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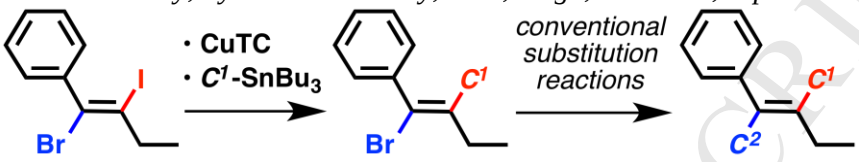

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Stereo-defined synthesis of differentially all-carbon tetrasubstituted alkenes derived from (*E*)-1-bromo-2-iodoalkenes.

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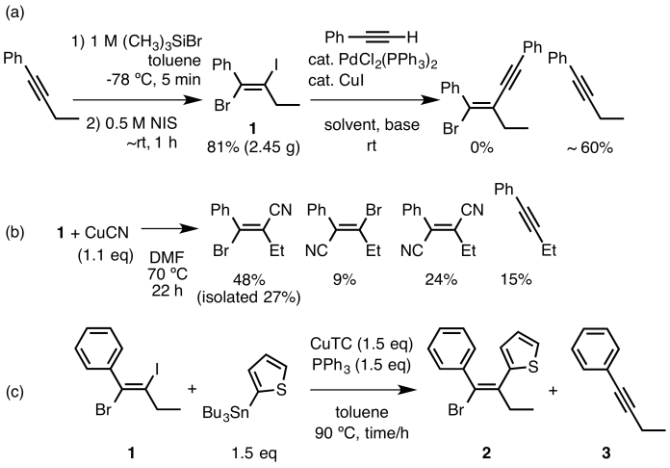
ABSTRACT

An intuitive approach to differentially all-carbon tetrasubstituted olefins from a scaffold of (*E*)-1-bromo-2-iodoalkenes is described. The iodine atom of the scaffold selectively undertook CuTC-mediated cross-coupling reactions with organotin reagents, suppressing a side-reaction of *β*-halogen elimination. The resultant vinyl bromides were successfully subjectd to various transformations into tetrasubstituted olefins bearing four different carbon-linked groups. The crystallographic analysis revealed that the configuration of the double bonds is fully retained in those two steps. Thus, the template strategy would provide a new entry for preparing stereo-defined tetrasubstituted alkenes.

1. Introduction

Efficient regio- and stereoselective synthesis of differentially all-carbon tetrasubstituted olefins still remains a grand challenge,[1,2] although their significance lies in medicinal[3,4] and material chemistry.[5,6] Even monumental approaches including carbometallation of alkynes,[7] carbonyl olefination,[8] elimination reaction,[9] and olefin metathesis,[10] would give *E*/*Z* or regio-isomeric mixtures. Based on these limitations, the use of diverse scaffold strategies seems to be an attractive option:[11] differentially substituted olefin templates enable forming various and stereo-defined tetrasubstituted olefins, provided that the configuration of the double bond is fully retained during the transformations.[12]

Recently, we have reported regio- and stereoselective iodobromination of internal alkynes; the triple bonds reacted with *in situ* IBr to yield *anti*-IBr adduct, like **1**, as a single isomer.[13] To establish **1** as a stereo-defined alkenyl template for a synthesis of differentially all-carbon tetrasubstituted olefins, **1** was subjected to conventional transformations using palladium catalyzed reaction (Scheme 1 (a)); however, the reaction didn't work and caused *β*-halogen elimination to yield numerous amounts of 1-phenyl-1-butyne.[13] A CuCN-mediated cyanation of **1** was also unworkable, giving side-products of bromine migration, double cyanation, and *β*-halogen elimination (Scheme 1 (b)).[14] For the *β*-halogen elimination, Rathore group[15] and Ogilvie group[16] reported similar observations: vicinal dihaloalkenes readily undertook this type of side-reactions, whatever mechanism the substrates follow. This unpleasant side-reaction provides chemists a continuing challenge toward stereo-controlled synthesis of tetrasubstituted olefins.[1]



Scheme 1. (a) *β*-Halogen elimination of **1** on palladium-catalyzed reaction condition; (b) Reactivity of **1** on a vinylic Rosenmund-von Braun cyanation; (c) Iodine-selective reaction of **1** with tributyl(thiophen-2-yl)stannane to give the corresponding full-substituted vinyl bromide **2**.

Herein we describe a scaffold strategy for synthesis of differentially all-carbon tetrasubstituted olefins utilizing a key compound of (*E*)-1-bromo-2-iodoalkene template (Scheme 1 (c)).

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First, the template took on CuTC-mediated carbon-carbon bond forming reactions with organotin reagents just at the iodine site, suppressing the *β*-halogen elimination side-reaction. Then, the following substitution reactions at the Br site yielded the corresponding tetrasubstituted alkenes as single isomeric compounds with full retention of stereochemistry. We carefully investigated reactivities of vinylic iodine and bromine for taking basic information to construct future synthetic chemistry of tetrasubstituted alkenes.

2. Results and Discussion

We started investigation with a CuTC-mediated cross-coupling of **1** undertaken as shown in Scheme 1(c)[17, 18] and the preliminary research after several tests reached initial criterion of entry 1 in Table 1: the combination of CuTC with PPh_3 in toluene solvent at 90 ºC consumed the starting **1**, yielding 76% of desired **2** along with <5% of side-product **3** derived from halogen elimination. To our surprise, any other products like as non-selective mono- or double-substituted molecules were not found even in crude states: the reaction was impressively clean. Rf values of **1**, **2**, and **3** were 0.52, 0.35, and 0.38 on TLC monitoring eluted with hexane only, respectively; the separation of **2** from **3** was not easy but careful chromatographic column isolated **2**. For entry 2, no use of PPh_3 made the reaction slow and gave 2 in 56%.[19] For entry 3, lowering the temperature to 70 ºC needed overnight reaction time, and yielded **1** in 68% along with 3% of **2**. It appeared to us that the condition of entry 1 (90 ºC, 3 h, CuTC/PPh_3) would be effective. For entry 4, even in 1.5 h of the reaction time, the reaction yielded **2** in 81% with trace amount of **3** This selective reaction was amenable to scale-up synthesis (entry 5); finally, 9 mmol of **1** afforded 2.1 g of **2** in 80% yield (entry 6). Thus, this unwavering transformation means that (*E*)-1-bromo-2-iodoalkene would be a template for singly constructing diverse tetrasubstituted olefins.

