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Regio-, and Stereoselective Iodobromination of Ynamides for Synthesis of (*E*)-1-Bromo-2-iodoenamides

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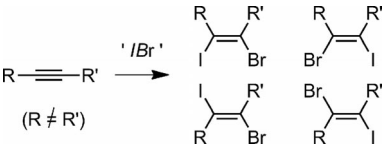
Keywords: Synthetic methods / Regioselectivity / Alkynes

One-step synthesis of vicinal bromoiodoenamides from ynamides through IBr addition is described. Two types of IBr were used: commercially available IBr, and in situ generated IBr. 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 tetrasubstituted olefins.

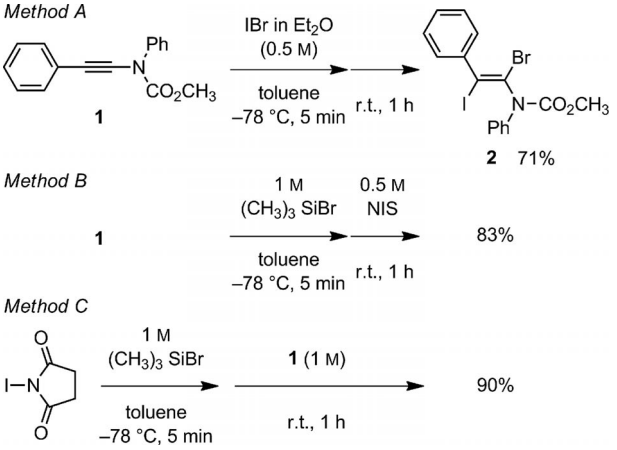
Introduction

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 substructures in bioactive natural products and pharmaceutically interesting compounds.[5] Moreover, they recently have emerged as a type of useful nucleophile in stereoselective C–C and C–N bond-forming reactions.[6] From a synthetic point of view, vicinal dihaloenamides are versatile variants of enamides. The reactive bonds between sp^2 carbon and halogen are advantageous to chemical transformation, and this beneficial point would expand the possibilities and importance of enamide structures. Bromoiodoenamides are especially useful, because they could be converted into various functional groups by halogen-metal exchange and be significant for carbon–carbon bond-forming reactions by way of transition-metal catalyzed cross-coupling reactions.[7–9] Thus, weakly bonded iodine/bromine and electron-rich olefins are highly reactive and potentially functional toward synthesized nitrogen-containing complex molecules.[10] Despite the utility of vicinal dihaloalkenes, their synthetic availability remains a challenge, because of the inherent difficulty in regio- and stereoselective iodobromination (Scheme 1). The stoichiometric addition of iodobromine to alkyne is one way to prepare a vicinal dihaloalkene; however IBr is inconvenient, hygroscopic and hazardous, and this method often results in poor regio- and stereochemical control.[11,12]



Scheme 1. Iodobromination of alkynes for synthesis of vicinal bromoiodoalkenes.

Herein we report the first example of a facile one-step synthesis[13] of vicinal bromoiodoenamides from ynamides in a highly regio- and stereoselective manner (Scheme 2). Commercially available IBr and/or in situ generated IBr accomplished the reaction. Commercially available IBr worked very well when used in diethyl ether solution. In situ IBr was successfully generated from bromotrimethylsilane (TMSBr) and *N*-iodosuccinimide (NIS). Thus, the methods provide simple general entry to (*E*)-1-bromo-2-iodoenamide substructures.



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

Results and Discussion

We started investigations with the reaction of **1** undertaken as shown in Scheme 2: three methods were used. For

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method A, a mixture of **1** and IBr (0.5 M) in diethyl ether was stirred at –78 °C, and the reaction was warmed to ambient temperature. The IBr is commercially available;[14] however, it is occasionally unpleasant to work with. Thus, it is worthwhile developing an alternative way to generate IBr in situ, such as for methods B and C. For method B, a mixture of **1** and TMSBr (1 M) in dichloromethane was stirred at –78 °C, then NIS (0.5 M) in acetonitrile was added, and the reaction was conducted at room temperature. For method C, a mixture of NIS and TMSBr solution was stirred at –78 °C, and then the appropriate amount of **1** in toluene was added. Luckily, for the crude mixture, both ^{1}H NMR and ^{13}C NMR spectroscopic analyses revealed a 97:3 isomeric ratio for method B and about 100:0 for methods A and C. Workup and purification with column chromatography gave corresponding IBr adduct **2** in 71, 83, and 90%, respectively, for methods A, B and C. Concerning iodobromination of **1**, the in situ version of methods B and C was better than method A. The molecular structure of **2** was determined by crystallographic analysis as shown in Figure 1, disclosing its stereochemistry as (*E*) fashion.[15]

