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Stereo-Defined Synthetic Route to (*E*)- and (*Z*)-Tamoxifen Derived from(*E*)-1-Bromo-2-iodoalkenes.

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Straightforwardly stereo-defined syntheses of (*E*)- and (*Z*)-Tamoxifens were described, including a description of chemo-selective activation of (*E*)-1-bromo-2-iodoalkenes. The (*E*)-1-bromo-2-iodoalkenes were employed as starting materials; first, the vinylic iodine was transformed into a phenyl group with employing CuTC and $PhSnBu_3$ reagents. Then the resultant vinylic bromine undertook Suzuki reaction to afford an all-carbon tetrasubstituted olefin; finally, the phenol-protective group was converted into the corresponding amino-moiety. The stereochemistry of the initial (*E*)-1-bromo-2-iodoalkenes was fully retained throughout. Thus, it would provide us a new entry for preparation of Tamoxifens and its related compounds.

Introduction

Tamoxifen is a historical tetrasubstituted alkene compound as a biological active molecule.[1,2] From the viewpoint of effect for estrogen receptor, Mother Nature gave a role of oestrogenic and antioestrogenic activity to non-steroid skeletal (*E*)- and (*Z*)-Tamoxifen, respectively (Figure 1).[3] The (*Z*)-form as a synthetic estrogen analogue is clinically used in the treatment of breast cancer to block the proliferative action of estrogens.[4] Thus, it has been noted that (*E*)- and (*Z*)-isomers of tetrasubstituted olefins are endowed with significantly different attribute. Despite the importance in tetrasubstituted olefins such as (*E*)- and (*Z*)-Tamoxifens, the development of concise and simple stereoselective protocol still remains a grand challenge.[5,6,7] We synthetic chemists have monumental approaches for constructing carbon-carbon double bonds such as carbonyl olefination, metathesis of 1,1-disubstituted olefins, carbometallation of alkynes; however, even these protocols would face difficulties in stereochemical control that were followed by producing isomeric mixtures of particularly acyclic tetrasubstituted alkenes.[8] The limitations have created the expectation of synthesizing single isomers on differentially substituted olefin templates and continuous efforts have aimed to refine the diverse scaffold strategy.[9,10]

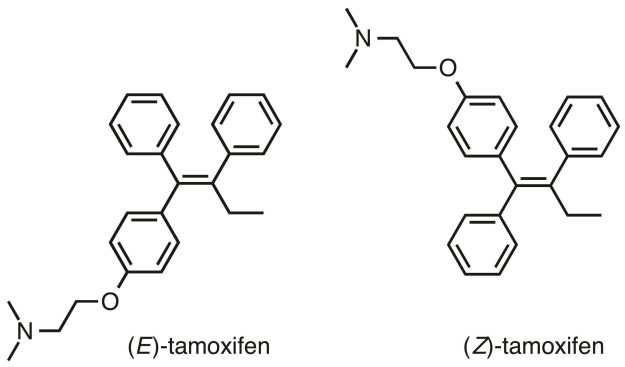
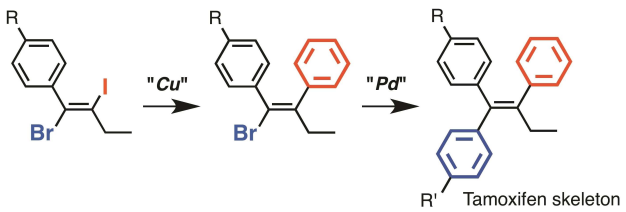


Figure 1. (*E*)-Tamoxifen for oestrogenic activity, and (*Z*)-Tamoxifen for antioestrogenic activity.

Herein we present a (*E*)-1-bromo-2-iodoalkenyl scaffold-based synthesis of (*E*)- and (*Z*)-Tamoxifens. The scaffolds are singly prepared *via* reactions between commercially available internal alkynes and the *in situ*-generated IBr from NIS and $(CH_3)_3SiBr$.[11] We anticipated that the first example of chemo-selective and stereo-retentive replacement of the vinylic iodine by a phenyl group enables to achieve a stereo-defined platform synthesis of (*E*)- and (*Z*)-Tamoxifens (Scheme 1).



Scheme 1. (*E*)-1-bromo-2-iodoalkenyl scaffold-based synthesis of Tamoxifen skeletons *via* chemo-selective and stereo-retentive substitution reactions.

