (d, *J*=8.6 Hz, 2H), 7.17 (d, *J*=8.6 Hz, 2H), 2.83 (t, *J*=7.4 Hz, 2H), 2.36 (s, 3H), 1.65 (tt, *J*=7.4, 7.4 Hz, 2H), 1.44–1.34 (m, 6H), 0.92 (t, *J*=7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 141.5, 138.8, 129.34, 129.30, 117.9, 102.5, 45.6, 32.0, 28.6, 28.4, 21.7, 14.4 ppm; MS (EI) *m*/*z*: 406 (M^+); IR (neat): 2923, 1606, 1505, 1454, 1180, 1110 cm^{-1}; HRMS (DI) calcd for $C_{15}H_{20}BrI$: 405.9793, found 405.9779.

*4.3.8. (E)-1-(1-Bromo-2-iodooct-1-en-1-yl)-2-methylbenzene (**9**).* 97% yield (97:3, 395 mg); a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.28–7.20 (m, 3H), 7.11 (d, *J*=7.7 Hz, 1H), 2.89 (dt, *J*=7.5, 7.5 Hz, 1H), 2.76 (dt, *J*=7.5, 7.5 Hz, 1H), 2.27 (s, 3H), 1.67 (tt, *J*=7.5, 7.5 Hz, 2H), 1.45–1.35 (m, 6H), 0.93 (t, *J*=10.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 143.8, 135.6, 130.7, 129.2, 129.1, 126.5, 117.8, 104.4, 44.5, 32.0, 28.7, 28.4, 23.0, 19.6, 14.5 ppm; MS (FAB) *m*/*z*: 406 (M^+); IR (neat): 3065, 3023, 2952, 2924, 2855, 1599, 1455, 1377 cm^{-1}; Anal. Calcd for $C_{15}H_{20}BrI$: C, 44.25; H, 4.95. Found: C, 44.49; H, 4.76.

*4.3.9. (E)-9-(1-Bromo-2-iodooct-1-en-1-yl)anthracene (**10**).* 70% yield (~100:0, 346 mg); yellow needles; mp: 128.9–129.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.55 (s, 1H), 8.06–8.04 (m, 2H), 7.62–7.48 (m, 4H), 3.11 (t, *J*=7.4 Hz, 2H), 1.91–1.84 (m, 2H), 1.65–1.41 (m, 6H), 1.00 (t, *J*=7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 136.9, 132.0, 129.1, 128.6, 128.1, 127.0, 126.0, 125.5, 115.5, 108.3, 44.9, 32.0, 29.1, 28.8, 23.0, 14.5 ppm; IR (neat): 3057, 2925, 2854, 1621, 1519, 1466, 1440 cm^{-1}; MS (FAB) *m*/*z*: 493 (M^+); Anal. Calcd for $C_{22}H_{22}BrI$: C, 53.57; H, 4.50. Found: C, 53.41; H, 4.31.

*4.3.10. (E)-1-(1-Bromo-2-iodooct-1-en-1-yl)-4-methoxybenzene (**11**).* 99% yield (>99:1, 420 mg); a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.24 (d, *J*=8.8 Hz, 2H), 6.88 (d, *J*=8.8 Hz, 2H), 3.83 (s, 3H), 2.82 (t, *J*=7.4 Hz, 2H), 1.65 (tt, *J*=7.4, 7.4 Hz, 2H), 1.44–1.33 (m, 6H), 0.92 (t, *J*=6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 159.8, 136.7, 130.9, 117.9, 113.9, 102.6, 55.5, 45.6, 31.9, 28.6, 28.4, 22.9, 14.4 ppm; MS (FAB) *m*/*z*: 422 (MH^+); IR (neat): 2952, 2924, 2854, 1602, 1505, 1462, 1291, 1247 cm^{-1}; Anal. Calcd for $C_{15}H_{20}BrIO$: C, 42.58; H, 4.76. Found: C, 42.68; H, 4.60.

*4.3.11. (E)-4-(1-Bromo-2-iodooct-1-en-1-yl)benzonitrile (**12**).* 52% yield (87:13, 216 mg); a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.67 (d, *J*=8.5 Hz, 2H), 7.40 (d, *J*=8.5 Hz, 2H), 2.84 (t, *J*=7.6 Hz, 2H), 1.65 (tt, *J*=7.6, 7.6 Hz, 2H), 1.44–1.35 (m, 6H), 0.92 (t, *J*=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 148.3, 132.5, 130.3, 118.5, 114.9, 112.6, 104.4, 45.3, 31.8, 28.5, 28.3, 22.8, 14.4 ppm; MS (FAB) *m*/*z*: 418 ($[MH]^+$); IR (neat): 2925, 2854, 2228, 1601, 1496, 1455, 1402, 1107, 831 cm^{-1}; Anal. Calcd for $C_{15}H_{17}BrIN$: C, 43.09; H, 4.10; N, 3.35. Found: C, 43.11; H, 4.15; N, 3.28.

*4.3.12. (E)-4-(1-Bromo-2-cyclohexyl-2-iodovinyl)benzonitrile (**13**).* 59% yield (97:3, 78 mg); a white solid; mp: 138.4–140.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.67 (d, *J*=8.6 Hz, 2H), 7.36 (d, *J*=8.6 Hz, 2H), 2.53–2.47 (m, 1H), 1.87–1.67 (m, 5H), 1.52–1.39 (m, 4H), 1.27–1.18 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 148.7, 132.7, 130.5, 118.7, 115.1, 112.6, 112.5, 48.4, 33.1, 25.8, 25.8 ppm; MS (FAB) *m*/*z*: 416 ($[MH]^+$); IR (neat): 2924, 2849, 2230, 1598, 1496, 1448, 1268, 1207 cm^{-1}; Anal. Calcd for $C_{15}H_{15}BrIN$: C, 43.30; H, 3.63; N, 3.37. Found: C, 43.23; H, 3.58; N, 3.36.