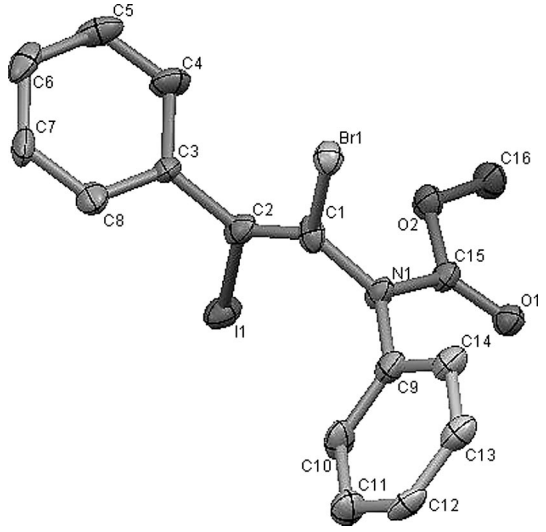
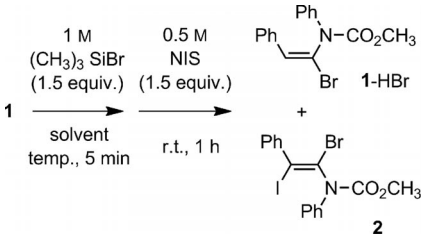


Figure 1. ORTEP drawing of **2** with thermal ellipsoids at the 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: N(1)–C(1) = 1.417, C(1)–Br(1) = 1.934, C(2)–I(1) = 2.114, C(1)–C(2) = 1.304.

As summarized in Table 1, screening of reaction conditions for method B was conducted with **1**. For Table 1, Entries 1–4, appropriate temperatures were surveyed, and low temperatures were needed to give **2** in good yield. Unfortunately, purification of **2** suffered from small amounts of by-product, which was the hydrobromination adduct of (*E*)-methyl-1-bromo-2-phenylvinyl(phenyl)carbamate, namely **1**-HBr.[16,17] For Table 1, Entries 5–8, yields in dichloromethane, acetonitrile, tetrahydrofuran (THF), and cyclopentyl methyl ether (CPME) were 70, 65, 36, and 72%, respectively; they were not higher than 83% in Table 1, Entry 1. For Table 1, Entry 9, method C accomplished clean iodobromination in a high 90% yield without producing byproduct **1**-HBr. However, these studies proved **2** to be fragile in the solution state: a colorless solution of **2** in several solvents gradually turned colored and gave several spots by TLC monitoring.

Table 1. Screening of reaction conditions for method B.[a]

