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Stereoselective Synthesis of Di- and Trisubstituted Alkenes
## via Intermolecular Addition of Vinyl Radicals to Alkenes

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Abstract: Vinyl radicals, generated from the reaction of vinyl iodides with tributylstannyl radical, react with electron-deficient alkenes to give di- or trisubstituted alkenes in moderate to good yields. The stereoselectivity is largely dependent on the substituent at 1- and 2-position of vinyl iodides.

Intra- and intermolecular addition of alkyl radicals to alkenes and acetylenes are important methodologies for carbon-carbon bond formation.[1] In contrast, synthetic application of vinyl radicals is limited to intramolecular fashion.[2] Except for a few examples,[3] the use of vinyl radicals for intermolecular carbon-carbon bond formation has remained still unexplored. This is probably because vinyl radicals are reactive compared with alkyl radicals, and readily cause hydrogen abstraction from a radical mediator such as Bu_3SnH or 1,5-hydrogen transfer.[4] In the course of studies on free radical reactions,[5] we now report that a variety of vinyl radicals add to electron-deficient alkenes by tin hydride method,[6] and this reaction is efficient for stereoselective synthesis of di- and trisubstituted alkenes.

We first examined the reaction of 2-iodo-1-dodecene (1) with acrylonitrile to develop standard reaction conditions. Treatment of a benzene solution of 1 and acrylonitrile with Bu_3SnH at 80 °C gave adduct 2 and 1-dodecene in 65% and 27% yields, respectively. Radical initiator was not necessary for this reaction.[7] Slow addition of Bu_3SnH by a syringe pump was ineffective to increase the yield of 2,[8] while intermittent addition (Method A) provided 2 in 76% yield.[9] The reaction proceeded even at room temperature and 2 was obtained in 68% yield by Method A. Although $(Me_3Si)_3SiH$, which is a useful substitute for Bu_3SnH, was employed to suppress the formation of 1-dodecene,[10] the yield of 2 dropped to 26% in the presence of AIBN at 80 °C. Under these conditions, the products via 1,5-hydrogen shift were not observed.

Syringe pump addition.	61%	8%
Intermittent addition (Method A).	76%	13%

(22% of 1 was recovered.)
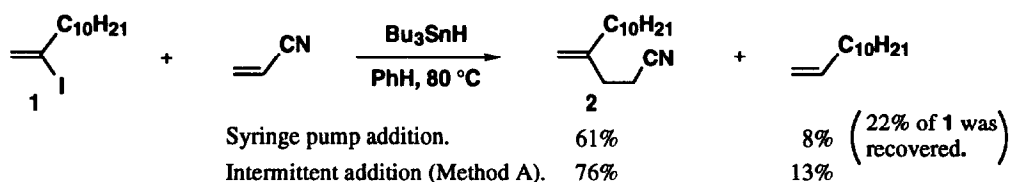
Scheme 1.

The results of reactions of 1 with several acceptors at 80 °C by Method A are as follows: acceptor (yield/%); methyl acrylate (64), methacrylonitrile (64), methyl methacrylate (61), phenyl vinyl sulfone (75),

dimethyl fumarate (31), butyl vinyl ether (5), and 1-hexene (0). Thus, electron-deficient terminal alkene was suitable for the acceptor of vinyl radicals as well as alkyl radicals.

Next, we attempted the reactions of several 1-substituted vinyl iodides with acrylonitrile (Table 1, entries 1-5). 2-Iodo-1-dodecene (1) and 3,3-dimethyl-2-iodo-1-butene were good precursors for inter-molecular radical addition (entries 1 and 2). This reaction was tolerant to the presence of hydroxy group on the substrate (entry 3). The use of α-iodostyrene diminished the yield of the adduct, however, silyl-substituted vinyl iodide gave the corresponding 1,1-disubstituted alkene in 56% yield (entries 4 and 5). These results demonstrate that the substitution of alkyl group on radical center improves the efficiency of intermolecular addition.

