Regio- and stereoselective synthesis of 1-(1-halovinyl)-1H-indoles from 1-ethynyl-1H-indoles with in situ generated HX

Akihiro H. Sato, Kazuhiro Ohashi, Kouhei Ito, Tetsuo Iwasawa *

Department of Materials Chemistry, Faculty of Science and Technology, Ryukoku University, Otsu, Shiga 520-2194, Japan

A B S T R A C T

A facile approach to 1-(1-halovinyl)-1H-indoles from readily accessible 1-ethynyl-1H-indoles with in situ generated HX is described. The simple protocol enables a regio- and stereoselective hydrohalogenation to the triple bonds in gram-scale, and provides a general entry for novel N-alkenylindole derivatives.

© 2013 Elsevier Ltd. All rights reserved.

Enamides are valuable intermediates in organic synthesis,[1–3] because of their ability to serve as building blocks in a wide variety of functional group transformations.[4] They have also been found as a substructure in numerous bioactive natural products and pharmaceutically interesting compounds.[5] In addition, they recently have emerged as a novel type of useful nucleophiles in stereoselective C–C and C–N bond-forming reactions.[6] From the synthetic point of view, haloenamides are versatile variants of enamides. Reactive bond between sp^2 carbon and halogen in haloenamide is advantageous to chemical transformation, and this beneficial point would expand the possibilities and importance of enamide structure. Iodoenamides are especially useful, as they are readily converted into various functional groups by halogen-metal exchange and are significant for carbon–carbon bond forming reactions by way of transition-metal catalyzed cross-coupling reactions.[7–9] Thus, the weakly bonded iodide and electron-rich olefin are highly reactive and potentially useful toward the synthesized nitrogen-containing complex molecules.[10,11] Despite the utility of iodoenamides, their synthetic availability still remains a challenge, because of the inherent difficulty in regio- and stereoselective hydrohalogenation.[12] The stoichiometric addition of hydrogen iodide (HI) to ynamide is one way to prepare iodoenamides; however the hygroscopic and gaseous HI is inconvenient, and this method often results in poor regio- and stereochemical control, and separation of the resultant isomeric mixtures is laborious.[13]

The pioneering work for efficient synthesis of iodoenamide from ynamide via addition of HI was reported by Hsung and co-workers in 2003.[14] The in situ generation of HI from MgI$_2$ and H$_2$O afforded α-iodoenamides with good selectivities of E/Z ratios. The outcome of stereoselective addition is dictated by the polarization of the triple bond caused by nitrogen.[15] According to the nature of the keteniminium resonance form, the iodine automatically unites with the α-carbon. There was still room for improvement in the reaction efficiency, especially in terms of its scale and purity; the prototype system worked using only 0.1 mmol of starting alkynes and giving the products with E/Z mixtures. On the other hand, very recently we successfully performed a synthesis of α-iodoenamide as a single isomer in gram-scale (up to 2.62 g) using in situ generated HX.[16] The in situ HX (X = I, Br) was generated from halotrimethylsilane (TMSX) and H$_2$O, and added to ynamide in nearly quantitative yields with perfect regio- and stereoselectivities.[14,17,18] The method completes the reaction quickly under routine conditions, and showed extensive substrate compatibility.

Herein we present a facile vinyl halogenation of 1-ethynyl-1H-indoles,[19,20] which regio- and stereoselectively yields 1-(1-halovinyl)-1H-indoles through the addition of the in situ generated HX (Scheme 1). Our previously reported method was successfully applicable to the triple bond of 1-ethynyl-1H-indoles: to the best of our knowledge, so far such a compound of 1-(1-halovinyl)-1H-indole has not been reported. Thus, the protocol provides a simple access to novel 1-(1-halovinyl)-1H-indole moieties.