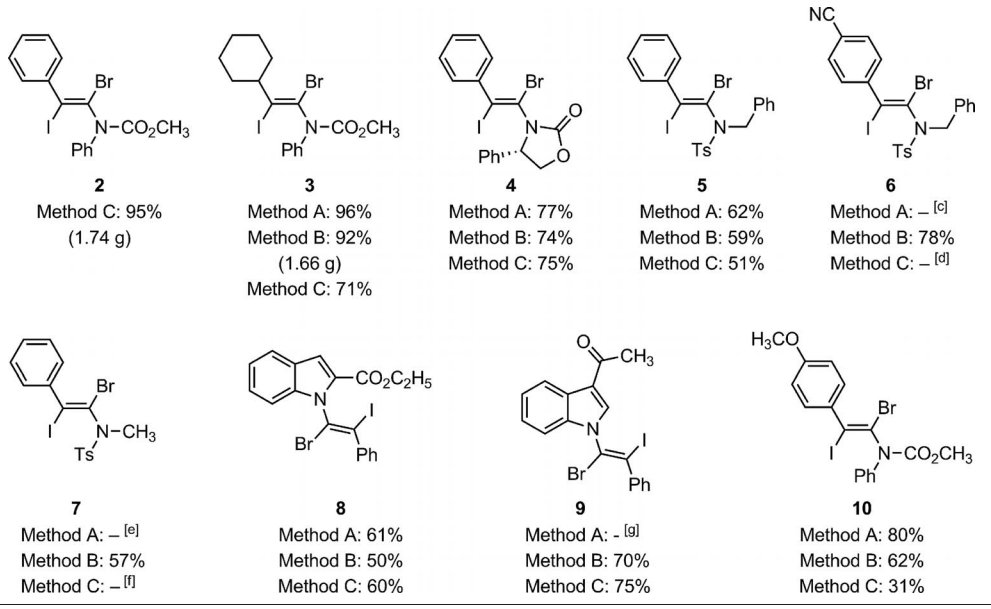


Entry	Solvent	Temp. [°C]	Yield [%][b]	
			2	**1**-HBr
1	toluene	–78	83	3
2	toluene	–45	87	5
3	toluene	–20	77	2
4	toluene	0	80	8
5	CH_2Cl_2	–78	70	5
6	CH_3CN	–20	65	1
7	THF	–78	36	7
8	CPME	–78	72	11
9[c]	toluene	–78	90	0

[a] Reaction conditions: **1** (126 mg, 0.50 mmol), solvent (2 mL), TMSBr (1 M) in dichloromethane, NIS (0.5 M) in acetonitrile. [b] Isolated yields for **2**, and yield calculated by NMR spectroscopy for **1**-HBr in the crude state, see ref.[17]. [c] Performed by method C.

With a workable protocol in hand, we studied the substrate scope for methods A, B and C (Table 2). The synthesis of **2** by method C and **3** by method B were readily amenable to the gram scale. Evans auxiliary **4** in methods A–C was afforded in about 75%, and there was no difference in procedure. As for **5**, unfortunately, the reaction showed multiple spots by TLC monitoring for all methods, and complex column chromatography was needed to isolate **5** from byproducts in 51–62% yield. For **6** and **7**, the in situ version of method B was effective in isolating the isomer as cleanly as possible with only a slight amount of by-product; however, methods A and C were unsuitable for the preparation of **6** and **7** because considerable amounts of the isomer and by-product were formed. For indole **8**, comparable yields for methods A–C were obtained. The products of **6**–**8**, unlike **2**–**5**, dissolved very sparingly in the solvent used for column chromatography, and precipitation and/or recrystallization were used to isolate the product.[18,19] Indole **9**, which has an acetyl group at the 3-position was readily soluble in organic solvents, unlike **8**, and facile column chromatography resulted in 70% yield for method B and 75% for method C; however, commercial IBr unworkable and resulted in isomeric mixtures. For viscous material **10**, method A unexpectedly gave high yields for the transformation relative to methods B and C.[20] Although **2** for method C, **3** for method B, and **9** for methods B and C were obtained as nearly single isomers, other reactions were slightly contaminated, in the crude state, with isomers or hydrohalogenated byproducts. Thus, the different vicinal iodo-

Table 2. Substrate scope.[a,b]

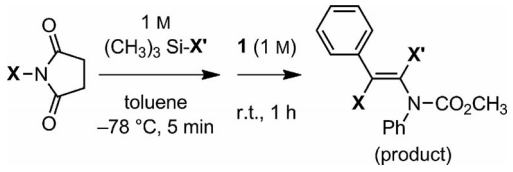


[a] Reactions were conducted on a 1 mmol scale of the ynamide, and yields are for isolated compounds as single isomers of 100% purity, unless otherwise noted. [b] Method A, to the ynamide in a flask commercial IBr (1.5 equiv.) in Et_2O was added; Method B, to the ynamide in a flask TMSBr (1.5 equiv.) in CH_2Cl_2 was initially loaded, then NIS (1.5 equiv.) in CH_3CN was added; Method C, to the flask charged with NIS (1.5 equiv.) in toluene TMSBr (1.5 equiv.) in CH_2Cl_2 was initially loaded, then the ynamide in CH_2Cl_2 was added. [c] A 61% yield calculated by NMR spectroscopy, **6**/isomer = 80:20. [d] Many by-products in the crude state. [e] 47% yield calculated by NMR spectroscopy, **7**/isomer = 81:19. [f] Messy NMR spectrum in the crude state. [g] 56% yield calculated by NMR spectroscopy, **9**/isomer = 83:17.

bromoenamides differ in method, solubility, stability, and purification.