Table 1. Evaluation of the reactivity of **1** conducted *via* Scheme 1(c).

Entry	Scale of **1** /mmol (g)	Time/h	%Yields[a]		
			2	**3**	**1**
1	0.5 (0.17)	3	76	<5	0
2[b]	0.5 (0.17)	3	56	3	17
3[c]	0.5 (0.17)	20	68	3	0
4	1.0 (0.34)	1.5	81	trace	trace
5	3.0 (1.0)	2	77	trace	0
6	9.0 (3.0)	2	80[d]	trace	0

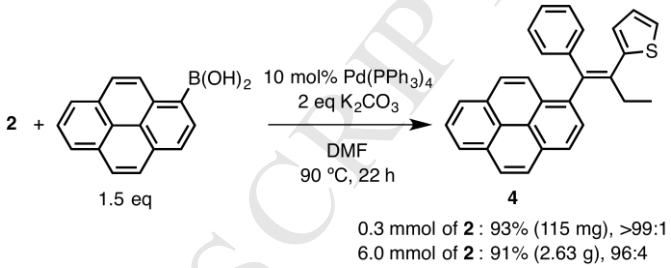
[a] Isolated yields.

[b] The reaction was conducted without PPh_3.

[c] The reaction was conducted at 70 ºC.

[d] 2.1 g of **2** was isolated.

As illustrated in Scheme 2, the resultant vinylic bromine atom in **2** served as a convenient handle for forming carbon-carbon bonds, which yielded a differentially all-carbon tetrasubstituted olefin.[20] The vinyl bromide **2** of 0.3 mmol under the condition of Suzuki-Miyaura cross-coupling with pyren-1-ylboronic acid afforded **4** of 115 mg in 93% yield: the ^{1}H NMR spectrum showed the product is practically single with a >99:1 isomeric ratio. When the use of **2** was scaled up in 6 mmol (2.05 g), **4** was given in 91% (2.63 g) with a 96:4 isomeric ratio.[21] Recrystallization from CH_3CN purified the sample, giving a perfect pure **4** in 60% (1.75 g). The molecular structure of the pure **4** was determined by crystallographic analysis (Figure 1),[22] which disclosed that nearly full retention of the stereochemistry throughout from **1** to **4** was accomplished.



Scheme 2. Synthesis of **4** from **2** via palladium-catalyzed reaction.

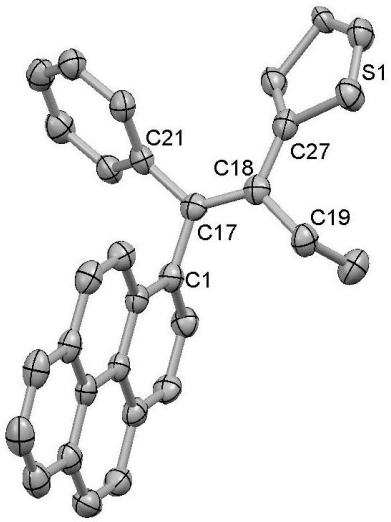
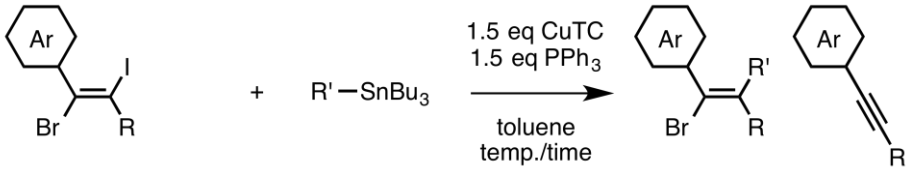


Figure 1. ORTEP drawing of **4** with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and angles [º] for **4**: C17-C18 1.354, C17-C21 1.499, C17-C1 1.496, C18-C27 1.462, C18-C19 1.520, C18-C17-C21 123.86, C1-C17-C21 115.17, C1-C17-C18 120.96, C17-C18-C27 124.42, C19-C18-C27 115.17, C17-C18-C19 120.31.

With a viable protocol in hand, we surveyed the reactivity of the vinylic iodine in (*E*)-1-bromo-2-iodoalkenes (Table 2): for entries 1-10, organotin was fixed, and reactivities of *ortho*-tolyl **5a**, *para*-methoxyphenyl **5b**, 9-anthryl **5c**, *para*-benzonitrile **5d** were evaluated. The starting **5a**, **5b**, and **5d** showed moderate reactivities, yielding **7a**, **7b**, and **7d** in around 60%. The side-production of the corresponding alkynes **8** were recognizably observed in 10-20%. For the starting **5c** in entries 6 and 7, TLC monitoring of the reaction process gave multi spots, and the yield of **7c** was low presumably due to the bulky 9-anthryl moiety. For entries 11-15, substrate **1** was fixed, and reactivities of *sp*-hybridized carbon-stannane **6a**, sp^2-hybridized carbon-stannane **6b** and **6c**, sp^3-hybridized carbon-stannane **6d** were evaluated. The **6a** and **6b** showed acceptable yields, 51% of **7e** and 75% of

7f (entries 12 and 13). However, for phenyl-**6c** and allyl-**6d** of entries 14 and 15, the reaction was not regulated as we expected, and the desired **7g** and **7h** were not obtained. The reaction system proved to be not perfect but rather effective for decreasing alkynes, which has not been reported so far.



5a : Ar = *o*-tolyl, R = *n*-C_6H_{13} **6a** : R' = CCPh
5b : Ar = *p*-MeO-Ph, R = *n*-C_6H_{13} **6b** : R' = 2-furyl
5c : Ar = 9-anthryl, R = *n*-C_6H_{13} **6c** : R' = Ph
5d : Ar = 4-CN-Ph, R = cyclo-C_6H_{11} **6d** : R' = allyl

Table 2. Evaluation of reactivities of vinylic iodines in (*E*)-1-bromo-2-iodoalkenes.[a]

Entry	Substrate **5** or **1**	Organotin	Temp./°C	Time/h	Product **7**	%Yield[b] **7**	**8**	**5** or **1**
1	**5a**		85	23	**7a**	65	11	trace
2	**5b**		90	17	**7b**	48[c]	24[c]	0
3			70	5		58[c]	15[c]	4
4[d]			70	19		61	11	0
5		tributyl(2-thienyl)tin	r.t.	25		11	0	68
6	**5c**		90	23	**7c**	25[e]	21	14
7			110	20		10	35	0
8	**5d**		90	11	**7d**	60	17	0
9			90	2		56	11	5
10			70	20		36	34	10
11	**1**	**6a**	90	20	**7e**	12	9	16
12			110	20		51[f]	10	4
13		**6b**	90	2	**7f**[g]	75	3	6
14[h]		**6c**	110	17	**7g**	0	-	-
15[h]		**6d**	110	17	**7h**	0	-	-

[a]Conditions: substrate (0.5 mmol), organotin (0.75 mmol), toluene (4 mL). Stereochemistry of **7** was inferred from evidence of the ORTEP drawing in Figure 1.