At the onset of our study, we focused on TMSI-mediated hydroiodation of **1**,[21,22] based on our previous report.[16,23] The

---

* Corresponding author. Tel.: +81 77 543 7461; fax: +81 77 543 7483.
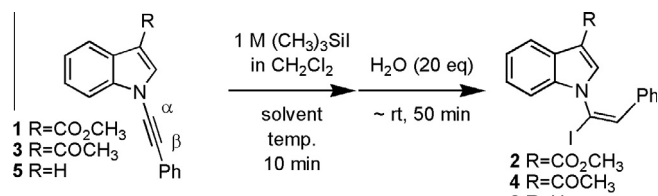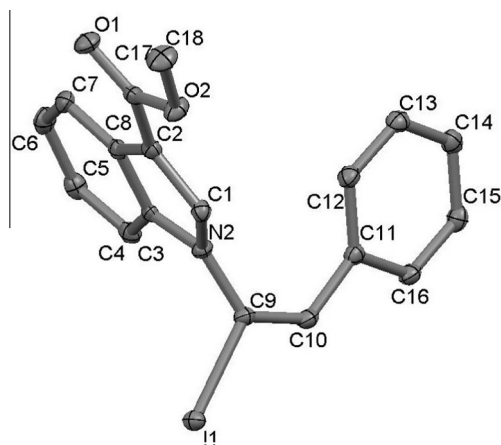*E-mail address:* iwasawa@rins.ryukoku.ac.jp (T. Iwasawa).

Scheme 1. Hydroiodation of **1**, **3**, and **5**.

Figure 1. ORTEP drawing of **2** with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): N(2)–C(9) = 1.415, C(9)–I(1) = 2.125, C(9)–C(10) = 1.327, C(10)–C(11) = 1.479.

Table 1
Evaluation of the reactivity of **1** conducted via Scheme 1[a]

Entry	TMSI (equiv)	Temp (°C)	Solvent	Yield[b] (%)	
				(E)-**2**	**1**
1	1.2	−78	CH_2Cl_2	73	12
2	1.5	−78	CH_2Cl_2	99	0
3	2.0	−78	CH_2Cl_2	Quant.	0
4	2.0	−45	CH_2Cl_2	95	0
5	2.0	0	CH_2Cl_2	94	0
6	2.0	rt	CH_2Cl_2	97	0
7[c]	2.0	−78	CH_2Cl_2	97	0
8[d]	2.0	−78	CH_2Cl_2	99 (96)[e]	0
9[f]	2.0	0[g]	CH_2Cl_2	Quant.	0
10[h]	2.0	0[g]	CH_2Cl_2	95	0
11	2.0	−78	CH_2Cl_2/H_2O (4% v/v)	99	0
12	2.0	rt	CH_2Cl_2/H_2O (4% v/v)	61	39
13	2.0	−78	Toluene	92	4
14	2.0	−78	CPME	96	4
15	2.0	−78	THF	68	31
16	2.0	−78	Hexane	<1	99
17	2.0	−20	CH_3CN	0	>99
18[i]	2.0	−78	CH_2Cl_2	88	9
19[j]	2.0	−78	CH_2Cl_2	Quant.	0
20[k]	2.0	−78	CH_2Cl_2	0	99

[a] Reaction conditions: **1** (1 mmol), solvent (8 mL), 1 M $(CH_3)_3SiI$ in CH_2Cl_2, H_2O (20 mmol).
[b] Isolated yields of **2** and recovered **1**.
[c] After addition of H_2O, the reaction was conducted at 0 °C.
[d] D_2O was used instead of H_2O.
[e] % D in parenthesis.
[f] 4 mL of CH_2Cl_2 was used.
[g] For dissolving **1** in CH_2Cl_2, the reaction was performed at 0 °C.
[h] 1 mL of CH_2Cl_2 was used.
[i] CH_3OH was used instead of H_2O.
[j] $(CH_3)_3SiBr$ was used instead of $(CH_3)_3SiI$.
[k] $(CH_3)_3SiCl$ was used instead of $(CH_3)_3SiI$.

Table 2
Evaluation of the reactivity of **3** and **5** conducted via Scheme 1[a]

Entry	Substrate	Solvent	Temp (°C)	Yield[b] (%)	
				4 or **6** (E/Z)	**3** or **5**
1	**3**	CH_2Cl_2	−78	95/4	Trace
2	**5**	CH_2Cl_2	−78	95/5	0
3	**3**	CH_2Cl_2	0	97/3	0
4	**5**	CH_2Cl_2	0	93/7	0
5[c]	**5**	CH_2Cl_2	rt	53/4	0
6	**3**	CH_2Cl_2/H_2O (4% v/v)	−78	95/4	Trace
7	**5**	CH_2Cl_2/H_2O (4% v/v)	−78	94/6	0
8[d]	**3**	CH_2Cl_2	0	98/2	0
9[d]	**5**	CH_2Cl_2	0	98/2	0
10[e]	**3**	CH_2Cl_2	0	97/3	0
11[f]	**3**	CH_2Cl_2	0	96/4	0
12[f]	**5**	CH_2Cl_2	0	98/2	0
13[g]	**3**	CH_2Cl_2	0	91/9	0
14[h]	**3**	CH_2Cl_2	−78	93/4	3
15[h]	**5**	CH_2Cl_2	−78	Quant./0	0