Different patterns of *N*-halosuccinimide/halotrimethylsilane were tested, and the results are summarized in Table 3. Interestingly, Table 3, Entry 4 shows a 63% yield of **2**, which is identical to the product resulting from methods A–C in Scheme 2. This means both combinations 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 method A. The use of TMSCl (Table 3, Entries 3, 6, and 9) showed no reaction. Even the use of NCS (Table 3, Entries 7 and 8) did not consume all of starting **1**, and gave 48 and 33% yield for **11** and **12**, respectively, in which the chloride atom was not installed as shown in Figure 2. In contrast, the combinations of halogens, except for chloride, (Table 3, Entries 1, 2, 4, and 5) gave better yields and afforded the desired products. Thus, the product distribution was affected by the difference of the easily cleavable N–X and Si–X bonds. In fact, the N–I bond in NIS generally possesses a lower bond-dissociation energy than the N–Br bond for NBS and N–Cl bond for NCS, reflecting the high yielding conversion of **1**. The bond energies of Si–Cl, Si–Br, and Si–I are 113, 96, and 77 kcal/mol, respectively:[21] the Si–Cl bond would be difficult to activate. Thus, as shown in Scheme 3, these observations are consistent with the plausible reaction mechanism that is composed of two stages. Initially, TMSBr reacts with NIS to give in situ IBr and *N*-trimethylsilylsuccinimide.[22,23] The complexation of starting ynamide and

Table 3. Evaluation of the reactivity of **1** under conditions shown in Scheme 3.[a]



Entry	X	X′	Product	Yield [%][b]	Recovered **1** [%][b]
1	I	I	**11**	76	0
2	I	Br	**2**	90	0
3	I	Cl	–	0	≈ 100
4	Br	I	**2**	63	0
5	Br	Br	**12**	61	10
6	Br	Cl	–	0	≈ 100
7	Cl	I	**11**	48	16
8	Cl	Br	**12**	33	25
9	Cl	Cl	–	0	≈ 100

[a] Reaction conditions: **1** (126 mg, 0.50 mmol), toluene (2 mL), NXS (0.5 M) in acetonitrile, TMSX′ (1 M) in dichloromethane. [b] Isolated yields.

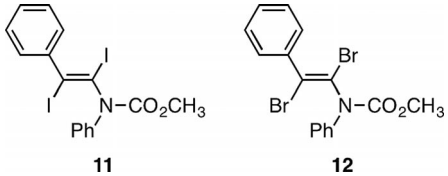
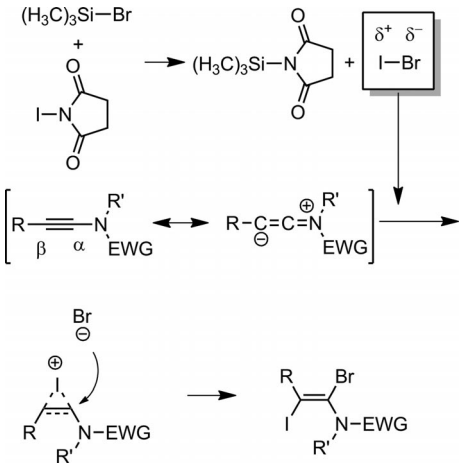


Figure 2. Iodide **11** and bromide **12**.

TMSX does not seem to be important.[16] Then, IBr that is charged with cationic iodide and anionic bromide[17] and undergoes an addition reaction to a ynamide substructure in *anti*-mode,[10–12] to give a single isomer. The ynamide moiety contains a keteniminium resonance form by polarization of the triple bond of the nitrogen atom, and the resultant charged α-carbon is more electrophilic than the β-carbon that is negatively charged. This is supported by the chemical shifts observed by ^{13}C NMR spectroscopy that showed the α-carbon downfield around 80 ppm, and the β-carbon upfield around 70 ppm (e.g. for ynamide **1**, signals appear at 83.1 ppm and 70.3 ppm).



Scheme 3. Plausible reaction mechanism.