[b]Isolated yields, unless otherwise noted.

[c]NMR yields as a mixture of **7** and **8** after chromatographic purification.

[d]Each 3 equiv of CuTC, **2**, and PPh_3 was used.

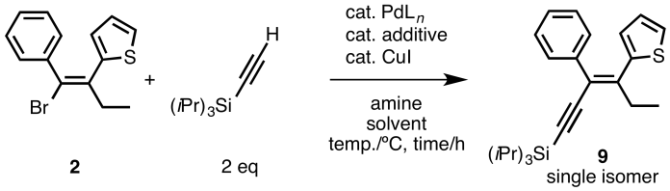
[e]95% purity.

[f]Average of two runs. In this entry, numerous amounts of homo-coupling adducts of **6a** were observed.

[g]**7f** was totally decomposed in ca. 4 h right after the purification.

[h]NMR spectra in the crude showed terribly messy peaks, although the slight peaks of apparently desired **7** appeared along with clear peaks of **8a** and **1**.

Next, we studied reactivity of the resultant vinylic bromine that is the second tag for synthesizing diverse tetrasubstituted olefins. As shown in Scheme 3, bromine **2** was evaluated in Sonogashira reaction that is known as a powerful tool for installation of alkynyl *sp*-hybridized carbon,[23] and the results were summarized in Table 3. For entries 1-3, conventional $PdCl_2(PPh_3)_2$ and $Pd(PPh_3)_4$ catalyzed the cross-coupling to give **9** as a single isomer, but the unreacted **2** remained anyhow. Even though Fu's protocol[24] (entry 4) and Alami's method[25] (entry 5) were attempted, the reactions didn't complete. These shortcomings would be caused by numerous amounts of side-products that were homo-coupling adducts of triisopropylsilylacetylenes.[26] We finally found the use of $Pd[P(t\text{-}Bu)_3]_2$ was effectual for not only high-yielding transformation but also consumption of **2** (entry 6). Although the additional $P(t\text{-}Bu)_3$ was indispensable for the completion, the reaction was relatively clean on TLC monitoring.



Scheme 3. Sonogashira cross-coupling reaction between **2** and triisopropylsilylacetylene.

Table 3. Evaluation of the reactivity of **2** conducted *via* Scheme 3.[a]

Entry	PdL_n, additive, CuI, solvent/amine (1/1 v/v), temp./°C, time/h	%Yield[b]	
		9	**2**
1	10 mol% $PdCl_2(PPh_3)_2$, 10 mol% PPh_3, 10 mol% CuI, toluene/Et_3N, 70 °C, 8 h	47	37
2	10 mol% $PdCl_2(PPh_3)_2$, 10 mol% CuI, toluene/Et_3N, 70 °C, 13 h	47	43
3	10 mol% $Pd(PPh_3)_4$, 20 mol% CuI, toluene/Et_3N, 70 °C, 13 h	68	22
4[c]	3 mol% $PdCl_2(PhCN)_2$, 6 mol% P(*t*-Bu)$_3$, 6 mol% CuI, dioxane/HN(*i*Pr)$_2$, r.t., 20 h	<83[e]	14
5	5 mol% $PdCl_2(PhCN)_2$, 10 mol% CuI, piperidine, 70 °C, 3 h	50	40
6[d]	5 mol% Pd[P(*t*-Bu)$_3$]$_2$, 10 mol% P(*t*-Bu)$_3$, 10 mol% CuI, toluene/Et_3N, 70 °C, 4 h	95	0

[a] Conditions: **2** (0.5 mmol), triisopropylsilylacetylene (0.75 mmol), solvent (0.5 mL), unless otherwise noted. Stereochemistry of **9** was inferred from evidence of the ORTEP drawing in Figure 1.

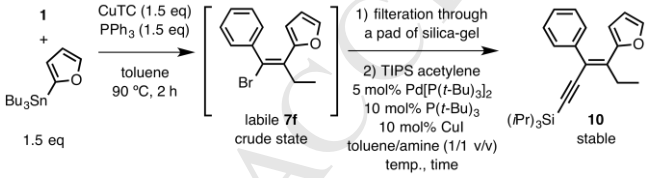
[b] Isolated yields.

[c] The reaction was conducted at 70 °C.

[d] 1 mmol of **2** was used.

[e] Inseparable impurities were included.

As illustrated in Scheme 4, this Sonogashira protocol was successfully applicable to labile **7f** that was obtained in Table 2; and the results were summarized in Table 4. The vinyl bromide **7f** decomposed totally within 4 h after chromatographic purification; so, right after the crude **7f** was filtered through a short-plugged silica-gel column chromatography, the sample was provided to the next coupling step. The reaction at 70 °C didn't completed (entry 1), but the raise to 85 °C consumed the starting **7f** and yielded **10** in 79% (entry 2). Luckily, the full-substituted **10** was stable as we expected. No use of additional P(*t*-Bu)$_3$ decreased the yield to 21% (entry 3). As the temperature went up to 95 °C, the production of **10** was suppressed owing to large side-production of homo-coupling adduct of triisopropylsilylacetylene (entry 4). Thus, the reactivity of the vinylic bromine in Sonogashira reaction seems to be relatively sensitive toward the reaction temperature.



Scheme 4. A through-process for use of labile **7f**: synthesis of tetrasubstituted **10**.

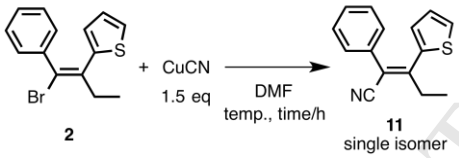
Table 4. Evaluation of the reactivity of **7f** conducted *via* Scheme 4.

Entry	amine	temp./°C	time/h	%Yield[b]	
				10	unreacted **7f**
1	Et_3N	70	15	37	36
2	Et_3N	85	17	79	0
3[c]	Et_3N	85	15	21	33
4	EtN(*i*Pr)$_2$	95	15	48	19

[a] Conditions: **1** (0.3 mmol), tributyl(thiophen-2-yl)stannane (0.45 mmol), toluene (0.5 mL), unless otherwise noted. Stereochemistry of **10** was inferred from evidence of the ORTEP drawing in Figure 1.