[a] Reaction conditions: **3** or **5** (0.5 mmol), solvent (4 mL), 1 M $(CH_3)_3SiI$ in CH_2Cl_2 (2 equiv), H_2O (10 mmol).
[b] Determined by ^{1}H NMR after column chromatography.
[c] Compound **6** was purified with short-plug column chromatography.
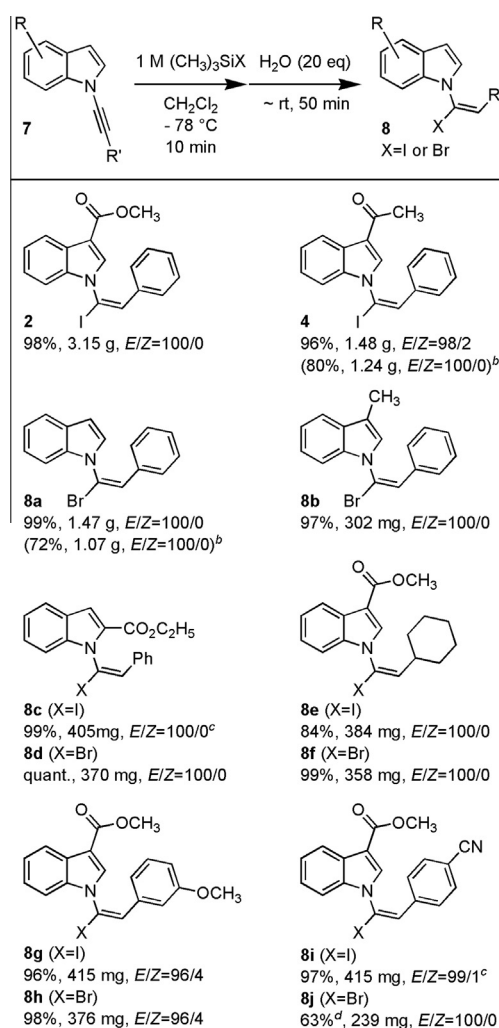[d] CH_3OH was added instead of H_2O.
[e] 1.5 equiv of $(CH_3)_3SiI$ was used.
[f] 2 mL of CH_2Cl_2 was used.
[g] 0.5 mL of CH_2Cl_2 was used.
[h] $(CH_3)_3SiBr$ was used instead of $(CH_3)_3SiI$.

mixture of **1** and TMSI[24] was stirred at −78 °C for 10 min, then water was added, and the reaction was allowed to warm to ambient temperature. After workup and purification, the product was isolated without decomposition, and both ^{1}H and ^{13}C NMR analyses revealed it to be a single isomer. The molecular structure of **2** was determined by crystallographic analysis as shown in Figure 1,[25] disclosing its stereochemistry as a (E)-α-iodovinyl adduct.[26]

As summarized in Table 1, the reactivity of **1** conducted via Scheme 1 was evaluated. More than 1.5 equiv of TMSI was needed for completion (entries 1–3), and a wide range of temperature was tolerated (entries 3–6). For entry 8, deuterioiodation of **1** was carried out with D_2O, and deuterium was incorporated in 96%. The concentration was increased in entries 9 and 10, and high yielding transformations were achieved. For entries 11 and 12, addition of H_2O to the solvent in advance yielded 99% at −78 °C and 61% at room temperature, respectively. Other solvents of toluene, cyclopentyl methyl ether, and THF gave an acceptable yield of (E)-**2** although some unreacted **1** remained (entries 13–15). For entry 18, methanol was used as a proton source in place of H_2O, however, 9% of the starting **1** remained. For entries 19 and 20, $(CH_3)_3SiBr$ and $(CH_3)_3SiCl$ were used instead of TMSI; the former quantitatively yielded the corresponding (E)-α-bromovinyl, while the latter resulted in 0%. The respective bond energies of Si–Cl, Si–Br, and Si–I are 113, 96, and 77 kcal/mol:[27] the obstinate bond of Si–Cl would be difficult to activate. It is worth noting that any (Z)- or β-isomer of **2** was not observed on NMR spectra and TLC analyses from entry 1 through entry 20.