Conclusions

In conclusion, highly regio-, and stereoselective iodobromination of ynamides was achieved by using commercially available IBr and/or in situ generated IBr. The resultant single isomer formed (*E*)-2-bromo-1-iodoenamides. In cases for which commercial IBr did not work well, in situ generated IBr proved an effective reagent. In situ IBr could be generated by reaction of TMSBr with NIS, which then added to the ynamide according to the nature of the keteniminium resonance form. Application of this methodology to simple alkynes is ongoing for the synthesis of tetra-substituted olefins bearing four different carbon-linked groups.

Experimental Section

General Methods: 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 60 F_{254}. Column chromatography was carried out with silica gel 60 N (Kanto Chemical Co.). HRMS were reported on the basis of TOF (time of flight), and EB (double-focusing) techniques. ^1H 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 [^1H 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.

Representative Procedure by Method A for Preparation of Methyl (*E*)-1-Bromo-2-iodo-2-phenylvinyl(phenyl)carbamate (2): (see Scheme 2). Under an argon atmosphere, to a solution of **1** (281 mg, 1.1 mmol) in toluene (4.5 mL) at –78 °C was added IBr (348 mg, 1.7 mmol) in diethyl ether (3.4 mL) dropwise over 5 min, and the mixture was warmed to room temperature. After 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 (10 mL × 3), and the combined organic phases were washed with brine (20 mL), and then dried with sodium sulfate, and concentrated to give 524 mg of crude products. Purification by short-plug column chromatography (eluent; dichloromethane) and precipitation from dichloromethane/hexane afforded 361 mg of **2** in 71% yield as a white solid. Analytical data are listed in the section below.

Representative Procedure by Method B for Preparation of Methyl (*E*)-1-Bromo-2-cyclohexyl-2-iodovinyl(phenyl)carbamate (3): (see Table 2). Under an argon atmosphere, to a solution of starting ynamide, methyl cyclohexylethynyl(phenyl)carbamate (1.00 g, 3.9 mmol), in anhydrous toluene (16 mL) at –78 °C was added TMSBr (5.9 mL of 1 M in dichloromethane) dropwise over 8 min, and the mixture was stirred for 3 min. Then, NIS (1.33 g, 5.9 mmol) in acetonitrile (12 mL) 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 1.94 g of crude products. Purification by silica gel column chromatography (eluent; toluene) afforded 1.66 g of **3** in 92% yield as a yellow viscous oil. Analytical data are listed in the section below.

Representative Procedure by Method C for Preparation of Methyl (*E*)-1-Bromo-2-iodo-2-phenylvinyl(phenyl)carbamate (2): (see Table 2). Under an argon atmosphere, to a solution of NIS (1.35 g, 6.0 mmol) in anhydrous toluene (16 mL) at –78 °C was added TMSBr (6.0 mL of 1 M in dichloromethane) dropwise over 7 min, and the mixture was stirred for 5 min. Then, ynamide **1** (1.00 g, 4.0 mmol) in toluene (12 mL) 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 1.86 g of crude products. Purification by silica gel column chromatography (eluent; hexane/dichloromethane = 2:1) afforded 1.74 g of **2** in 95% yield as a yellowish solid. Analytical data are listed in the section below.

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 ^1H NMR spectroscopy was observed only in 24 h.

Methyl (*E*)-1-Bromo-2-iodo-2-phenylvinyl(phenyl)carbamate (2): 71% yield, 361 mg (Method A), 82% yield, 199 mg (Method B), and 90% yield, 208 mg (Method C) as a yellowish white solid (recrystallization from methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (dd, J = 7.5, 1.3 Hz, 2 H), 7.46–7.31 (m, 8 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 142.5, 138.8, 129.3, 129.2, 128.8, 128.7, 127.4, 125.5, 119.5, 99.3, 54.4 ppm. MS (FAB): m/z = 458 $[MH]^+$, 330 $[M - I]^+$. IR (neat): $\tilde{\nu}$ = 2962, 1724, 1627, 1492, 1435, 1311, 1265, 1218 cm^{-1}. $C_{16}H_{13}BrINO_2$ (458.09): calcd. C 41.95, H 2.86, N 3.06; found C 41.83, H 2.87, N 2.71.