Results and Discussion

Our initial experiment utilizing between (*E*)-1-bromo-2-iodoalkene **1** and tributyl(phenyl)tin was performed in the presence of CuTC and PPh_3 that was effective mediators for chemo-

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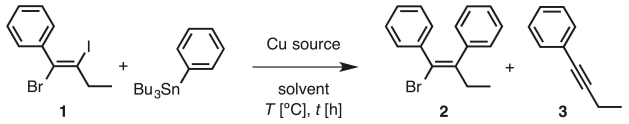
selective cross-coupling in our previous report (Table 1, entry 1).[12] However, the chemical yield of desired adduct **2** resulted in miserable 10% along with numerous 53% yield of side-products **3** that arose from problematic beta-halogen elimination.[13] On the other hand, when the PPh_3 was absent in entry 2, the CuTC yielded **2** in higher 20% and decreased **3** to 20%. Although we tried several copper precursors such as CuMeSal[14] and CuDPP[15] in entries 3 and 4, and other solvents like as dioxane in entries 5–7, it was so difficult to find good systems. For entries 8 and 9, the reactions were performed at 135 °C and 105 °C. While both reactions gave similar results, the latter proceeded cleaner than the former.

Table 1. Evaluation of reactivities of **1** in the copper-mediated reactions with $PhSnBu_3$.[a]



Entry	Cu	Solvent	T [°C]	t [h]	Yield [%][b] **2**[c]	**3**	**1**
1	CuTC(1.5 eq PPh_3)	toluene	90	10	~10	53	15
2	CuTC	toluene	90	6	20	20	37
3	CuMeSal[e]	toluene	90	6	<3	-	-
4	CuDPP[f]	toluene	90	3	~0	-	-
5	CuTC	dioxane	90	2	<7	-	-
6	CuMeSal	dioxane	90	2	~0	-	-
7	CuDPP	dioxane	90	2	<6	-	-
8	CuTC	*o*-xylene	135	6	<47[d]	10	4
9	CuTC	toluene	105	6	44	11	8

[a] Conditions: **1** (101 mg, 0.3 mmol), tributylphenyltin (167 mg, 0.45 mmol), toluene (2 mL), copper precursor (85 mg for CuTC, 0.45 mmol). [b] Isolated yields. [c] **2** was formed as a single isomer, but 5% of impurities (not isomers) was included. [d] The sample accompanied small amounts of the corresponding isomer. [e] Copper (I) 3-methylsalicylate (CAS# 326477–70-7). [f] Copper (I) diphenylphosphinate (CAS# 1011257–42-3).

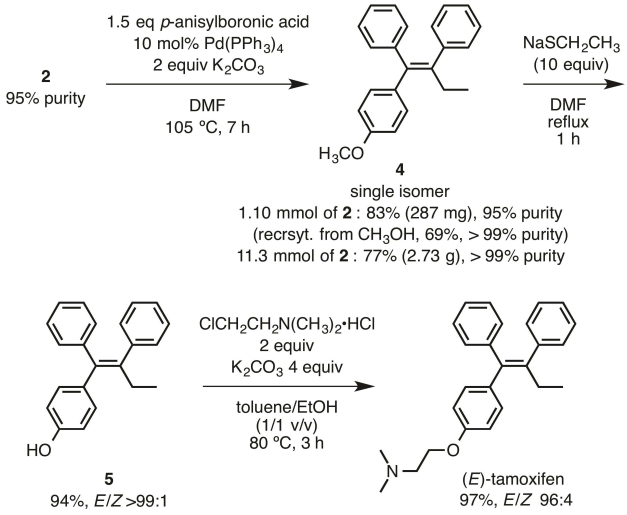
We somehow managed a single preparation of **2** on the condition of entry 9 in Table 1, and proceeded to expand the protocol reliability in large-scale production. Actually, the condition was readily amenable to scale-up synthesis, which was summarized in Table 2. Finally, the use of 5.4 g (16 mmol) of **1** afforded 2.9 g of **2** in 63% yield, although 21% of **3** was obtained and 6% of **1** remained unreacted (entry 4). In all entries, **2** included 5% of unknown impurities at this stage. These impurities don't correspond to isomers, because the upfield of its ^{1}H NMR spectrum has only a set of clean ethyl peaks of **2**.[16]

Table 2. Scalable synthesis of **2** under the reaction condition of entry 9 in Table 1.