On the other hand, as shown in Table 2, the hydrohalogenation of **3** and **5** conducted via Scheme 1 afforded the E/Z isomeric mixtures of **4** and **6**, in high yields. For entries 1–5, small amounts of (Z)-**4** and (Z)-**6** were observed at a wide range of temperatures. Addition of 20 equiv water in advance (entries 6 and 7), and the employment of methanol (entries 8 and 9), and the increased concentration (entries 11–13) did not afford **4** or **6** as a single isomer. For entry 15, surprisingly, the hydrobromination of **5** exclusively gave (E)-**6** in quantitative yield. Noteworthy is that highly stereochemical controls were achieved at all entries in Table 2.

Table 3
Scope of the reaction[a]

R–indole(7) with alkyne ⟶ 1 M (CH₃)₃SiX, CH₂Cl₂, −78 °C, 10 min; H₂O (20 eq), ~ rt, 50 min ⟶ 8 (X=I or Br)

2
98%, 3.15 g, E/Z=100/0

4
96%, 1.48 g, E/Z=98/2
(80%, 1.24 g, E/Z=100/0)[b]

8a
99%, 1.47 g, E/Z=100/0
(72%, 1.07 g, E/Z=100/0)[b]

8b
97%, 302 mg, E/Z=100/0

8c (X=I)
99%, 405mg, E/Z=100/0[c]
8d (X=Br)
quant., 370 mg, E/Z=100/0

8e (X=I)
84%, 384 mg, E/Z=100/0
8f (X=Br)
99%, 358 mg, E/Z=100/0

8g (X=I)
96%, 415 mg, E/Z=96/4
8h (X=Br)
98%, 376 mg, E/Z=96/4

8i (X=I)
97%, 415 mg, E/Z=99/1[c]
8j (X=Br)
63%[d], 239 mg, E/Z=100/0

[a] Reaction conditions: **7** (1 equiv), CH₂Cl₂ (8 mL/mmol of **7**), 1 M (CH₃)₃SiX in CH₂Cl₂ (2 equiv).
[b] Recrystallization from ethanol.
[c] Reaction was conducted at −20 °C.
[d] Determined by ¹H NMR. 37% of unreacted **7j** was observed.

With optimized conditions in hand for the TMSX-mediated synthesis of 1-(1-halovinyl)-1H-indoles, we next turned our attention to the scope of this reaction. The results are summarized in Table 3. The reactions at gram-scale successfully performed in synthesizing **2** of 3.15 g and **8a** of 1.47 g without any isomers, respectively.[28,29] Recrystallization of acetyl **4** on a E/Z = 98/2 mixture afforded a single (E)-isomer of 1.24 g in 80% yield. Methyl indole **8b** as only E-form was suitably obtained in 97% yield. The ester group at 2-position of the indole frame was accepted for the hydrohalogenation in high yields (**8c** and **8d**), and the substrate derived from aliphatic alkynes was converted into the corresponding halovinyls with perfect stereo-control (**8e** and **8f**). In the presence of functional groups such as OMe and CN (**8g–8j**) the transformation worked well with high stereoselectivity, although **8j** was produced along with 37% of the unreacted **7j**. Notably, all the 1-(1-halovinyl)-1H-indoles in Table 3 were stable without decomposition, whereas the similar stability of the vinyl halides was not observed in (E)-α-haloenamides and (1-iodovinyl)arene.[16]

The mechanism resulting in high stereochemical control to produce predominantly (E)-adducts is not yet fully known. Preliminary mechanistic investigations were performed through the deuterioiodation of **1** (Table 1, entry 8) and competitive reactions (Table 4). The deuterioiodation of **1** was carried out with D₂O, and the deuterium was thoroughly incorporated for H of (E)-**2**. As for competitive reactions, **5** dominated over **1** in reactivity (run 1 and 2): **5** was quantitatively transformed into **6**, while ca. 80% of **1** was unreacted. These indicate that the hydrohalogenation does not follow a stepwise path, and carbonyl substituents such as ester or ketone on indole did not affect the selectivities: the nitrogen atom of indole scaffold likely coordinate to the silicon atom, involving the exact syn-addition of HBr.[14,30–32] Actually, diphenylacetylene was tested on this hydrohalogenation system, and no reaction was observed.[16a]