[b] Isolated yields in 2 steps.

[c] Without additional 10 mol% P(*t*-Bu)$_3$.



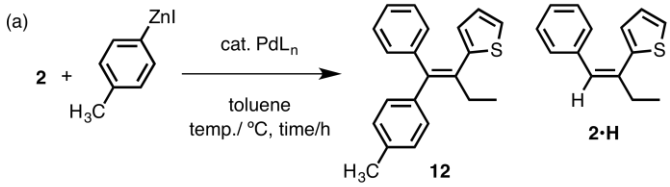
temp./°C	time/h	%Yield **11**	%Yield **2**
90	20	40	53
110	20	90	7
135	5	91	0

Scheme 5. Vinylic Rosenmund-von Braun cyanation of **2** to give **11**.

The vinyl bromide **2** was also subjected to vinylic Rosenmund-von Braun cyanation that attaches *sp*-hybridized carbon (Scheme 5). Although the high temperature of 135 °C was needed for smooth reaction completion, desired **11** was singly formed in 91% yield.[27, 28]

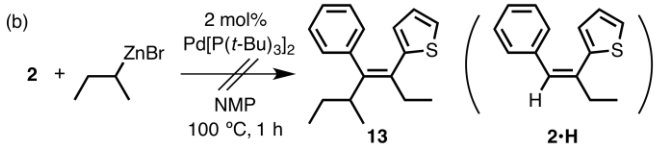
Negishi reaction is known as one of the most convenient methods for installation of sp^2- and sp^3-carbon into the vinylic bromine, which proceeds under neutral condition unlike Suzuki-Miyaura reaction utilizing basic condition. We evaluated the reactivity of **2** on Negishi cross-coupling (Scheme 6). For the part of (a), the use of $Pd(PPh_3)_4$ didn't consume all of the starting **2** (entries 1 and 2), but Pd[P(*t*-Bu)$_3$]$_2$ was effective for using up **2** although the aid of additional 10 mol% P(*t*-Bu)$_3$ was required (entry 4). The reaction gave **2•H** as a side-product that was not observed in Suzuki protocol of Scheme 2. For part (b), *sec*-butylzinc(II) bromide was employed as a reaction partner. The conventional condition utilizing $Pd(PPh_3)_4$ as well as Fu's method were attempted; [29, 30] however, these didn't afford desired **13**, and gave numerous amounts of de-halogenated **2•H** along with other unidentified side-products. We also tried reactions utilizing alkylboronic acids instead of alkylzinc halides, which ended up in complicated mixtures including **2•H**.

Scheme 6. Evaluation of reactivity of **2** in Negishi cross-coupling



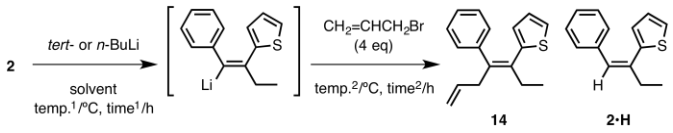
entry	cat. PdL_n	temp./°C	time/h	%Yield **12**	**2**	**2•H**
1[a]	5 mol% $Pd(PPh_3)_4$	65	2	23	67	9
2[a]	5 mol% $Pd(PPh_3)_4$	85	5	58	16	16
3[a]	5 mol% Pd[P(*t*-Bu)$_3$]$_2$ + 10 mol% P(*t*-Bu)$_3$	65	2	53	8	7
4[b]	5 mol% Pd[P(*t*-Bu)$_3$]$_2$ + 10 mol% P(*t*-Bu)$_3$	85	2	72	0	13

[a] 0.3 mmol of **2** (88 mg) was used.
[b] 1.0 mmol of **2** (293 mg) was used.



reaction employing a) *p*-tolylzinc iodide, and b) *sec*-butylzinc bromide.

Alternatively, lithium-halogen exchange is one of the most monumental, reliable and established protocols for replacement of the vinylic bromine with sp^3-hybridized carbon.[31] As illustrated in Scheme 7, the bromide **2** could be activated with *tert*- or *n*-butyl lithium, and its resultant vinyl lithium was exposed to allyl bromide. The results were summarized in Table 5. For entry 1, the conventional method employing *tert*-BuLi in THF solvent at low temperature consumed all of the starting **2**, but unfortunately gave many side-products including **2•H**. The ^{1}H NMR ratio of **14**/**2•H** after short-plugged silica-gel column chromatography showed 3.5/1. For entries 2 and 3, the lithiation in toluene solvent was found to proceed at 0 ºC, and the addition of THF (4 eq) drastically improved the productivity of **14** with up to 30/1 ratio of **14**/**2•H**. Although the separation of **14** from **2** was laborious, use of many amounts of silica-gel barely isolated **14** in 50% yield. We expected that more convenient *n*-BuLi supplies the place of *tert*-BuLi (entries 4 and 5); however, the obtained crude products consisted of many side-products.



Scheme 7. Substitution of allyl moiety for the vinylic bromine of **2** through lithium–halogen exchange reaction to synthesize **14**.

Table 5. Evaluation of the reactivity of **2** conducted *via* Scheme 7.[a]

Entry	BuLi (eq)	Solv.	Add. (eq)	temp.^{1}/ºC, time^1/h temp.^{2}/ºC, time^2/h	NMR ratios[b]	Isolated yields[%]
					14/2•H	**14**
1	*t*BuLi (2.2)	THF	-	-78, 0.25 r.t., 1	3.5/1	-
2	*t*BuLi (2.2)	toluene	-	0, 0.25 0, 1	0/100	-
3[c]	*t*BuLi (2.2)	toluene	THF (4)	0, 0.25 0, 1	30/1	50
4	*n*BuLi (1.1)	toluene	THF (4)	r.t., 0.25 r.t., 2	2.1/1	-
5	*n*BuLi (1.1)	THF	-	-78, 0.2 r.t., 2	4.7/1	-

[a] 0.3 mmol of **2** was used, unless otherwise noted.

[b] The ratios were determined on the basis of the crude sample that was purified through a short-plugged silica-gel (eluent, hexane/EtOAc = 50/1).

[c] 1 mmol of **2** was used.