Methyl (*E*)-(1-Bromo-2-cyclohexyl-2-iodovinyl)(phenyl)carbamate (3): 96% yield, 235 mg (Method A), 83% yield, 387 mg (Method B), 71% yield, 329 mg (Method C) as a yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.43 (m, 2 H), 7.39–7.35 (m, 2 H), 7.28–7.25 (m, 1 H), 3.84 (s, 3 H), 2.36–2.29 (m, 1 H), 1.81–1.79 (m, 2 H), 1.74–1.70 (m, 2 H), 1.61–1.59 (m, 1 H), 1.48–1.36 (m, 4 H), 1.26–1.19 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 138.8, 129.1, 126.9, 124.9, 117.5, 54.2, 47.4, 33.0, 32.8, 25.8, 25.7 ppm. MS (FAB): m/z = 464 $[MH]^+$, 336 $[M - I]^+$. IR (neat): $\tilde{\nu}$ = 2923, 2849, 1735, 1593, 1489, 1442, 1298, 1231 cm^{-1}. $C_{16}H_{19}BrINO_2$ (464.14): calcd. C 41.40, H 4.13, N 3.02; found C 41.42, H 4.01, N 2.82.

(*S*,*E*)-3-(1-Bromo-2-iodo-2-phenylvinyl)-4-phenyloxazolidin-2-one (4): Dichloromethane was used as solvent instead of toluene that sparingly dissolved **4**. 77% yield, 180 mg (Method A), 74% yield, 349 mg (Method B), 75% yield, 353 mg (Method C) of a yellowish solid (recrystallization from dichloromethane/methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.21 (m, 8 H), 7.15 (dd, J = 7.6, 2.3 Hz, 2 H), 5.25 (dd, J = 9.2, 9.2 Hz, 1 H), 4.74 (dd, J = 9.2, 9.2 Hz, 1 H), 4.44 (dd, J = 9.2, 9.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.0, 142.3, 134.2, 130.0, 129.2, 129.1, 129.0, 128.8, 128.5, 114.9, 99.2, 70.1, 62.3 ppm. MS (FAB): m/z = 469 $[MH]^+$. IR (neat): $\tilde{\nu}$ = 2922, 1455, 1440, 1338, 1207, 1165, 1100, 1061, 1018 cm^{-1}. $C_{17}H_{13}BrINO_2$ (470.10): calcd. C 43.43, H 2.79, N 2.98; found C 43.31, H 2.78, N 2.75.

(*E*)-*N*-Benzyl-*N*-(1-bromo-2-iodo-2-phenylvinyl)-4-methylbenzenesulfonamide (5): 62% yield, 195 mg (Method A), 59% yield, 336 mg (Method B), 51% yield, 228 mg (Method C) as a white solid (recrystallization from benzene). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.3 Hz, 2 H), 7.50–7.48 (m, 2 H), 7.38–7.22 (m, 8 H), 7.02 (dd, J = 8.1, 1.7 Hz, 2 H), 4.83 (d, J = 12.8 Hz, 1 H), 4.00 (d, J = 12.8 Hz, 1 H), 2.47 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 143.4, 135.0, 132.9, 131.2, 123.0, 129.4, 129.0, 128.9, 128.6, 128.5, 128.1, 118.9, 104.5, 53.3, 22.0 ppm. MS (MALDI-TOF): m/z = 567 $[MH]^+$. IR (neat): $\tilde{\nu}$ = 2921, 1594, 1456, 1347, 1165 cm^{-1}. $C_{22}H_{19}BrINO_2S$ (568.27): calcd. C 46.50, H 3.37, N 2.46; found C 46.49, H 3.29, N 2.37.

(*E*)-*N*-Benzyl-*N*-[1-bromo-2-(4-cyanophenyl)-2-iodovinyl]-4-methylbenzenesulfonamide (6): 61% yield as calculated by NMR spectroscopy (Method A), 78% yield, 462 mg (Method B) as a whitish yellow solid (recrystallization from acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 8.2 Hz, 2 H), 7.58 (d, J = 8.5 Hz, 2 H), 7.48–7.46 (m, 2 H), 7.39–7.38 (m, 5 H), 7.09 (d, J = 8.2 Hz, 2 H), 4.84 (d, J = 12.9 Hz, 1 H), 3.96 (d, J = 12.9 Hz, 1 H), 2.48 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 145.4, 134.7, 132.7, 132.6, 131.2, 130.1, 129.3, 129.2, 129.1, 128.6, 120.5, 118.6, 112.6, 101.4, 53.4, 22.1 ppm. MS (MALDI-TOF): m/z = 592 $[M]^+$. IR (neat): $\tilde{\nu}$ = 2222, 1594, 1495, 1456, 1346, 1164 cm^{-1}. $C_{23}H_{18}BrIN_2O_2S$ (593.28): calcd. C 46.56, H 3.06, N 4.72; found C 46.56, H 3.07, N 4.57.

