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Indium(I) iodide-mediated chemio-, regio-, and stereoselective hydroselenation of 2-alkyn-1-ol derivatives

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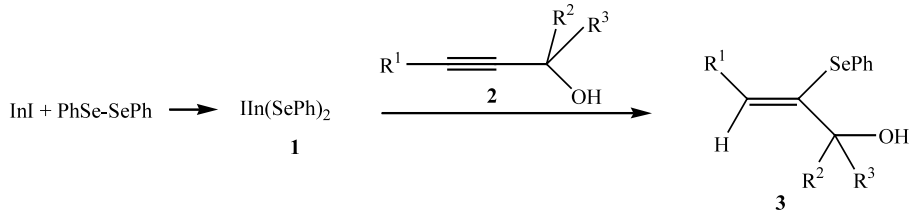
Abstract—Indium(I) iodide efficiently promotes the chemio-, regio-, and stereoselective hydroselenation of 2-alkyn-1-ol derivatives with diphenyl diselenide to produce the Markovnikov adducts with stereochemistry corresponding to an *anti* addition of the selenol constituents across the triple bond. © 2002 Elsevier Science Ltd. All rights reserved.

Preparation of olefins with a rigorous regio-, and stereochemical control is of great interest. Among the extensive applications of vinyl selenides in organic synthesis,[1] the nickel catalyzed cross-coupling of the selenides with organomagnesium reagents[2] produces olefins retaining the stereochemistry of the parent vinyl selenide.

Many protocols leading to vinyl selenides can be found in the literature. The most obvious involves the addition of selenols across an alkyne triple bond to produce, preferentially, the (*Z*)-*anti*-Markovnikov isomer after 10 days at room temperature; the reaction is faster at higher temperatures (24 h at 120°C), but its stereoselectivity is completely lost.[3] Long reaction times, toxicity and the unpleasant odour of the selenol starting material are serious drawbacks of this process. The preferential preparation of the Markovnikov regioisomers was achieved by adding PhSeBr to terminal olefins under rigid kinetic controlled conditions (−78°C), followed by dehydrohalogenation; nevertheless a mixture of the *E* and *Z* stereoisomers of the *anti*-Markovnikov adduct was obtained at higher temperatures.[4] Alternatively, the $Pd(OAc)_2$-catalyzed hydroselenation with selenol,[5] and the dialkyl-phenylseleno-aluminum(III)-intermediated reaction,[6] gave the regiochemical production of the Markovnikov adduct, but the stereochemistry of the addition was not determined, in both cases.

Motivated by the need to develop a rigorous chemio-, regio-, and stereochemical controlled protocol for the hydroselenation of alkyne derivatives, we have set out to study hydroselenation of triple bonds promoted by indium(III) selenolates. We choose, as the indium reagent, bis(phenylseleno)-iodo-indium(III), **1** readily obtained by reacting equimolar quantities of InI and diphenyl diselenide in dichloromethane, tetrahydrofuran or 1,4-dioxan (Scheme 1).[7] We found that **1** does not react with 1-heptyne and ethyl propiolate in anhydrous conditions (CH_2Cl_2 and THF at room temperature or at 100°C in refluxing dioxane). On the other hand, **1** reacts smoothly with an equimolar amount of propargyl alcohol, **2a** in THF or CH_2Cl_2 at room temperature (Table 1, entry a) to produce 2-phenylseleno-2-propen-1-ol, **3a** (Scheme 1) in 80% of yield.[8] Reaction with the molar proportion **1**:**2a** = 1:2, gave **3a**



Scheme 1.

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Table 1. Indium(I) iodide-mediated regio and stereoselective hydroselenation of alkynols

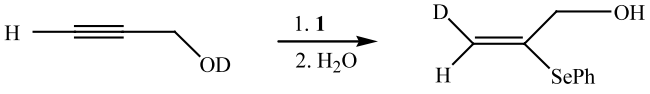
Entry	R^1	R^2	R^3	Time (h)	Yield (%)
a	H	H	H	12	80[a,b,c]
b	H	H	CH_3	12	85[a,c]
c	H	CH_3	CH_3	12	27[d,e]
d	H	H	C_6H_5	12	63[d,h]
e	H	H	n-C_5H_{11}	12	67[b,h]
f	C_6H_5	H	H	36	NR
g	n-C_3H_7	H	H	24	55[b,f,h]
h	n-C_4H_9	H	H	24	40[b,f,g,h]
i	C_6H_5Se	H	H	36	46[b,f]
j	n-$C_4H_9C{\equiv}C$	H	H	12	80[b,f,h]