3. Conclusion

In summary, we demonstrated a straightforward synthesis of differentially all-carbon tetrasubstituted olefins in two steps from (*E*)-1-bromo-2-iodoalkene templates. Particularly, the reagent combination of CuTC/PPh_3/organotin in the first step plays an important role in this "differentially substituted olefin template strategy". The results suggest that the strategy provides three salient features: One, the use of CuTC and organostannane selectively substitutes a carbon group for the vinylic iodine. Two, the copper-mediated reaction greatly suppresses unpleasant side-reaction of *β*-halogen elimination. Three, the template retains its configuration during these two-step conversions, exclusively giving singly defined tetrasubstituted alkenes. Clearly, these features would constitute an illustration of the high potential of (*E*)-1-bromo-2-iodoalkene template for general use to synthesize new tetrasubstituted olefins. On the other hand, it is certain that this sequential approach doesn't yet reach mature level. There are two major points needing improvement: poor reactivity of $PhSnBu_3$ and CH_2=$CHCH_2SnBu_3$, and difficult induction of sp^3-hybridezed carbons to the vinylic bromine.[32, 33] Our progress reported herein about the synthetic route is the decisive evidence showing the template utility of (*E*)-1-bromo-2-iodoalkene that is a simple, small, and intuitive molecule. Further synthetic development and improvement 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 60_N (Kanto Chemical Co.). LRMS and HRMS were reported on the basis of TOF (time of flight)-MS (LCMS-IT-TOF; Shimadzu), and DART (Direct Analysis in Real Time)-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), C_7H_8 (2.08), C_6H_6 (7.16), CH_2Cl_2 (5.32); ^{13}C NMR: $CDCl_3$ (77.0)]. Signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

4.2 General procedure of (*E*)-2-(1-bromo-1-phenylbut-1-en-2-yl)thiophene 2, for Table 1, entry 6: Under an argon atmosphere, to a solution of **1** (3.03 g, 9.00 mmol) and PPh_3 (3.54 g, 13.5 mmol) in toluene (60 mL) was added tributyl(2-thienyl)tin (4.3 mL, 13.5 mmol), and then Copper (I) thiophene-2-carboxylate (2.57 g, 13.5 mmol), namely CuTC, was suspended. After stirred at 90 ºC for 2 h, the reaction mixture was allowed to cool to ambient temperature, and followed by filtration through a pad of celite and frolisil, and evaporation. The resultant residue was dissolved into toluene (100 mL), and washed with brine (40 mL), and dried over Na_2SO_4, and concentrated *in vacuo* to give a crude product as a mixture of orange oil and brown solid. The crude was washed with hexane (3.3 mL/g) at room temperature, and the filtrate was concentrated *in vacuo* to give a yellow oil. Purification with silica gel column chromatography (hexane only) afforded 2.10 g of **2** as a yellow oil in 80% yield. Analytical data are listed in the section below.

4.2.1. (*E*)-2-(1-bromo-1-phenylbut-1-en-2-yl)thiophene *(2)*. 80% yield (2.1 g); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.27-7.22 (m, 5H), 6.92 (dd, *J* = 5.1 Hz, 1.0 Hz, 1H), 6.76 (dd, *J* = 5.1 Hz,

3.6 Hz, 1H), 6.64 (dd, *J* = 3.6 Hz, 1.0 Hz, 1H), 2.86 (q, *J* = 7.5 Hz, 2H), 1.17 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 141.9, 141.8, 137.1, 130.1, 128.6, 128.4, 127.7, 126.7, 125.9, 121.4, 33.7, 12.5 ppm; MS (DART-TOF) *m/z*: 294 $[M(Br81)]^+$ (100%); IR (neat): 3072, 2967, 2927, 2867, 1595, 1439, 1217, 1072, 1016, 855, 678 cm^{-1}; HRMS (DART-TOF) calcd for $C_{14}H_{13}Br(81)S$: 293.9901 $[M(Br81)]^+$, Found 293.9881; Anal. Calcd for $C_{14}H_{13}BrS$: C, 57.35; H, 4.47. Found: C, 57.30; H, 4.33.

4.2.2. (E)-2-(1-bromo-1-(o-tolyl)oct-1-en-2-yl)thiophene ***(7a)***. 65% yield (235 mg); pale yellow viscous materials; ^{1}H NMR (400 MHz, $CDCl_3$) 7.24-7.20 (m, 1H), 7.18-7.17 (m, 3H), 7.04 (dd, *J* = 5.1 Hz, 1.2 Hz 1H), 6.77 (dd, *J* = 5.1 Hz, 3.7 Hz, 1H), 6.71 (dd, *J* = 3.7 Hz, 1.2 Hz, 1H), 2.21 (s, 3H), 2.89 (dt, *J* = 13.3 Hz, 5.4 Hz, 1H), 2.87 (dt, *J* = 15.1 Hz, 5.4 Hz, 1H), 1.67 (tt, *J* = 7.8 Hz, 2H), 1.49-1.42 Hz (m, 2H), 1.37-1.33 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 141.5, 141.1, 136.9, 135.9, 130.9, 130.2, 129.2, 126.9, 126.5, 126.1, 120.9, 38.9, 32.0, 29.6, 28.5, 23.0, 19.6, 14.4 ppm; MS (DART-TOF) *m/z*: 363 $[M(79)+H]^+$; IR (neat): 2955, 2923, 2855, 1595, 1456, 1217, 855, 694 cm^{-1}; HRMS (DART-TOF) calcd for $C_{19}H_{24}Br(79)S$: 363.0782 $[M(Br79)+H]^+$, Found 363.0756; Anal. Calcd for $C_{19}H_{23}BrS$: C, 62.51; H, 6.44. Found: C, 62.80; H, 6.38.

4.2.3. (E)-2-(1-bromo-1-(4-methoxyphenyl)oct-1-en-2-yl)thiophene ***(7b)***. 61% yield (116 mg); pale yellow viscous materials; ^{1}H NMR (400 MHz, $CDCl_3$) 7.18 (d, *J* = 8.9 Hz, 2H), 7.09 (dd, *J* = 5.1 Hz, 1.2 Hz, 1H), 6.79-6.76 (m, 3H), 6.66 (dd, *J* = 3.7 Hz, 1.2 Hz 1H), 3.79 (s, 3H), 2.80 (t, *J* = 7.8 Hz, 2H), 1.60-1.52 (m, 2H), 1.44-1.37 (m, 2H), 1.33-1.29 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 159.6, 142.5, 135.5, 134.3, 131.5, 127.4, 126.7, 125.7, 122.1, 114.0, 55.5, 40.3, 31.9, 29.5, 28.0, 23.0, 14.4 ppm; MS (DART-TOF) *m/z*: 379 $[M(79)+H]^+$; IR (neat): 2950, 2919, 2856, 1603, 1502, 1450, 1293, 1229, 1172, 1030 cm^{-1}; HRMS (DART-TOF) calcd for $C_{19}H_{24}Br(79)OS$: 379.0731 $[M(79)+H]^+$, Found 379.0706.