(*E*)-*N*-(1-Bromo-2-iodo-2-phenylvinyl)-*N*,4-dimethylbenzenesulfonamide (7): 47% yield as calculated by NMR spectroscopy (Method A), 57% yield, 148 mg (Method B) as a white solid (recrystallization from methanol). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.9 Hz, 2 H), 7.39–7.29 (m, 7 H), 2.96 (s, 3 H), 2.45 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 142.4, 134.5, 129.8, 129.3, 129.2, 128.7, 128.6, 120.1, 101.5, 36.2, 22.0 ppm. MS (FAB): m/z = 492 $[MH]^+$. IR (neat): $\tilde{\nu}$ = 2922, 1595, 1440, 1354, 1260, 1163, 1086, 982 cm^{-1}. $C_{16}H_{15}BrINO_2S$ (492.17): calcd. C 39.05, H 3.07, N 2.85; found C 39.06, H 3.09, N 2.82.

Ethyl (*E*)-1-(1-Bromo-2-iodo-2-phenylvinyl)-1*H*-indole-2-carboxylate (8): 61% yield, 153 mg (Method A), 50% yield, 249 mg (Method B), 60% yield, 300 mg (Method C) as a white solid (precipitation from dichloromethane/hexane for Method A and B; recrystallization from ethanol for Method C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 7.8 Hz, 1 H), 7.62–7.59 (m, 2 H), 7.53–7.44 (m, 5 H), 7.41–7.37 (m, 1 H), 7.33–7.29 (m, 1 H), 4.47 (q, J = 7.1 Hz, 2 H), 1.46 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 142.3, 137.4, 129.4, 129.0, 128.9, 127.9, 127.2, 126.9, 123.3, 123.0, 114.3, 114.1, 112.0, 99.5, 61.4, 14.8 ppm. MS (FAB): m/z = 496 $[MH]^+$, 368, ($[M - I]^+$). IR (neat): $\tilde{\nu}$ = 1708, 1534, 1474, 1442, 1396, 1380, 1325, 1261, 1200, 1144 cm^{-1}. $C_{19}H_{15}BrINO_2$ (496.14): calcd. C 46.00, H 3.05, N 2.82; found C 45.75, H 3.02, N 2.59.

(*E*)-1-[1-(1-Bromo-2-iodo-2-phenylvinyl)-1*H*-indol-3-yl]ethan-1-one (9): 56% yield as calculated by NMR spectroscopy (Method A), 70% yield, 327 mg (Method B), 75% yield, 350 mg (Method C) as a white solid (recrystallization from acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (dd, J = 8.4, 1.6 Hz, 1 H), 7.89 (s, 1 H), 7.55–7.52 (m, 2 H), 7.50–7.39 (m, 6 H), 2.61 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.6, 141.8, 135.6, 133.9, 129.8, 129.0, 128.9, 126.4, 125.0, 124.2, 123.4, 120.8, 112.6, 111.6, 99.8, 28.1 ppm. MS (FAB): m/z = 466 $[MH]^+$, 386, $[M - Br]^+$. IR (neat): $\tilde{\nu}$ = 1660, 1527, 1475, 1448, 1346, 1302, 1221 cm^{-1}. $C_{18}H_{13}BrINO$ (466.12): calcd. C 46.38, H 2.81, N 3.01; found C 46.26, H 2.78, N 2.72.

