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Scandium–bipyridine-catalyzed, enantioselective selenol addition to aromatic *meso*-epoxides

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Abstract

A chiral scandium–bipyridine complex catalyzes the highly enantioselective addition of phenylselenol to aromatic *meso*-epoxides and furnishes 1,2-seleno alcohols in good yields and up to 94% ee. In addition, a sequential, one-pot epoxide opening-reduction protocol has been developed for the direct synthesis of 1,2-diaryl carbinols.

Keywords: Bipyridine; Catalysis; Epoxides; Scandium; 1,2-Seleno alcohol

The catalytic asymmetric ring-opening of *meso*-epoxides continues to be a powerful strategy to furnish chiral 1,2-difunctionalized fine chemicals with two contiguous stereogenic centers in just one step.[1] According to this strategy a number of protocols have been developed for the synthesis of enantiomerically highly enriched 1,2-azido alcohols,[2] 1,2-amino alcohols,[3] 1,2-diol derivatives,[4] 1,2-cyano alcohols,[5] 1,2-mercapto alcohols,[6] and 1,2-halohydrins.[7] Recently, Zhu and co-workers reported the first catalytic, enantioselective addition of aryl selenols to a range of *meso*-epoxides with a heterobimetallic titanium–gallium(salen) complex, which was shown to act as a mixed Lewis acid–Lewis base catalyst.[8] Excellent enantioselectivities were obtained for cyclic epoxides whereas acyclic and in particular aromatic epoxides turned out to be less suitable substrates for this protocol delivering the ring-opened 1,2-seleno alcohols in just over 70% ee.

We have previously developed highly enantioselective scandium– and indium–bipyridine-catalyzed processes for the addition of alcohols, amines, and thiols to *meso*-epoxides furnishing valuable and highly enantiomerically enriched 1,2-diol monoethers,[9] 1,2-amino alcohols,[10] and 1,2-mercapto alcohols,[11] respectively, in partly excellent enantioselectivities of up to 98% ee. We report here that this protocol can be extended to the addition of phenylselenol to aromatic *meso*-epoxides giving rise to 1,2-seleno alcohols in good yields and up to 94% ee, which nicely complements the Zhu process. Furthermore, a direct access to 1,2-diaryl carbinols via an in situ epoxide opening-reduction sequence has been developed by a slight modification of the reaction conditions.

We started our studies with the reaction of *cis*-stilbene oxide **(1a)** and phenylselenol **(2)** (2 equiv) in CH_2Cl_2 and treated this mixture with 10 mol % of each $Sc(OTf)_3$ and bipyridine **3** for 12 h at rt (Scheme 1). The ring-opened 1,2-seleno alcohol **4a** was obtained in 60% yield and 93% ee along with 20% of the corresponding deselenated carbinol **5a** in almost identical ee. Control experiments revealed that the formation of carbinol **5a** proceeded via the 1,2-seleno alcohol **4a** as purified **4a** when submitted to the reaction again furnished **5a** in good yield and identical ee.[12]

Since this deselenation reaction most likely proceeded in a radical manner,[13] we carefully excluded oxygen and light in subsequent experiments and added phenylselenol (total of 3 equiv) portionwise during the reaction. In fact, 1,2-seleno alcohol **4a** was now obtained in 77% yield and

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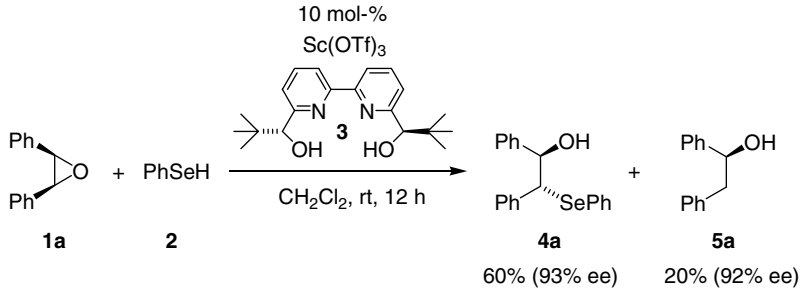


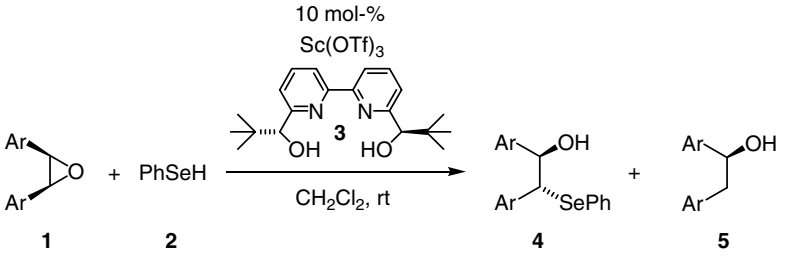
Scheme 1. Scandium–bipyridine-catalyzed phenylselenol addition to *cis*-stilbene oxide (**1a**).