4.2.4. (E)-2-(1-(anthracen-9-yl)-1-bromo-oct-1-en-2-yl)thiophene ***(7c)***. 25% yield (57 mg); yellow viscous materials; ^{1}H NMR (400 MHz, $CDCl_3$) 8.50 (s, 1H), 8.12 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 2H), 7.39 (m, 4H), 6.75 (d, *J* = 5.0 Hz, 1H), 6.66 (d, *J* = 3.8 Hz, 1H) 6.53 (dd, *J* = 5.0, 3.8 Hz, 1H), 3.18 (t, *J* = 8.0 Hz, 2H), 1.91 (tt, *J* = 8.0, 8.0 Hz, 2H), 1.61 (m, 2H), 1.44 (m, 4H), 0.97 (t, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 140.7, 139.4, 134.6, 132.1, 129.4, 129.0, 128.8, 126.9, 126.7, 126.6, 126.1, 125.9, 125.7, 117.7, 39.1, 32.0, 29.9, 28.8, 14.5 ppm; MS (DART-TOF) m/z: 451 $[M(81)+H]^+$; IR (neat): 2924, 2851, 1521, 1437, 1255, 1219, 1156, 1006 cm^{-1}; HRMS (DART-TOF) calcd for $C_{26}H_{26}Br(81)S$: 451.0918 $[M(81)+H]^+$, Found 451.0896.

4.2.5. (E)-4-(1-bromo-2-cyclohexyl-2-(thiophen-2-yl)vinyl)benzonitrile ***(7d)***. 60% yield (58 mg); yellowish white viscous materials; ^{1}H NMR (400 MHz, $CDCl_3$) 7.41 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 7.14 (dd, *J* = 5.2 Hz, 1.2Hz, 1H), 6.79 (dd, *J* = 5.2 Hz, 3.5 Hz, 1H), 6.53 (dd, *J* = 3.5 Hz, 1.2 Hz, 1H), 3.14 (tt, *J* = 12 Hz, 3.2 Hz, 1H), 1.81-1.78 (m, 4H), 1.69-1.66 (m, 1H), 1.45-1.35 (m, 2H), 1.29-1.19 (m, 2H), 1.15-1.04 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 146.1, 143.2, 138.0, 131.8, 130.5, 128.5, 126.8, 126.4, 121.0, 118.9, 111.3, 46.3, 30.7, 26.6, 26.0 ppm; MS (DART-TOF) *m/z*: 391 $[M(81)+NH_4]^+$; IR (neat): 2929, 2845, 2227 (CN), 1598, 1432, 1401, 1213, 845 cm^{-1}; HRMS (DART-TOF) calcd for $C_{19}H_{22}Br(81)N_2S$: 391.0667 $[M(81)+NH_4]^+$, Found 391.0644; Anal. Calcd for $C_{19}H_{18}Br(79)NS$: C, 61.29; H, 4.87; N, 3.76. Found: C, 61.52; H, 4.79; N, 3.88.

4.2.6. (E)-(1-bromo-2-ethylbut-1-en-3-yne-1,4-diyl)dibenzene ***(7e)***. 51% yield (95 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.65 (d, *J* = 7.0 Hz, 2H), 7.39-7.20 (m, 8H), 2.63 (q, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 140.7, 131.6, 130.0, 129.9, 128.9, 128.6, 128.5, 128.0, 126.3, 123.5, 94.1, 88.6, 31.4, 12.6 ppm; MS (DART-TOF) *m/z*: 313 $[M(81)+H]^+$; IR (neat): 3048, 2969, 2873, 2337, 2210, 1947, 1800, 1597, 1487, 1441, 752, 687 cm^{-1}; HRMS (DART-TOF) calcd for $C_{18}H_{16}Br(81)$: 313.0415 $[M(81)+H]^+$, Found 313.0412; Anal. Calcd for $C_{18}H_{15}Br(79)$: C, 69.47; H, 4.86. Found: C,69.50; H, 4.82.

4.2.7. (E)-2-(1-bromo-1-phenylbut-1-en-2-yl)furan ***(7f)***. This compound is very labile; actually, its decomposition was observed within 4 h after chromatographic purification. Identification of this molecule was ensured in this derivative **10** shown in Scheme 4, which is described in the section below. 75% yield (101 mg); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.32-7.24 (m, 5H), 7.18 (m, 1H), 6.16-6.14 (m, 1H), 5.61 (d, *J* = 3.4 Hz, 1H), 2.81 (q, *J* = 7.5 Hz, 2H), 1.16 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 152.1, 142.4, 141.6, 133.7, 129.4, 128.7, 128.4, 121.7, 111.3, 110.5, 29.7, 12.8 ppm.

4.3 Synthesis of (*E*)-2-(1-phenyl-1-(pyren-1-yl)but-1-en-2-yl)thiophene 4, for Scheme 2. Under an argon atmosphere, to a solution of **2** (2.05 g, 7.0 mmol) in DMF (35 mL) was added 1-Pyreneboronic acid (2.58 g, 10.5 mmol), and K_2CO_3 (1.93 g, 14 mmol), and $Pd(PPh_3)_4$ (809 mg, 0.7 mmol). After stirred at 90 ºC for 20 h, the reaction mixture was allowed to cool to ambient temperature. The mixture was filtered through a pad of celite and frolisil, and the filtrate was evaporated off. The resultant residue was dissolved into toluene (100 mL), and washed with water (40 mL). The aqueous phase was extracted with toluene (15 mL x 3), and the combined organic layers were washed with brine (40 mL), and dried over Na_2SO_4, and concentrated *in vacuo* to give a crude product as a yellowish brown solid. Purification with silica gel column chromatography (hexane/toluene=4/1) afforded 2.63 g of **4** as a yellowish white solid in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 8.38 (d, *J* = 9.2 Hz, 1H) 8.21-8.16 (m, 3H), 8.10-8.08 (m, 3H), 8.00 (dd, *J* = 7.6 Hz, 7.6 Hz, 1H) 7.94 (d, *J* = 7.8 Hz, 1H), 7.25-7.22 (m, 3H), 7.14-7.08 (m, 3H), 6.93-6.92 (m, 2H) 2.31 (q, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 144.2, 143.1, 138.6, 138.4, 136.9, 131.7, 131.4, 130.7, 130.2, 129.0, 128.3, 128.0, 127.74, 127.71, 127.60, 127.58, 126.91, 126.90, 126.3, 125.8, 125.48, 125.46 (two peaks are overlapped), 125.28, 125.26, 125.21, 30.6, 13.6 ppm; MS (DART-TOF) *m/z*: 415 $[M+H]^+$. IR (neat): 3036, 1595, 1490, 1441, 1176, 1066, 841, 681 cm^{-1}. HRMS (DART-TOF) calcd for $C_{30}H_{23}S$: 415.1520 $[M+H]^+$, Found 415.1507; Anal. Calcd for $C_{30}H_{22}S$: C, 86.92; H, 5.35. Found: C, 86.91; H, 5.36.