The reactions of 2-substituted vinyl iodides were also investigated at 80 °C or room temperature (Table 1, entries 6-10). In any case (E)-1,2-disubstituted alkene was obtained selectively. (E)- and (Z)-1-iodo-1-decen-3-ol formed the same isomeric mixture of (E)- and (Z)-adducts (entry 8). Employment of bulky group such as t-butyl, silyl, and phenyl as R[1] enhanced the (E)-selectivity (entries 7, 9, and 10). The influence of reaction temperature on the stereoselectivity was not observed, although the yields at room temperature were much lower than those at 80 °C. This result suggests that the (E)-selectivity is not attributed to the isomerization of the product by addition-elimination sequences of $Bu_3Sn\bullet$ because the isomerization is faster at 80 °C than room temperature.[11] In addition, (Z)-1,2-disubstituted alkenes hardly isomerized to (E)-isomers without radical initiators in Bu_3SnH-reduction of vinyl iodides.[12]

Table 1. Reactions of 1- and 2-Substituted Vinyl Iodides with Acrylonitrile[a]

entry	substrate R^2 (R^1=H)	yield /%	entry	substrate R^1 (R^2=H)	80 °C yield/%	80 °C E : Z[b]	r.t. yield/%	r.t. E : Z[b]
1	$C_{10}H_{21}$	76	6	$C_{10}H_{21}$	64	67 : 33	35	68 : 32
2	t-Bu	77	7	t-Bu	55	97 : 3	32	98 : 2
3	$CH(OH)C_7H_{15}$	58	8	$C_7H_{15}CH(OH)$	51	80 : 20[c,d]	19	78 : 22
4	Ph	31	9	Ph	28	94 : 6	14	94 : 6
5	$SiMe_2Ph$	56	10	$PhMe_2Si$	65	97 : 3	54	96 : 4

[a]All reactions were performed with 1.0 mmol of vinyl iodide, 5 mmol of acrylonitrile, and 1.2 mmol of Bu_3SnH in benzene at 80 °C or room temperature (entries 6-10). [b]The stereochemistry and ratios were determined by ^{1}H NMR. [c]0.1 mmol of AIBN was employed. [d](Z)-1-iodo-1-decen-3-ol gave a 81:19 mixture of adducts in 51% yield.

Transition metal-catalyzed cross coupling is a powerful method for the stereoselective synthesis of trisubstituted alkenes, but there are a few drawbacks in this method. For instance, the protection of functional groups and the stereoselective synthesis of alkenyl halide or alkenyl metal as a substrate are required. It is expected that the carbon-carbon bond formation via radical process can solve these problems. Then we examined the addition of 1,2-disubstituted vinyl radicals to alkenes (Table 2).

6-Iodo-6-dodecene reacted with acrylonitrile and methyl acrylate at room temperature to yield the corresponding trisubstituted alkenes without any selectivity (entries 1 and 2). When R^1 was changed from pentyl to t-butyl or silyl group, the ratio of 3 to 4 increased remarkably (entries 3-7). Although the reactions were carried out at 80 °C, this attempt resulted in a slight decrease of selectivities. Introduction of phenyl group as R^2 was also effective for the improvement of stereoselectivity (entries 10-14). In particular, the substrate bearing both phenyl and t-butyl group formed a single isomer of adducts. These stereochemical tendencies are consist with those of hydrogen abstraction of vinyl radicals.[12,13] The present intermolecular addition exhibited higher stereoselectivity than the hydrogen abstraction. 1-Cyclohexenyl radical easily added to acceptors in good yields (entries 15 and 16).

Table 2. Reactions of 1,2-Disubstituted Vinyl Iodides with Acrylonitrile and Methyl Acrylate[a]

entry	substrate R^1	R^2	acceptor E	yield[b] /%	3 : 4[b, c]
1	C_5H_{11}	C_5H_{11}[d]	CN	60	50 : 50
2			COOMe	54	50 : 50
3	t-Bu	Bu[d]	CN	65 (64)	95 : 5 (92 : 8)
4			COOMe	45 (43)	95 : 5 (91 : 9)
5			SO_2Ph	66 (59)	96 : 4 (94 : 6)
6	$PhMe_2Si$	Bu[e]	CN	58	97 : 3
7			COOMe	69	96 : 4
8	Bu	$SiMe_3$[d]	CN	43	77 : 23
9			COOMe	42	69 : 31
10	Bu	Ph[d]	CN	49 (67)	93 : 7 (91 : 9)
11			COOMe	36 (41)	92 : 8 (89 : 11)
12			SO_2Ph	55 (58)	95 : 5 (93 : 7)
13	t-Bu	Ph[f]	CN	51	>99 : 1
14			COOMe	33	>99 : 1
15	$(CH_2)_4$		CN	74	—
16			COOMe	55	—