In summary, a simple procedure for regio- and stereoselective hydrohalogenation of 1-ethynyl-1H-indoles has been developed. This approach afforded a variety of new and potentially useful 1-(1-halovinyl)-1H-indoles in high yields along with the practically perfect stereochemical outcomes. The method quickly completes the reaction under routine conditions, and was readily amenable to scale-up. Mechanistically, nitrogen of indole scaffold likely coordinates to silicon, involving the exact syn-addition of HI. We hope this reliable methodology finds widespread use in organic synthesis. Application and mechanistic elucidation are ongoing for further development of this reaction and will be reported in due course.

Table 4
Competitive experiments of hydrobromination between **1** and **5**

1 0.5 mmol (Ph) + **5** 0.5 mmol (Ph) ⟶ conditions ⟶ **1** + **2** + **5** + **6**
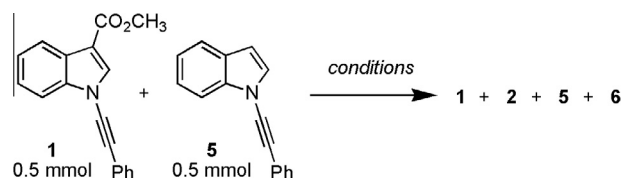
Run	Conditions	Amount (mmol)			
		1	**2**	**5**	**6**
1	(1) CH₂Cl₂ (8 mL), −78 °C, 10 min; then 1 M TMSBr (1.5 equiv)	0.41	0.09	0	0.50
	(2) H₂O (0.4 mL), rt, 50 min				
2	(1) CH₂Cl₂ (8 mL)/H₂O (0.4 mL), −78 °C, 10 min; then 1 M TMSBr (1.5 equiv)	0.40	0.10	0	0.50
	(2) rt, 50 min				

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.107.