4.4 Synthesis of (*E*)-triisopropyl(3-phenyl-4-(thiophen-2-yl)hex-3-en-1-ynyl)silane 9, for Table 3, entry 6. Under an argon atmosphere, to a solution of **2** (147 mg, 0.5 mmol) in toluene (1 mL) and Et_3N (1 mL) was added triisopropylsilylacetylene (0.22 mL, 1 mmol) and P(*t*-Bu)$_3$ (10 wt% in hexane, 0.15 mL, 0.05 mmol). After $Pd[P(t\text{-}Bu)_3]_2$ (13 mg, 0.025 mmol) and CuI (10 mg, 0.05 mmol) was added, the reaction was heated to 70 ºC and stirred for 4 h. The mixture was allowed to cool to ambient temperature, and filtered through a pad of celite with eluent of toluene. The filtrate was transferred into a separatory funnel, and washed with water (15 mL) and brine (15 mL), and dried over Na_2SO_4, and concentrated *in vacuo* to give a crude of 259 mg as a dark brown oil. Purification with silica gel column chromatography (hexane) afforded 187 mg of **9** as a yellow oil in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 7.30-7.22 (m, 5H), 7.14 (d, *J* = 5.1 Hz, 1H), 6.82 (dd, *J* = 5.1, 3.7 Hz,

1H), 6.71 (d, *J* = 3.7 Hz, 1H), 2.97 (q, *J* = 7.5 Hz, 2H), 1.19 (t, *J* = 7.5 Hz, 3H), 1.10 (s, 21H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 144.5, 142.7, 139.5, 130.0, 128.5, 128.0, 127.5, 126.9, 126.5, 121.1, 107.8, 97.4, 32.1, 19.0, 13.5, 11.8 ppm; MS (DART-TOF) *m/z*: 395 $[M+H]^+$; IR (neat): 2940, 2863, 2128, 1461, 1232, 994, 693 cm^{-1}; HRMS (DART-TOF) calcd for $C_{25}H_{35}SSi$: 395.2229 $[M+H]^+$, Found 395.2236; Anal. Calcd for $C_{25}H_{34}SSi$: C, 76.08; H, 8.68. Found: C, 75.95; H, 8.57.

4.5 Synthesis of (*E*)-(4-(furan-2-yl)-3-phenylhex-3-en-1-ynyl)triisopropylsilane 10, for Scheme 4. [We observed this compound partially decayed two weeks after its purification.] Under an argon atmosphere, to a solution of **1** (337 mg, 1.0 mmol) and PPh_3 (393 mg, 1.5 mmol) in toluene (7 mL) was added tributyl(2-furyl)tin (0.47 mL, 1.5 mmol). After CuTC (286 mg, 1.5 mmol) was added, the reaction was heated to 90 ºC and stirred for 1 h. The mixture was allowed to cool to ambient temperature, and filtered through a pad of celite. The filtrate was transferred into a 50 mL separatory funnel, and washed with brine (20 mL), and dried over Na_2SO_4, and concentrated *in vacuo* to give a crude of 1.12 g. Purification of short-plugged silica-gel column chromatography with eluent of hexane afford 413 mg as a pale yellow oil that included a desired **7f**. Right after the sample was dried under vacuum at room temperature for 15 min, the fragile sample was provided into the next step. Under an argon atmosphere, to a solution of the sample 413 mg including **7f** in toluene (1.5 mL) and Et_3N (1.5 mL) was added triisopropylsilylacetylene (0.45 mL, 2 mmol) and P(*t*-Bu)$_3$ (10 wt% in hexane, 0.3 mL, 0.1 mmol). After the Pd[P(*t*-Bu)$_3$]$_2$ (26 mg, 0.05 mmol) and CuI (19 mg, 0.1 mmol) was added, the reaction was conducted at 85 ºC and stirred for 17 h. The mixture was allowed to cool to room temperature, and filtered through a pad of celite. The filtrate was transferred into a 100 mL separatory funnel, and washed with water and brine (each 20 mL), and dried over Na_2SO_4, and concentrated *in vacuo* to give a crude of dark brown oil (705 mg). Purification with silica gel column chromatography (hexane) afforded 299 mg of **10** as a yellow oil in 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 7.29-7.24 (m, 6H), 6.22 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.76 (d, *J* = 3.4 Hz, 1H), 2.92 (q, *J* = 7.4 Hz, 2H), 1.19 (t, *J* = 7.4 Hz, 3H), 1.09 (brs, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 153.4, 142.1, 140.20, 140.18, 129.4, 128.5, 127.4, 120.3, 111.63, 111.56, 107.9, 97.6, 28.0, 19.0, 13.9, 11.8 ppm; MS (DART-TOF) *m/z*: 379 $[M+H]^+$; IR (neat): 2941, 2864, 2125, 1461, 882, 661 cm^{-1}; HRMS (DART-TOF) calcd for $C_{25}H_{35}OSi$: 379.2457 $[M+H]^+$, Found 379.2462; Anal. Calcd for $C_{25}H_{34}OSi$: C, 79.31; H, 9.05. Found: C, 79.35; H, 8.92.