[a] In anhydrous THF.
[b] In anhydrous CH_2Cl_2.
[c] Purified by column chromatography on basic alumina, all the other examples in silica gel.
[d] Reflux in anhydrous 1,4-dioxan.
[e] Plus traces of an unidentified by-product.
[f] Exclusive (Z) stereoisomer.
[g] Reaction in anhydrous THF produced 48% of a mixture of Z:E = 10:3.
[h] New compounds; analytical and spectroscopic data is available as supplementary material.

in 47% of yield based on the alkynol, demonstrating that only one phenylseleno group of the indium reagent participated in the addition reaction. This set of experiments demonstrates the chemioselectivity of **1** towards the alkynol and its regioselectivity to form the Markovnikov adduct.

The role of the hydroxylic hydrogen on the process was determined from reaction with OD-labeled propargyl alcohol, in CH_2Cl_2,[9] which produced stereoselectively (*E*)-3-deuterium-2-(phenylseleno)-2-propen-1-ol (Scheme 2). This result indicates that the hydroselenation across the triple bond follows, rigorously, an *anti*-pathway of addition. This pathway was confirmed by the stereoselective preparation of (*Z*)-3-alkyl-2-(phenylseleno)-2-propen-1-ol (alkyl = n-C_3H_7, **3g**; n-C_4H_9, **3h**) from 3-alkyl-2-propyn-1-ol; the stereochemistry of **3g** and **3h** was determined by 2D NOE spectroscopy (NOE effect between the olefinic and allylic protons). These experiments confirm that the hydroselenation reaction promoted by **1** is also regio-, and stereoselective.

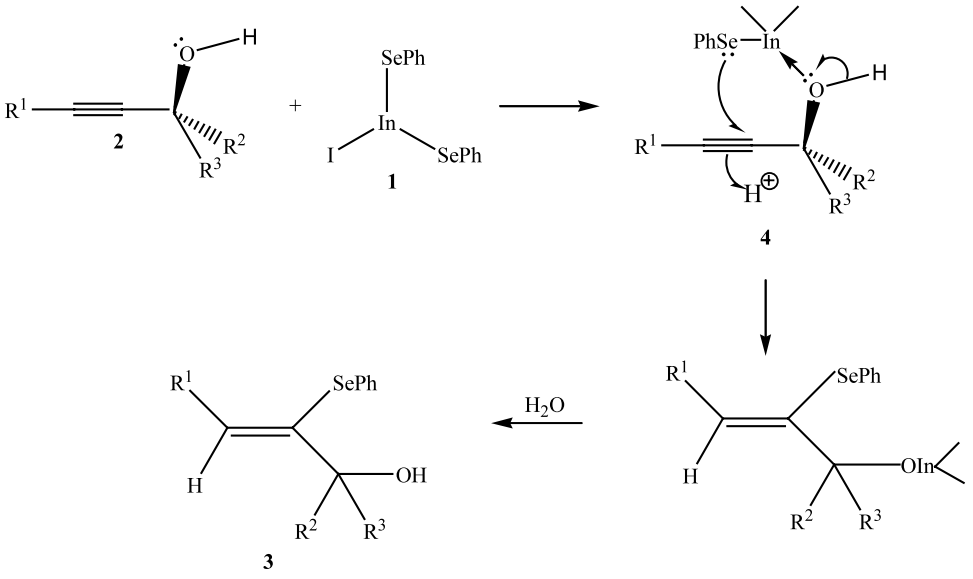
Reactions with other 2-alkyn-1-ol derivatives, **2** are summarized in Table 1, which shows that a variety of compounds **2** were successfully transformed into **3**. With terminal alkyne derivatives, the best yields were obtained when reactions were carried out in THF at room temperature (entries a, b) or refluxing 1,4-dioxane (entries c, d), when poorer yields were obtained at room temperature. With internal alkyne derivatives, the reactions were conducted in CH_2Cl_2 (entries g–j), to produce, exclusively and in every case, the corresponding derivative **3** of *Z*-stereochemistry; if the reaction is conducted in THF (entry h) a slight increase in the yield was obtained, but a considerable loss of the stereochemical control was observed (Z:E = 10:3). To illustrate the relevance of the stereochemical control imposed by compound **1** on these reactions, we have synthesized (*Z*)-2,3-bis(phenylseleno)-2-propen-1-ol, **3i** which otherwise is produced only via the $Pd(PPh_3)_4$-catalyzed addition of diphenyl diselenide to propargyl alcohol.[10] We have also conducted the hydroselenation of 1-hydroxy-2,4-nonadiyne to produce, in 80% of yield, (*Z*)-1-hydroxy-2-phenylseleno-2-nonen-4-yne, **3j** whose stereochemistry was determined by 2D NOE spectroscopy (NOE effect between the olefinic and allylic protons).[11] The last result clearly shows the rigorous selectivity, especially when compared to the hydroselenation, using sodium phenylselenolate, of a similar compound, 2-hydroxy-2-methyl-3,5-dodecadiyne, which produced a 3:2 mixture of (*Z*)-2-hydroxy-2-methyl-3-phenylseleno-3-dodecen-5-yne and (*Z*)-2-hydroxy-2-methyl-6-phenylseleno-5-dodecen-3-yne, respectively.[12]



Scheme 2.