93% ee after 8 h according to this protocol with only trace amounts of the deselenated carbinol **5a** being formed (Table 1, entry 1).[14] Subsequently, various other 1,2-seleno alcohols **4b**–**e** carrying different aryl substituents were obtained in typically moderate yields and very good enantioselectivities of up to 94% ee (entries 2–5). Varying amounts of the deselenated alcohols **5** were still obtained in typically slightly lower enantioselectivities. The principal other side reaction which we have encountered also with other less reactive nucleophiles is the Lewis acid-catalyzed epoxide rearrangement furnishing the corresponding aldehydes in yields <10%, which appears to compete effectively when the nucleophilic epoxide opening event is rather slow. Unfortunately, aliphatic *meso*-epoxides turned out to be not suitable substrates for this process delivering the products in low enantioselectivities.

To turn the sequential epoxide opening-deselenation reaction into the dominant reaction pathway we employed normal reagent-grade solvent and ran the reaction under usual daylight conditions for 48 h.[14] In fact, the deselenated carbinols **5a**–**e** were now obtained as major products in up to 65% yield and high enantioselectivities (entries 6–10) while the 1,2-seleno alcohols **4** were isolated as minor products, which could be easily removed by chromatography. We suspect that the slight decrease in enantiomeric purity of carbinols **5** as opposed to the 1,2-seleno alcohols **4** stems from partial hydrogen abstraction at the benzylic carbinol center under the radical conditions leading to partial racemization. Notably, this one-pot sequence constitutes an elegant alternative to the currently not possible enantioselective hydride addition to *meso*-epoxides.[15]

The facile deselenation reaction of the 1,2-seleno alcohols **4** initially formed apparently rests upon the stabilization of the transient benzyl radical. Thus, 1,2-seleno alcohol **4f**, which was obtained in 71% yield albeit only

Table 1
Scandium–bipyridine-catalyzed selenol addition to aromatic *meso*-epoxides (**1**)

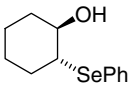


Entry	Epoxide **1** (Ar)	Cond.[a]	Yield of **4**[b,c] (%)	Yield of **5**[b,c] (%)
1	**1a** (Ph)	A	77 (93% ee)	<5 (92% ee)
2	**1b** (4-F–Ph)	A	51 (93% ee)	16 (80% ee)
3	**1c** (4-Cl–Ph)	A	51 (89% ee)	17 (85% ee)
4	**1d** (4-Br–Ph)	A	67 (91% ee)	5 (91% ee)
5	**1e** (3-Me–Ph)	A	51 (94% ee)	18 (86% ee)
6	**1a** (Ph)	B	7 (94% ee)	63 (90% ee)
7	**1b** (4-F–Ph)	B	6 (n.d.)	60 (75% ee)
8	**1c** (4-Cl–Ph)	B	10 (89% ee)	64 (87% ee)
9	**1d** (4-Br–Ph)	B	12 (92% ee)	64 (92% ee)
10	**1e** (3-Me–Ph)	B	<5 (94% ee)	64 (92% ee)

[a] Reaction conditions A: reaction in the dark with degassed solvent, 1.5 equiv PhSeH added at the start of the reaction followed by addition of 3 × 0.5 equiv of PhSeH over 8 h; B: reaction with reagent-grade solvent under daylight, 2 equiv PhSeH added at the start of the reaction followed by another 2 equiv after 24 h.

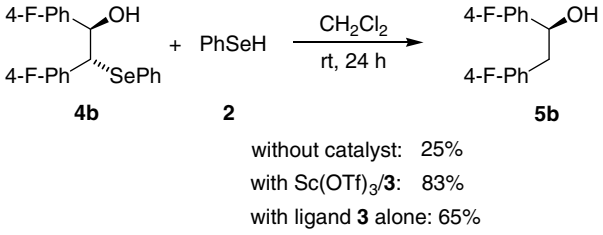
[b] Yields refer to isolated and chromatographically purified product.

[c] Ee was determined by chiral HPLC on a Daicel OD-H-column.