Entry	Scale of **1** mmol (g)	t[h]	Yield [%][a] **2**[b]	**3**	**1**
1	1.5 (0.51)	18	53	16	5
2	4.0 (1.3)	6	60	18	13
3	8.0 (2.7)	22	62	17	6
4	16 (5.4)	19	63[c]	21	6

[a] Isolated yields. [b] **2** was formed as a single isomer, but 5% of impurities (not isomers) was included. [c] 2.9 g of **2** was isolated.

The vinyl bromide **2** is a very useful intermediate in preparation of (*E*)-Tamoxifen; thus, **2** in 95% purity was provided to the chemical transformations as depicted in Scheme 2. As we expected, **2** undertook conventional Suzuki cross-coupling to afford **4** in 83% yield with full retention of stereochemistry,[17] which means the product **4** is practically single. The starting 5% of impurities in **2** didn't affect the single isomeric formation of **4**. Recrystallization from CH_3OH purified the sample, giving a totally pure **4** in 69%. This conventional method was also amenable to scale-up preparation utilizing 11.3 mmol of **2**, singly constructing 2.73 g of **4** in 77% yield as a totally pure form just after silica-gel column chromatography. The molecular structure of **4** was determined by crystallographic analysis (Figure 2),[18] which disclosed that full retention of the stereochemistry throughout from **1** to **4** was accomplished. Then, **4** undertook the demethylation process utilizing the conventional ways of BBr_3 and TMSI; however, BBr_3 gave 1:1 isomeric phenol mixtures, and the use of TMSI remained the starting **4** intact. We finally employed a reagent of sodium ethane thiolate ($NaSCH_2CH_3$) that was reported by Miller's report, which successfully lead phenolic **5** with nearly full maintenance of the initial stereochemistry.[19] The final etherification step to (*E*)-Tamoxifen achieved high-yielding transformation of 97% with *E*/*Z* ratio of 96/4.[20,21]



Scheme 2. Synthesis of (*E*)-Tamoxifen from **2** through the intermediate **4** and **5** with nearly full retention of the initial stereochemistry.

In a similar vein, we attempted a synthesis of (*Z*)-Tamoxifen from a stereo-defined scaffold of vicinal dihaloalkene **6** through a substitution reaction of its vinylic iodine (Scheme 3). The CuTC-mediated cross-coupling between **6** and $PhSnBu_3$ was

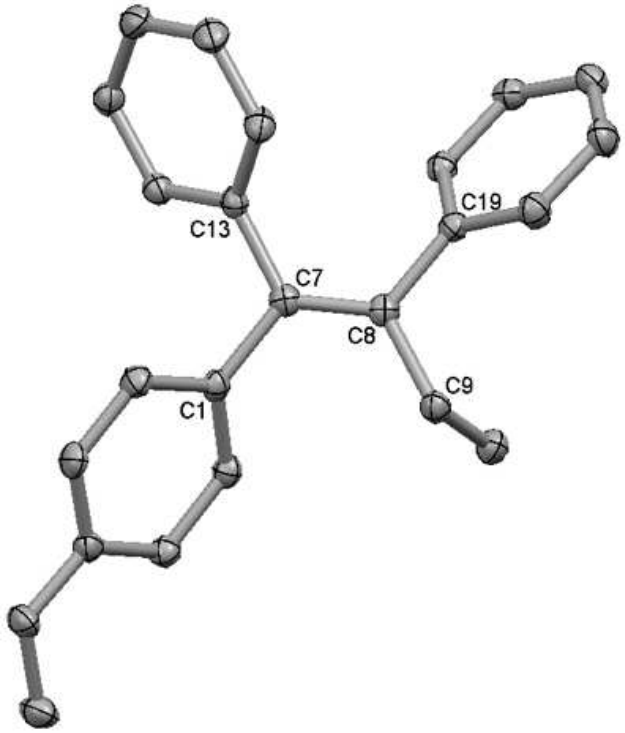
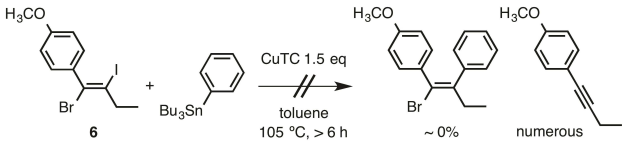


Figure 2. ORTEP drawing of **4**, with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] C7-C8 1.353, C7-C13 1.497, C7-C1 1.495, C8-C19 1.497, C2-C6 1.515. Selected bond angles [deg] C13-C7-C8 123.1(6), C13-C7-C1 114.1(3), C1-C7-C8 122.6(3), C19-C8-C7 122.8(3), C19-C8-C9 113.53, C9-C8-C7 123.6(3).