References and notes

1. (a) Larock, R. C. Comprehensive Organic Transformations: A Guide to Functional Group Preparations; Wiley-VCH: New York, 1999; (b) Rappoport, Z. The Chemistry of Enamines. In The Chemistry of Functional Groups; John Wiley and Sons: New York, 1994.
2. (a) Shen, R.; Porco, J. A., Jr. Org. Lett. 2000, 2, 1333; (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. Org. Lett. 2003, 5, 3667.
3. For reviews on enamides, see: (a) Dehli, J. R.; Legros, J.; Bolm, C. Chem. Commun. 2005, 41, 973; (b) Whitesell, J. K.; Whitesell, M. A. Synthesis 1983, 517; (c) Hickmott, P. W. Tetrahedron Lett. 1982, 38, 1975; (d) Hickmott, P. W. Tetrahedron Lett. 1982, 38, 3363; (e) Lenz, G. R. Synthesis 1978, 489.
4. (a) Ruan, J.; Xiao, J. Acc. Chem. Res. 2011, 44, 614–626; (b) Ma, D.; Cai, Q. Acc. Chem. Res. 2008, 41, 1450–1460.
5. (a) Nielsene, P. H.; Anthoni, U.; Christophersen, C. Acta Chem. Scand. 1988, B42, 489–491; (b) Anthoni, U.; Bock, K.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. J. Org. Chem. 1987, 52, 5638–5639; Anthoni, U.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. J. Org. Chem. 1987, 52, 4709–4719; (d) Chevolot, L.; Chevolot, A.-M.; Gajhede, M.; Larsen, C.; Anthoni, U. J. Am. Chem. Soc. 1985, 107, 4542–4543; (e) Lin, X.; Weinreb, S. M. Tetrahedron Lett. 2001, 42, 2631–2633; (f) Pinder, J. L.; Weinreb, S. M. Tetrahedron Lett. 2003, 44, 4141–4143; (g) Nishikawa, T.; Kajii, S.; Isobe, M. Synlett 2004, 2025–2027; (h) Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. Angew. Chem., Int. Ed. 2005, 44, 3714–3717; (i) Sun, C.; Camp, J. E.; Weireb, S. M. Org. Lett. 2006, 8, 1779–1781.
6. Matsubara, R.; Kobayashi, S. Acc. Chem. Res. 2008, 41, 292. and references therein.
7. (a) Brandsma, L.; Verkruijsse, H. Preparative Polar Organometallic Chemistry 1; Springer: Berlin, 1987; (b) Wakefield, B. J. Organolithium Methods; Academic Press: London, 1988; (c) Brandsma, L. Preparative Polar Organometallic Chemistry 2; Springer: Berlin, 1990; (d) Schlosser, M. In Organometallics in Synthesis A Manual; Schlosser, M., Ed., 2nd ed.; Wiley: Chichester, UK, 2002; pp 1–352.
8. (a) Neumann, H.; Seebach, D. Chem. Ber. 1978, 111, 2785; (b) Evans, D. A.; Crawford, T. C.; Thomas, R. C.; Walker, J. A. J. Org. Chem. 1976, 41, 3947.
9. Galli, C.; Rappoport, Z. Acc. Chem. Res. 2003, 36, 580.
10. (a) Funk, R. L.; Hentley, R. J. Tetrahedron Lett. 2011, 52, 6671; (b) Heffernan, S.; Carbery, D. R. Tetrahedron Lett. 2012, 53, 5180.
11. (a) Yu, Z.; Jin, Z. J. Am. Chem. Soc 2000, 122, 9840; (b) Liu, X.; Henderson, J. A.; Sasaki, T.; Kishi, Y. J. Am. Chem. Soc. 2009, 131, 16678.
12. (a) Reddy, Ch. K.; Periasamy, M. Tetrahedron Lett. 1919, 1990, 31; (b) Stewart, L. J.; Gray, D.; Pagni, R. N.; Kabalka, G. W. Tetrahedron Lett. 1987, 28, 4497; (c) Stone, H.; Schecher, H. Org. Synth. Coll. 1963, 4, 543.
13. (a) Kropp, P. J.; Craword, S. D. J. Org. Chem. 1994, 59, 3102; (b) Hudrlik, P. F.; Kulkarni, A. K.; Jain, S.; Hudrlik, A. M. Tetrahedron Lett. 1983, 39, 877; (c) Griesbaum, K.; El-Abed, M. Chem. Ber. 2001, 1973, 106.
14. Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. Org. Lett. 2003, 5, 1547.
15. (a) Compain, G.; Jouvin, K.; Martin-Mingot, A.; Evano, G.; Marrot, J.; Thibaudeau, S. Chem. Commun. 2012, 48, 5196; (b) Evano, G.; Coste, A.; Jouvin, K. Angew. Chem., Int. Ed. 2010, 49, 2840; (c) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. Chem. Rev. 2010, 110, 5064; (d) Mulder, J. A.; Kurtz, K. C. M.; Hsung, P. R. Synlett 2003, 1379.
16. (a) Sato, A. H.; Mihara, S.; Iwasawa, T. Tetrahedron Lett. 2012, 53, 3585–3589; (b) Sato, A. H.; Ohashi, K.; Iwasawa, T. Tetrahedron Lett. 2013, 54, 1309–1311.
17. Kamiya, N.; Chikami, Y.; Ishii, Y. Synlett 1990, 675–676.
18. Jouvin, K.; Coste, A.; Bayle, A.; Legrand, F.; Karthikeyan, G.; Tadiparthi, K.; Evano, G. Organometallics 2012, 31, 7933–7947.