All the experimental details discussed above are accommodated in the mechanistic description of the reaction given at Scheme 3, where the adduct **4** obtained from coordination of the alkynol to **1** is the key intermediate on the process. Addition of the PhSeH constituents across the triple bond occurs in an *anti* fashion to produce stereoselectively the (*Z*)-Markovnikov adduct **3**. Intermediate **4** also accounts for the lowest yield obtained from the tertiary alcohol **2c**, from which it is expected the maximum sterical hindrance during coordination to **1**. Finally, the loss on stereoselectivity observed during formation of **2h**, when the reaction is carried out in THF, is easily understood, because the coordinating solvent will inhibit formation of **4**.

The effect of increasing the length of the methylene chain in the alkynol during reaction with **1** was examined with 4-pentyn-1-ol. 5-Phenylseleno-2-pentanone



Scheme 3.

was produced.[13] The generality of this process leading to seleno-functionalized ketones was not fully explored and it will be discussed elsewhere.

In summary, we have developed a rigorous chemio-, regio-, and stereoselective protocol for hydroselenation of 2-alkyn-1-ol derivatives using an indium(III) selenolate. The Markovnikov adducts with stereochemistry corresponding to an *anti* addition of the selenol constituents across the triple bond were obtained. This protocol gives comparable yields to the previous methods described in the literature, and completely suppress the use of the stench, toxic and air-sensitive selenols,[5] and the need of protecting the hydroxylic groups in the alkynols.[6] We expect that this reaction associated with the nickel-catalyzed cross-coupling of vinyl selenides with organometallics will constitute an interesting alternative route for the regio-, and stereoselective preparation of allylic alcohols and derivatives.

Acknowledgements

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8. GC chromatography established the purity of **3a**; *m/z* (for ^{80}Se): 214 ($M^{+\bullet}$, 100%)]; ^{1}H NMR [$CDCl_3$, δ from TMS: 2.20 (s, br, 1H), 4.18 (dd, 2H, $J=1.5$ and 1.2 Hz), 5.42 (t, 1H, $J=1.2$ Hz), 5.86 (t, 1H, $J=1.5$ Hz), 7.25 (m, 3H), 7.60 (m, 2H)]; ^{13}C NMR [$CDCl_3$, δ from TMS: 66.37, 118.38, 127.80, 129.29, 128.09, 133.89, 141.38] established its identity.
9. $HC{\equiv}CCH_2OD$ was prepared (50% of deuteration) from equimolar quantities of propargyl alcohol and ethyl-magnesium-bromide in ether followed by hydrolysis with D_2O.
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11. ^{1}H NMR [$CDCl_3$, δ from TMS: 0.92 (t, 3H, $J=7.0$ Hz), 1.52 (m, 4H), 1.68 (s, br, 1H), 2.40 (t, 2H, $J=7.0$ Hz), 4.05 (s, 2H), 6.14 (s, 1H), 7.31 (m, 3 H), 7.61 (m, 2H)]; ^{13}C NMR [$CDCl_3$, δ from TMS: 13.59, 19.39, 21.92, 30.64, 65.81, 77.62, 98.67, 110.84, 126.82, 128.29, 129.22, 135.19, 144.30]; 2D NOE [$CDCl_3$, δ from TMS: 4.05 (s) –6.14 (s)].
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13. *m/z* (for ^{80}Se): 242 ($M^{+\bullet}$, 17%), 85 $(M–SePh)^+$, 100%); iv = 1708 (νC=O); ^{1}H NMR [$CDCl_3$, δ from TMS: 1.36 (quintet, 2H, $J=7.5$ Hz), 2.10 (s, 3H), 2,58 (t, 2H, $J=7.5$ Hz), 2.92 (t, 2H, $J=7.5$ Hz), 7.26 (m, 3 H), 7.48 (m, 2H)]; ^{13}C NMR [$CDCl_3$, δ from TMS: 23.88, 27.11, 29.98, 42.94, 126.85, 129.06, 129.88, 132.56].