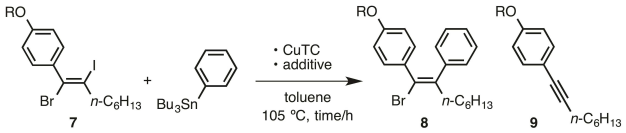


Scheme 3. **6** didn't undertake the CuTC-mediated activation of its vinylic iodine, unlike **1**.

conducted; however, the substitution reaction didn't proceed at all, and side-reaction of beta-halogen elimination occurred to give numerous amounts of 1-(*p*-anisyl)-1-butyne. Not only CuTC but also other conventional copper reagents were tried, but always causing the elimination side-reactions.[22] Then, we focused on the sharp difference in reactivity between **1** and **6**, and designed to replace the *para*-positioned MeO- moiety of **6** with $(iPr)_3SiO$-, TsO-, and BzO- substructures that work as protective groups of phenolic OH. Among them, the BzO-protected substrate showed good reactivity with $PhSnBu_3$ in the presence of CuTC.[23] Thus, we evaluated the influence of *para*-positioned substituents R in model compounds **7** tethered to n-C_6H_{13} side-chains (Table 3). The starting substrates **7** having masked R with carbonyls or CF_3 reacted within 2–4 hours, affording the desired **8** along with side-product **9** and unreacted **7**. The BzO-protected **8a** in entry 2 gave the best 45% isolated yields, although the desired products in entries 9–11 were not isolated owing to the close Rf values. The reactions really needed 4.5 equiv. of CuTC and $PhSnBu_3$ for improving the chemical yields of **8** and for suppressing the side-production of **9** (entries 2, 7 and 8).

With a viable substructure of (*Z*)-Tamoxifen in hand, we demonstrated the scalable synthesis of the benzoate-protected **11** utilizing the scaffold of **10** that has an ethyl group in 90% isomeric purity[24] (Table 4). For entry 1, the ethyl **10** was

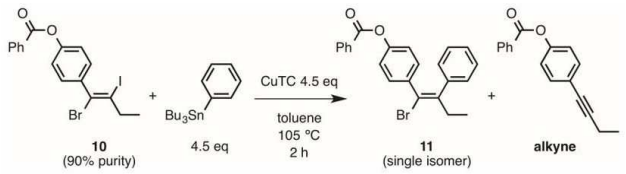
Table 3. *para*-Substituent-induced activation of the vinylic iodines of (*E*)-1-bromo-2-iodoalkenes **7** (R = protective group).[a][b]



Entry	R	CuTC (equiv)	*T* [h]	Product	Yield [%][c] **8**	**9**	**7**
1	PhCO	1.5	3	**8a**	28	24	24
2		4.5	2		61(45)	19	19
3[d]		4.5	2		49	14	5
4[e]		1.5	2		< 10	-	-
5[f]		1.5	2		< 6	-	-
6	CF_3	4.5	4	**8b**	42	20	10
7		4.5	16		44(33)	16	4
8	C_6F_5CO	4.5	4	**8c**	54(6)	32	6
9[g]	2-Naph-CO	4.5	2	-	47	13	10
10	4-CF_3PhCO	4.5	4	-	43	15	9
11	CH_3CO	4.5	3	-	46	28	12

[a] Standard conditions: **7** (0.5 mmol), $PhSnBu_3$ (844 mg, 2.25 mmol), CuTC (439 mg, 2.25 mmol), toluene (5 mL), 105 °C. [b] $PhSnBu_3$ usage amounts were equal to those of CuTC. [c] NMR yields based on mixtures that were collected after silica gel column chromatography. Isolated yields were listed in parentheses. [d] The reaction was performed in xylene at 135 °C. [e] 1.5 equiv. of PPh_3 was added. [f] 1.5 equiv. of O=PPh_3 was added. [g] 2-Naphthoyl group.

Table 4. Scalable synthesis of benzoate-protected **11** under the reaction condition of entry 2 in Table 3.