Methyl (*E*)-[1-Bromo-2-iodo-2-(4-methoxyphenyl)vinyl](phenyl)carbamate (10): 80% yield, 206 mg (Method A), 62% yield, 249 mg (Method B), 31% yield, 300 mg (Method C) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57, (d, J = 8.2 Hz, 2 H), 7.43 (d, J = 8.2 Hz, 2 H), 7.36–7.31 (m, 3 H), 6.87 (d, J = 8.7 Hz, 2 H), 3.93 (s, 3 H), 3.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 160.8, 153.3, 139.5, 135.4, 130.9 (two peaks overlapped), 129.7, 127.5, 125.5, 114.6, 100.8, 55.7, 54.3 ppm. MS (FAB): m/z = 487 $[M]^+$. HRMS: calcd. for $C_{17}H_{15}BrINO_3$ $[M^+]$ 486.9280; found 486,9255.

Methyl (*E*)-(1,2-Diiodo-2-phenylvinyl)(phenyl)carbamate (11): 76% yield, 192 mg as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (dd, J = 8.5, 1.5 Hz, 2 H), 7.46–7.33 (m, 8 H), 3.94 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3CN): δ = 153.4, 146.0, 139.6, 130.1 (two peaks overlapped), 129.7, 129.3, 127.9, 125.9, 102.5, 98.5, 54.7 ppm. MS (FAB): m/z = 506 $[MH]^+$, 378 $[M - I]^+$. IR (neat): $\tilde{\nu}$ = 3054, 2969, 2930, 2871, 1593, 1487, 1455, 1441 cm^{-1}. $C_{16}H_{13}I_2NO_2$ (505.09): calcd. C 38.05, H 2.59, N 2.77; found C 37.91, H 2.64, N 2.70.

Methyl (*E*)-(1,2-Dibromo-2-phenylvinyl)(phenyl)carbamate (12): 61% yield, 250 mg as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.16 (m, 8 H), 6.92 (d, J = 7.9 Hz, 2 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 140.2, 138.1, 130.4, 129.6, 129.0, 128.8, 128.0, 127.2, 125.2, 123.3, 54.2 ppm. MS (FAB): m/z = 412 $[MH]^+$, 330 $[M - Br]^+$. IR (neat): $\tilde{\nu}$ = 1724, 1490, 1435, 1321, 1254, 1223, 1195, 1161, 1059 cm^{-1}. $C_{16}H_{13}Br_2NO_2$ (411.09): calcd. C 46.75, H 3.19, N 3.41; found C 46.59, H 3.24, N 3.13.

Supporting Information (see footnote on the first page of this article): The ^{1}H NMR and ^{13}C NMR spectra of all new compounds.

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[14] 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.

[15] Crystal data of **2**: orthorhombic, space group $Pca2_1$, colorless, a = 12.272(3) Å, b = 11.030(7) Å, c = 11.831(1) Å, $\alpha = \beta = \gamma$ = 90°, V = 1601.6 Å^3, Z = 4, T = 93 K, $d_{calcd.}$ = 1.900 g cm^{-3}, μ(Mo-K_α) = 4.505 mm^{-1}, R_1 = 0.0648, wR_2 = 0.1639, GOF = 1.070.

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[17] **1**-HBr, methyl (*E*)-1-bromo-2-phenylvinyl(phenyl)carbamate, was identified with an authentic sample, which was previously reported in ref.[16]. We discussed the pathway to produce **1**-HBr previously, and formally the transformation was depicted as follows: initially, TMSBr reacts with H_2O to give TMSOH and HBr (TMSBr + $H_2O \rightarrow$ TMSOH + HBr), and then in situ HBr adds to **1** to afford **1**-HBr (**1** + HBr → **1**-HBr). Because of a polarized keteniminium resonance form inherent in the ynamide C≡C–N moiety, the protonation selectively occurred at the anionic β-carbon, and bromination at the cationic α-carbon; bromide ion was charged with anionic character. Given the previously observed bromide anion, we suggested the reaction species IBr in the present work was composed of anionic bromide and cationic iodide; this explains that resultant product **2** selectively holds Br at the cationic α-carbon and I at the anionic β-carbon.

[18] Because nitrile **6** sparingly dissolved in several organic solvents for recrystallization, careful precipitation from a combination of dichloromethane and methanol gave purified **6**.

[19] The recrystallization of **7** from methanol was achieved with 5 mg employing a micro-tube; however, scale-up to 200 mg resulted in complete decomposition of **7**.

[20] Viscous **10** easily decomposed relative to other dihaloenamides.

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