4f

24% ee through ring-opening of cyclohexene oxide did not show any tendency to undergo the deselenation reaction even under reaction conditions B, which typically favor the formation of the deselenated alcohols. To probe the influence of the chiral catalyst to facilitate the deselenation reaction we treated 1,2-seleno alcohol **4b** with 2 equiv of PhSeH with and without the chiral catalyst (Scheme 2). In the absence of the catalyst a slow deselenation occurred giving rise to deselenated alcohol **5b** in just 25% along with 52% of recovered seleno alcohol **4b** after 1 day at rt. In the presence of either the scandium–bipyridine catalyst or simply ligand **3** alone, however, **5b** was obtained in good yields under otherwise identical reaction conditions with only trace amounts of the starting material being recovered. We suspect that the basic bipyridine ligand assists in the abstraction of the selenol proton, which most likely is the first step towards the formation of the selenol radical.



Scheme 2. Control experiments for the deselenation reaction.

In conclusion, we have shown that the chiral scandium–bipyridine complex effectively catalyzed the selenol addition to aromatic *meso*-epoxides and furnished 1,2-seleno alcohols in moderate to good yields and typically high enantioselectivities. Furthermore, a sequential epoxide opening-deselenation protocol has been developed, which gave rise to formal hydride addition products in moderate yields and high ee's.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.006.

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for 10 min followed by the addition of phenylselenol (0.375 mmol). Every 2 h further phenylselenol (0.125 mmol) was added and the reaction was stopped after 8 h. The solvent was evaporated in vacuo and the product was purified by flash column chromatography over silica gel (ethyl acetate/petroleum ether, 1:9). Yield 68 mg (77%) of a yellow oil. $[\alpha]_D^{23}$ −152.9 (*c* 1.83, $CHCl_3$); ee = 93%. The enantiomeric assay: Chiralcel OD-H, isocratic (*n*-hexane/*i*PrOH, 90:10, flow 0.5 mL/min) $\lambda_{max} = 204$ nm, (1*R*,2*R*): 23.3 min (major); (1*S*,2*S*): 27.4 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.20$ (s, 1H, O*H*), 4.47 (d, $J = 9.0$ Hz, 1H, C*H*-Se), 5.03 (d, $J = 9.0$ Hz, 1H, C*H*-OH), 6.96–6.98 (m, 2 H, Ar-*H*), 7.07–7.27 (m, 11H, Ar-*H*), 7.36–7.39 (m, 2 H, Ar-*H*). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 59.86, 76.55, 126.7, 127.0, 127.7, 127.9, 128.0, 128.1, 128.4, 128.7, 128.9, 135.3, 139.9, 140.7$. IR (film): $\tilde{\nu} = 3440, 3060, 3029, 1600, 1578, 1493, 1476, 1452, 1437, 1188, 1197, 1048\ cm^{-1}$. MS (ESI): $m/z = 377.0$ $[M+Na]^+$. Sequential epoxide opening-deselenation reaction: a solution of $Sc(OTf)_3$ (0.025 mmol) and chiral bipyridine **3** (0.030 mmol) in dichloromethane (1 mL) was stirred under argon for 10 min, after which *cis*-stilbene oxide (**1a**) (0.25 mmol) dissolved in dichloromethane (0.5 mL) was added. The mixture was stirred for 10 min followed by the addition of phenylselenol (0.50 mmol). After 24 h additional phenylselenol (0.50 mmol) was added and the reaction was stopped after 48 h. The solvent was evaporated in vacuo and the product was purified by flash column chromatography over silica gel (ethyl acetate/petroleum ether, 1:9). Yield 31 mg (63%) of a colorless solid, mp 60–62 °C. $[\alpha]_D^{23}$ −13.7 (*c* 1.25, $CHCl_3$); ee = 90%. The enantiomeric assay: Chiralcel OD-H, isocratic (*n*-hexane/*i*PrOH, 90:10, flow 0.5 mL/min) $\lambda_{max} = 204$ nm, (*R*): 19.0 min (minor); (*S*): 20.8 min (major). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.95$ (br s, 1H, O*H*), 2.97 (dd, $J = 13.5$, 8.0 Hz, 1H, CH_AH_B), 3.04(dd, $J = 13.5$, 5.0 Hz, 1H, CH_AH_B), 4.87 (dd, $J = 8.0$, 5.0 Hz, 1H, C*H*-OH), 7.17–7.35 (m, 10 H, Ar-*H*). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 46.05, 75.30, 125.9, 126.6, 127.6, 128.4, 128.5, 129.5, 138.0, 143.8$. IR (film): $\tilde{\nu} = 3365, 3025, 2921, 2857, 1495, 1453, 1072, 1040\ cm^{-1}$. MS (ESI): $m/z = 221.0$ $[M + Na]^+$.

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