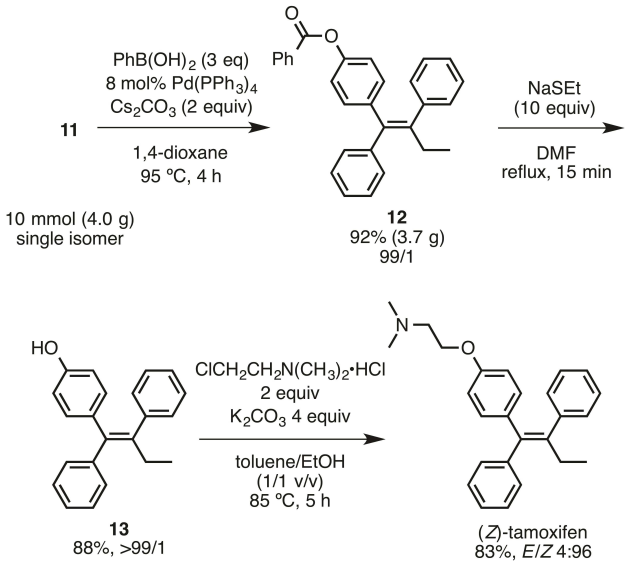


Entry	Scale of **10** mmol (g)	Yield [%][a] **11**[b]	**Alkyne**	**10**
1	0.5 (0.23)	41 (19)	11	15
2	1.5 (0.69)	60 (40)	12	16
3	4.0 (1.8)	60 (45)	13	13
4	8.0 (3.7)	60 (47)	14	25
5	16 (7.4)	61 (45)[c]	15	9

[a] NMR yields based on mixtures that were collected after silica gel column chromatography. Isolated yields for **11** were listed in parentheses. [b] **11** was formed as a single isomer. [c] 3.0 g of **11** was isolated in pure form.

subjected to the CuTC-mediated iodine-selective substitution reaction as well as *n*-hexyl version. The reaction was readily amenable to scale-up synthesis (entries 2–4), and the maximum load of **10** in entry 5 (7.4 g, 16 mmol) afforded 61% of **11** although side-production of the corresponding alkyne and unreacted **10** were observed in 15% and 9%, respectively.

We finally assessed utility of **11** by synthesizing (*Z*)-Tamoxifen (Scheme 4). The conventional palladium-catalyzed



Scheme 4. Synthesis of (*Z*)-Tamoxifen from **11** through the intermediate **12** and **13** with nearly full retention of the initial stereochemistry.

Suzuki reaction at the vinylic bromine proceeded, singly giving **12** in up to 92% yield of 3.7 g. For immobilization of the alkene geometry, the base of Cs_2CO_3 reached perfection while K_2CO_3 was ineffective owing to erosion of the stereochemistry.[25] The molecular structure of **12** was ensured by crystallographic analysis (Figure 3),[26,27] which disclosed that full retention of the stereochemistry throughout from **10** to **12** was accomplished. Then, **12** successfully undertook deprotection of benzoate group with $NaSCH_2CH_3$,[28] which afforded phenolic compounds **13** in 88% yield as a single isomer. The final etherification step to (*Z*)-Tamoxifen achieved high-yielding transformation of 83% with *E*/*Z* ratio of 4/96.

Conclusions

In summary, we successfully synthesized (*E*)- and (*Z*)-Tamoxifens through a new synthetic route that employs starting (*E*)-1-bromo-2-iodoalkenes. This study provides a salient feature: the CuTC-mediated iodine-selective activation of the starting (*E*)-1-bromo-2-iodoalkene with a reagent of $PhSnBu_3$ keeps the starting alkene geometry, significantly suppressing a side-reaction of beta-halogen elimination that gives a byproduct of alkyne. And furthermore, we should state clearly that the remaining three steps proceeded with retention of the stereo-