19. (a) Gupta, L.; Talwar, A.; Chauhan, M. S. Curr. Med. Chem. 2007, 14, 1789–1803; (b) Gul, W.; Hamann, M. T. Life Sci. 2005, 78, 442–453; (c) Aygun, A.; Pindur, U. Curr. Med. Chem. 2003, 10, 1113–1127; (d) Skibo, E. B.; Xing, C.; Dorr, R. T. J. Med. Chem. 2001, 44, 3545–3562; (e) McLeay, L. M.; Smith, B. L.; Munday-Finch, S. C. Res. Vet. Sci. 1999, 66, 119–127; (f) Katritzky, A. R.; Zhang, G.; Xie, L.; Ghiviriga, I. J. Org. Chem. 1996, 61, 7558–7563; (g) Bergman, J.; Venemalm, L.; Gogoll, A. Tetrahedron Lett. 1990, 46, 6067–6084.
20. (a) Li, H.; Boonnak, N.; Padwa, A. J. Org. Chem. 2011, 76, 9488–9496; (b) Joshi, M.; Patel, M.; Tiwari, R.; Verma, A. K. J. Org. Chem. 2012, 77, 5633–5645.
21. (a) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. Org. Lett. 2004, 6, 1151–1154; (b) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. J. Org. Chem. 2006, 71, 4170–4177.
22. Our improved procedure for preparing 1-ethynyl-1H-indoles affords high yields, see Supplementary data.
23. Representative procedure for synthesizing (E)-2 (Table 1, entry 3): to a solution of 1 (1 mmol) in anhydrous CH_2Cl_2 (8 mL) at −78 °C was added TMSI (1 M in CH_2Cl_2) dropwise over 5 min, and the mixture was stirred for 10 min. Then, H_2O (20 mmol) was added, and the cooling-bath was removed to warm to room temperature. After additional stirring for 50 min, the reaction was quenched at 0 °C with saturated aqueous sodium thiosulfate, and stirred for 30 min, and allowed to warm to ambient temperature. To the mixture was added CH_2Cl_2, and organic phases were washed with brine, and then dried over Na_2SO_4, and concentrated to give a crude product. Purification by silica gel column chromatography (eluent; toluene/EtOAc = 100/1) afforded 403 mg of (E)-2 in quantitative yield as a pale yellow solid material. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 8.1, 1.5 Hz, 1H), 7.79 (s, 1H), 7.45 (s, 1H), 7.42–7.30 (m, 3H), 7.20–7.16 (m, 1H), 7.13–7.09 (m, 2H), 6.76 (dd, J = 9.0, 1.4 Hz, 2H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.3, 127.0, 124.5, 123.7, 122.2, 112.3, 111.7, 84.1, 51.6. MS (EI) m/z: 403 (M^+), 372 ([M−OCH_3]$^+$), 276 ([M−I]$^+$). IR (neat): 3121, 3048, 1697 (C=O), 1621 (C=C) cm^{-1}. Anal. Calcd for $C_{18}H_{14}INO_2$: C, 53.62; H, 3.50; N, 3.47. Found: C, 53.46; H, 3.60; N, 3.73.
24. Preparation of 1 M TMSI in CH_2Cl_2, see Supplementary data.
25. Crystal data of (E)-2: orthorhombic, space group P212121, colorless, a = 10.247(3) Å, b = 10.904(3) Å, c = 13.780(3) Å, α β γ = 90°, V = 1539.7 Å^3, Z = 4, T = −180 °C, d_{calcd} = 1.739 g cm^{-3}, μ(Mo, Kα) = 2.09 mm^{-1}, R_1 = 0.0193, wR_2 = 0.0451, GOF = 1.241.
26. Compound 5 was converted to the corresponding olefin using tert-BuLi for lithium–halogen exchange, and the (Z)-olefin was obtained in 94% yield with typical coupling constant J = 9.2 Hz for cis-form: in brief, the compound 5 was in (E)-fashion.
27. (a) Walsh, R. Acc. Chem. Res. 1981, 14, 246–252; (b) Doncaster, A. M.; Walsh, R. J. Phys. Chem. 1979, 83, 3037–3040.
28. Noyori, R. Angew. Chem., Int. Ed. 2002, 41, 2008–2022.
29. (a) Mullard, A. Nat. Rev. Drug Disc. 2011, 10, 643–644; (b) Prinz, F.; Schlange, T.; Asadullah, K. Nat. Rev. Drug Disc. 2011, 10, 712.
30. The alternative to the concerted way is synchronous mechanism, see: (a) Fischer, J.; Steglich, W. Angew. Chem., Int. Ed. 1979, 18, 167–168; (b) Bearpark, M.; Bernardi, F.; Olivucci, M.; Robb, M. A. J. Am. Chem. Soc. 1990, 112, 1732–1737.
31. Ihara, M.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. J. Org. Chem. 1994, 59, 8092–8100.
32. We have carried out some mechanistic studies with NMR experiments. The ^{1}H and ^{13}C NMR spectra for the mixture before addition of water were totally same with the starting alkynes. In addition, the reaction after addition of water was monitored with ^{1}H NMR spectra; the spectra were completely identical to the product. In brief, halosilylation of the starting alkyne did not occurred and the addition of HX was too fast to pursuit the reaction intermediates.