[a]All reactions were performed with 1.0 mmol of vinyl iodide, 5 mmol of acceptor, and 1.2 mmol of Bu_3SnH in benzene at room temperature. [b]Value in paretheses for the reaction carried out at 80 °C. [c]The stereochemistry and ratios were determined by ^1H NMR including the measurement of NOE. [d](E)-isomer. [e](Z)-isomer. [f]E : Z = 89 : 11.

As shown in Scheme 2, the structures of vinyl radicals are distinguished into bent (5 and 5') and linear form (6). The bent form is rapidly inverting. Therefore, the stereochemical outcome of the reaction *via* a vinyl radical does not generally depended on the stereochemistry of the precursor. In the present reaction, the stereochemistry of the product was determined when the vinyl radical adds to an acceptor. Regardless of the

structure of vinyl radical, the acceptor attacks the radical center from the *anti* side of R^1 to avoid the steric hindrance. As R^1 is bulkier, the attack from the *syn* side becomes harder and **3** was formed more selectively. It is known that 1-alkyl-substituted vinyl radicals are bent, while 1-phenyl-substituted ones linear.[14] When R^2 is phenyl group, acceptor attacks the radical center perpendicularly.[12, 13] The perpendicular approach from the *syn* side of R^1 yields a severe steric repulsion between the acceptor and R^1 compared with the angular approach to the bent radical. For this reason, the substrate bearing phenyl as R^2 gives a high stereoselectivity.
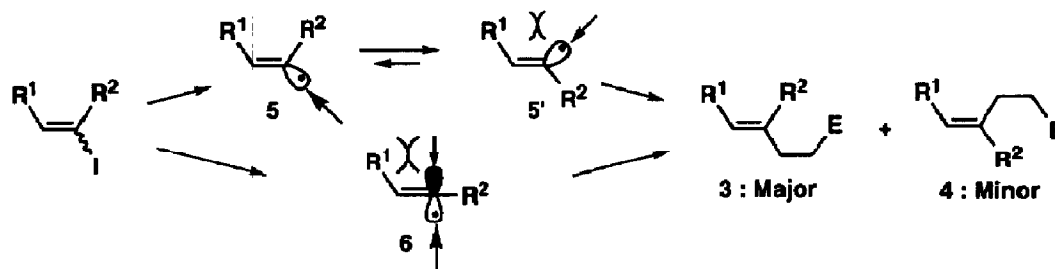
Scheme 2.

We conclude that intermolecular addition of vinyl radical is available for stereoselective synthesis of di- and trisubstituted alkenes. However, the yield of the adduct is not necessarily good. Investigations of the scope and limitations of this reaction are continuing to direct higher efficiency, and the results of these studies will be present in due course.

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8. Although the addition of AIBN enhanced the conversion of **1**, the yield of **2** was not improved.

9. The following procedure (Method A) is representative: To a benzene (2.5 mL) solution of 2-iodo-1-dodecene (294 mg, 1.00 mmol) and acrylonitrile (0.33 mL, 5.0 mmol), 0.30 mL portion of 0.5 M Bu_3SnH in benzene was added 8 times at 30 minutes intervals at 80 °C. After stirring for 1.5 h, the reaction mixture was concentrated *in vacuo*. The residual oil was treated with saturated aqueous KF (2 mL) and anhydrous KF (1 g) in CH_2Cl_2 (10 mL) for 15 h. The resultant mixture was filtered through a short column of silica gel eluting with CH_2Cl_2. The filtrate was concentrated *in vacuo*. The tin-free crude product was purified by flash chromatography to give 4-decyl-4-pentenenitrile (**2**) in 76% yield. DBU-workup developed by Curran *et al.* is available for this reaction. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140-3157.

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