*4.3.13. (E)-1-(1-Bromo-2-iodooct-1-en-1-yl)-4-nitrobenzene (**14**).* 55% yield (76:24, 245 mg); a yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 8.24 (d, *J*=8.8 Hz, 2H), 7.46 (d, *J*=8.8 Hz, 2H), 2.85 (t, *J*=7.5 Hz,

2H), 1.67 (tt, J=7.5, 7.5 Hz, 2H), 1.45–1.34 (m, 6H), 0.93 (t, J=7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 150.2, 147.7, 130.7, 124.3, 114.5, 104.8, 45.3, 31.9, 28.6, 28.4, 22.9, 14.4 ppm; MS (FAB) m/z: 437 (M^+); IR (neat): 3108, 3077, 2925, 2854, 1601, 1519, 1488, 1456, 1342 cm^{-1}; Anal. Calcd for $C_{14}H_{17}BrINO_2$: C, 38.38; H, 3.91; N, 3.20. Found: C, 38.26; H, 3.91; N, 3.20.

*4.3.14. (E)-1-(1-Bromo-2-cyclohexyl-2-iodovinyl)-4-nitrobenzene (**15**).* 37% yield (95:5, 161 mg); yellowish white needles; mp: 119.5–120.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.22 (d, J=8.8 Hz, 2H), 7.42 (d, J=8.8 Hz, 2H), 2.54–2.48 (m, 1H), 1.86–1.83 (m, 2H), 1.75–1.68 (m, 3H), 1.54–1.39 (m, 4H), 1.27–1.20 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 150.5, 147.6, 130.8, 124.2, 115.3, 112.1, 48.4, 33.1, 25.8, 25.7 ppm; MS (FAB) m/z: 435 (M^+); IR (neat) 2925, 2850, 1600, 1517, 1442, 1341 cm^{-1}; Anal. Calcd for $C_{14}H_{15}BrINO_2$: C, 38.56; H, 3.47; N, 3.21. Found: C, 38.64; H, 3.34; N, 3.14.

*4.3.15. (E)-(1,2-Diiodobut-1-en-1-yl)benzene (**16**).* 26% yield (~100:0, 305 mg); a whitish orange solid; mp: 49.0–50.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.37–7.33 (m, 2H), 7.30–7.26 (m, 1H), 7.22–7.20 (m, 2H), 2.88 (q, J=7.4 Hz, 2H), 1.18 (t, J=7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 148.3, 128.8, 128.7, 128.5, 106.9, 94.0, 45.2, 13.3 ppm; MS (FAB) m/z: 384 (M^+); IR (neat): 3050, 2963, 2925, 1572, 1485, 1451, 1437, 1368 cm^{-1}; Anal. Calcd for $C_{10}H_{10}I_2$: C, 31.28; H, 2.62. Found: C, 31.50; H, 2.66.

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Supplementary data

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23. Crystal data of **2**, numbered with CCDC (Cambridge Crystallographic Data Centre) 1014387: triclinic, space group P-1, colorless, a=7.1633(3) Å, b=11.5854(5) Å, c=15.0892(6) Å, α=92°, β=99°, γ=103°, V=1199.7 A3, Z=2, T=93 K, d_{calcd}=1.587 g cm^{-3}, μ(Mo, Kα)=3.018 mm^{-1}, $R1$=0.0646, $wR2$=0.1776, GOF=1.067.
24. Commercial IBr (25 g) enclosed in an ample was purchased from Nacalai Tesque, Inc., and its purity is higher than 95% (catalog number 19222-62, CAS 7789-33-5). Freshly prepared and opened IBr was employed for all experiments.
25. The experiment by inverse addition was also performed: to the flask charged with NIS in toluene TMSBr in CH_2Cl_2 was initially loaded, then methyl 3-phenylpropiolate in toluene was added. The chemical yield was given in 46% along with a 78:9:13 isomeric ratio, and 54% of unreacted alkyne remained intact.
26. The employment of TMSBr and NIS in each 3 equiv increased the yield to 57% along with a 90:10 isomeric ratio, although unreacted methyl 3-phenylpropiolate was recovered in 43%.
27. The current method is not suitable for constructing tetraarylethene moieties that recently attract much attention in material chemistry. The platform protocol reported by Itami and Yoshida enables to prepare the substructure, see: Itami, K.; Yoshida, J. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 811–824 and references therein.

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30. The similar observation was ensured in the iodobromination of 3-(oct-1-yn-1-yl)pyridine, though TLC monitoring and NMR analyzing. During the course of the reaction, the substrate seemed to be smoothly transformed into the corresponding IBr-adduct of (*E*)-3-(1-bromo-2-iodooct-1-en-1-yl)pyridine; however, right after workup operation, the pale yellow-colored reaction mixtures turned to dark brown-colored oil along with production of the starting 3-(oct-1-yn-1-yl)pyridine. These indicate the iodobromination could be reversible reaction: the iodobromination for **7** at Scheme 5, **12**–**15** at Table 1 might reach to equilibrium.
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