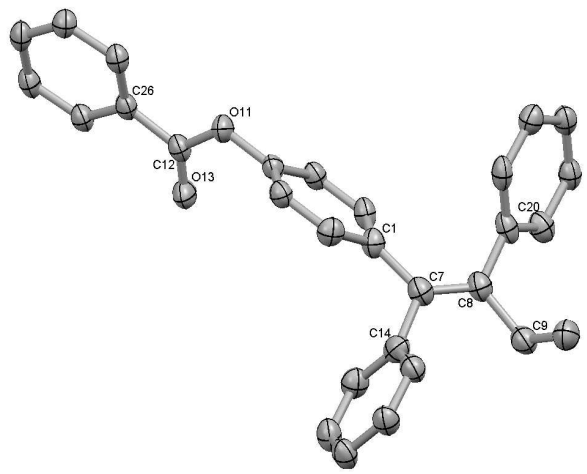


Figure 3. ORTEP drawing of **12**, with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] C7-C8 1.352, C7-C1 1.498, C7-C14 1.501, C8-C9 1.520, C8-C20 1.511. Selected bond angles [deg] C8-C7-C1 124.8(7), C1-C7-C14 114.2(3), C14-C7-C8 120.8(0), C7-C8-C9 121.9(0), C9-C8-C20 115.7(0), C20-C8-C7 122.3(7).

chemistry: the Suzuki reaction of the vinyl bromide, and deprotection of MeO and BzO groups by NaSEt, and etherification of amino-ethyl moiety, these passed off successfully without loss of original olefin arrangement. Our synthetic development shown here would impact syntheses of biologically interesting molecules in terms of Tamoxifen related drugs, because the starting (*E*)-1-bromo-2-iodoalkene is a scaffold for diverse preparation of singly well-arrayed tetrasubstituted template. We hope this intuitive methodology finds widespread use in organic synthesis.

Supporting Information Summary

Synthetic procedures as well as ^{1}H and ^{13}C NMR spectra of all new compounds.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Alkene geometry · Tamoxifen · Template synthesis · Tetrasubstituted olefins · Vicinal hetero-dihaloalkenes

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[18] CCDC-1816552 (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*1 21/n 1, colorless, $a=12.8105(1)$ Å, $b=8.6984(1)$ Å, $c=15.6763(1)$ Å, $\alpha=90°$, $\beta=93.844(1)°$, $\gamma=90°$, $V=1742.89(3)$ Å^3, $Z=4$, $T=293$ K, $d_{calcd.}=1.198$ g cm^{-3}, μ(Mo-$K\alpha$)$=0.548$ mm^{-1}, $R_1=0.0445$, $wR_2=0.1162$, GOF$=1.079$.
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[20] Although we run the experiments twice, the 4% erosion of *E*/*Z* ratios was observed. It seems likely that the phenolate anions produced during alkylation step would be prone to isomerization.
[21] Recrystallization from hexane yielded 45% of (*E*)-Tamoxifen with *E*/*Z* ratio of 100/0.
[22] For example, the usage of CuOTf•1/2(C_6H_6), $Cu(OTf)_2$, CuI, CuBr, CuCl, Cu_2O, CuOAc, $Cu(OAc)_2$, $(CH_3CN)_4Cu^+BF_4^-$ didn't work at all..
[23] The $(iPr)_3SiO$-protected substrate substrate resulted in only production of alkyne byproduct of 80% yield, under refluxing toluene condition. The TsO-protected substrate afforded the coupling adduct in ~40% NMR yield along with 36% of alkyne byproduct and 21% of starting material; but Rf values of these compounds were too close to separate the products.
[24] We prepared **10** through the reaction between the *in situ* generated IBr and corresponding alkyne, according to our previously reported method of ref. 11 (see Supporting Information): the product was consisted of 90:10 isomeric mixtures. Lots of efforts to separate two isomers were unsuccessful. The major isomer formed the trans-mode as illustrated **10**; however, the shape of the other minor isomer was unidentified.
[25] *E*/*Z* ratio was around 10:90 with chemical yield of 40%.
[26] CCDC-1878062 (for **12**) 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.ac.uk/data_request/cif. Monoclinic, space group *P*-1, colorless, $a=5.5973(2)$Å,□$b=9.1931(2)$ Å, $c=21.5700(4)$, $\alpha=95.264(2)°$, $\beta=95.978(2)°$, $\gamma=98.388(2)°$, $V=1085.60(5)$ Å^3, $Z=2$, $T=293$ K, $d_{calcd.}=1.237$ g cm^{-3}, μ(Mo-$K\alpha$)$=0.595$ mm^{-1}, $R_1=0.0820$, $wR_2=0.2300$, GOF$=1.029$.
[27] Single crystal of **12** was formed in 2-propanol.
[28] a) A. K. Chakraborti, M. K. Nayak, L. Sharma, *J. Org. Chem.* **2002**, *67*, 1776–1780; b) A. K. Chakraborti, M. K. Nayak, L. Sharma, *J. Org. Chem.* **1999**, *64*, 8027–8030.

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