4.6 Synthesis of (*E*)-2-phenyl-3-(thiophen-2-yl)pent-2-enenitrile 11, for Scheme 5. Under an argon atmosphere, to a charged Schlenk tube with **2** (88 mg, 0.3 mmol) in DMF (0.75 mL) was added CuCN (32 mg, 0.36 mmol), and the reaction was heated to 130 ºC. After stirred for 5 h, the mixture was allowed to cool to room temperature. To the vessel was added toluene (10 mL), and the mixture was transferred into a 25 mL flask, and 3 M aqueous NH_3 (4 mL) was added. After stirred for 30 min at ambient temperature, the mixture was diluted with toluene (10 mL). The aqueous layer was extracted with toluene (10 mL x 3), and combined organic phases were washed with brine (15 mL), and dried over Na_2SO_4, and filtered, and concentrated *in vacuo* to give a crude as a brown oil of 75 mg. The crude was short-plugged through a pad of silica-gel (hexane/acetone 9/1). Purification with silica gel column chromatography (hexane/toluene=1/1) afforded 66 mg of **11** as an orange oil in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 7.35-7.28 (m, 6H), 6.93-6.88 (m, 2H), 3.01 (q, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 153.0, 139.4, 134.5, 130.2, 129.9, 129.3 (two peaks are overlapped), 129.1, 127.3, 119.3, 109.8, 32.2, 14.1 ppm; MS (DART-TOF) *m/z*: 240 $[M+H]^+$; IR (neat): 3100, 2970, 2197 (CN), 1573, 1416, 1244, 1049, 718 cm^{-1}; HRMS (DART-TOF) calcd for $C_{15}H_{14}NS$: 240.0847 $[M+H]^+$, Found 240.0834; Anal. Calcd for $C_{15}H_{13}NS$: C, 75.28; H, 5.47; N, 5.85. Found: C, 75.48; H, 5.72; H, 5.92.

4.7 Synthesis of (*E*)-2-(1-phenyl-1-(*p*-tolyl)but-1-en-2-yl)thiophene 12, for Scheme 6(a). Under an argon atmosphere, to a solution of **2** (293 mg, 1.0 mmol) in toluene (3.5 mL) was added 4-methylphenylzinc iodide (0.5 M in THF, 3 mL, 1.5 mmol), and P(*t*-Bu)$_3$ (10wt% in hexane, 0.3 mL, 0.1 mmol), and Pd[P(*t*-Bu)$_3$]$_2$ (26 mg, 0.05 mmol). After stirred at 85 ºC for 2 h, the mixture was allowed to cool to ambient temperature (the starting **2** was disappeared on TLC monitoring), and the reaction was quenched with satd. aq. NH_4Cl (10 mL) at 0 ºC. The mixture was diluted with toluene (15 mL), and the aqueous phase was extracted with toluene (10 mL x 3). The combined organic layer was washed with brine (20 mL), and dried over Na_2SO_4, and concentrated to give a crude of dark brown oil in 368 mg. The mixture was filtered through a short-plugged chromatographic column (silica-gel, hexane eluent), and followed by purification with silica-gel column chromatography (hexane eluent), which afforded 219 mg of desired **12** in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 7.17-7.05 (m, 10H), 6.81 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.70 (dd, *J* = 3.6 Hz, 1.2 Hz, 1H), 2.52 (q, *J* = 7.4 Hz, 2H), 2.36 (s, 3H), 1.08 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 144.9, 143.8, 140.7, 140.4, 136.7, 134.6, 130.6, 129.3, 129.2, 128.2, 127.4, 126.69, 126.68, 125.0, 30.0, 21.5, 14.5 ppm; MS (DART-TOF) *m/z*: 305 $[M+H]^+$; IR (neat): 2960, 1440, 1069, 814, 692 cm^{-1}; HRMS (DART-TOF) calcd for $C_{21}H_{21}S$: 305.1364 $[M+H]^+$, Found 305.1360; Anal. Calcd for $C_{21}H_{20}S$: C, 82.85; H, 6.62. Found: C, 82.90 ; H, 6.66.

4.8 Synthesis of (*Z*)-2-(4-phenylhepta-3,6-dien-3-yl)thiophene 14, for Table 5, entry 3. Under an argon atmosphere, to a solution of **2** (293 mg, 1.0 mmol) in toluene (2 mL) and THF (0.32 mL, 4 mmol) at 0 ºC was added *t*-BuLi (1.9 M in pentane, 1.16 mL, 2.2 mmol) dropwise over 2 min, and the mixture was stirred at 0 ºC for 15 min. Then, 3-bromoprop-1-ene (0.51 mL, 6 mL) was slowly added over 1 min. Conducted at 0 ºC for 1 h, the reaction was quenched with saturated aqueous NH_4Cl (14 mL). The aqueous phase was extracted with toluene (10 mL x 3), and the combined organic layers were washed with brine (20 mL), and dried over Na_2SO_4, and concentrated *in vacuo* to give a crude of 302 mg as a yellow oil. The crude was filtered through a short-plugged silica-gel (hexane/EtOAc 50/1), and followed by purification with silica-gel column chromatography (hexane/EtOAc 200/1), which yielded 127 mg of the title compound **14** in 50% as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$), 7.35 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.29-7.25 (m, 2H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.03 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.98 (dd, *J* = 3.5, 1.2 Hz, 1H), 5.70 (ddt, *J* = 17.0, 10.3, 6.4 Hz, 1H), 4.92 (dd, *J* = 10.3, 1.8 Hz, 1H), 4.90 (dd, *J* = 17.0, 1.8 Hz, 1H), 3.14 (d, *J* = 6.4 Hz, 2H), 2.21 (q, *J* = 7.4, 2H), 0.89 (t, *J* = 7.4, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) 143.9, 142.7, 138.7, 136.5, 134.0, 128.8, 128.4, 127.0, 126.9, 126.3, 124.7, 116.1, 41.0, 30.0, 14.1 ppm; MS (DART-TOF) *m/z*: 255 $[M+H]^+$; IR (neat): 3072, 2968, 2869, 1945, 1802, 1637, 1431, 1235, 911, 692 cm^{-1}; HRMS (DART-TOF) calcd for $C_{17}H_{19}S$: 255.1207 $[M+H]^+$, Found 255.1189.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.xxxx.xx.xx.

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22. CCDC-1546653 (for **4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ca.uk/data_request/cif. Monoclinic, space group P 21/n, colorless, a = 14.3026(7) Å, b = 11.8400(5) Å, c = 25.2918(12) Å, α = 90°, β = 96.499(7)°, γ = 90°, V = 4255.5(3) Å^3, Z = 8, T = 123 K, $d_{calcd.}$ = 1.294 g cm^{-3}, μ(Mo-$K\alpha$) = 0.167 mm^{-1}, R_1 = 0.0746, wR_2 = 0.1770, GOF = 1.027.
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