Asymmetric Organocatalysis

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Organocatalytic Asymmetric α-Selenenylation of Aldehydes**

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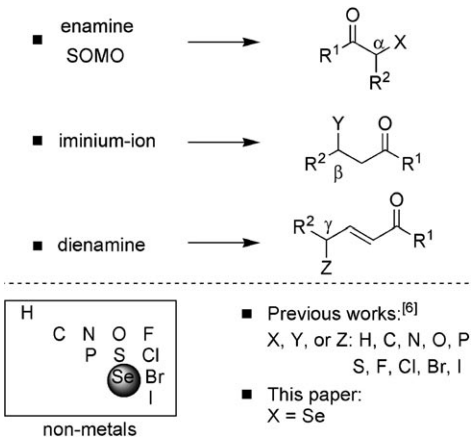
Asymmetric organocatalysis has become a field of central importance for the stereoselective preparation of chiral, enantioenriched molecules.[1] In particular, chiral secondary amine catalysis has proven to be a powerful procedure for the enantioselective transformation of carbonyl compounds. Aminocatalysis has enabled the asymmetric α-, β-, and γ-functionalization of aldehydes and ketones with a wide range of electrophiles and nucleophiles by exploiting catalytic enamine,[2] SOMO (singly occupied molecular orbital),[3] iminium ion,[4] and dienamine[5] activation modes (Scheme 1). Within the realm of the non-inert elements classified as "non-metals" in the periodic table, only selenium-based compounds have yet to be stereoselectively incorporated into carbonyl compounds by organocatalysis.[6]



Scheme 1. Activation modes for the asymmetric aminocatalysis.

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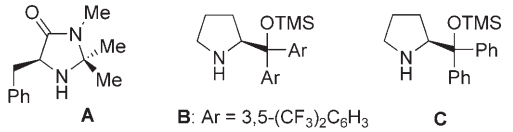
Herein we report the exploitation of the enamine activation strategy in the first highly enantioselective α-selenenylation of aldehydes catalyzed by a readily available chiral secondary amine.[7] This process provides access to highly attractive α-seleno aldehydes in high yield and with excellent enantiomeric excess (95–99%) from commercially available starting materials under mild and simple reaction conditions. The synthetic utility of such intermediates[8] is demonstrated by their easy and rapid conversion into valuable chiral building blocks.

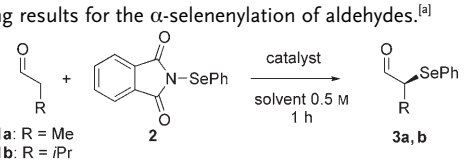
The only access to chiral α-seleno aldehydes reported to date relies on a "chiral-pool" approach that involves multistep procedures.[9] To the best of our knowledge, no catalytic enantioselective processes are available for the preparation of these optically active building blocks. In light of this, and considering our recent efforts to expand the scope of asymmetric aminocatalysis,[10] we wondered whether the enamine activation concept might be extended to the highly enantioselective addition of selenium-based compounds to aldehydes.

To assess the feasibility of such an asymmetric organocatalytic α-selenenylation strategy, we focused on air-stable, commercially available *N*-(phenylseleno)phthalimide (**2**) as the electrophilic selenium source.[11] Thus, treatment of propanal (**1a**) with **2** in the presence of 10 mol% of L-proline in CH_2Cl_2 (0.5 M) resulted in a clean but poorly selective selenenylation of the aldehyde (Table 1, entry 1). We then turned our attention to the use of imidazolidinone **A**[12] and the diarylprolinol silyl ethers **B** and **C** (TMS = trimethylsilyl),[13] which have recently emerged as potentially general enamine organocatalysts for a broad range of highly selective α-functionalizations of aldehydes.



As can be seen from Table 1, preliminary studies indicated that both catalyst **B** and the TFA salt of catalyst **A** were able to promote the reaction with good enantioselectivity (Table 1, entries 2–5). Extensive evaluation of a variety of catalyst salts (Table 1, entries 7–12) revealed that imidazolidinone **A**·DCA and **B**·*p*-$NO_2C_6H_4COOH$ exhibited superior selectivity and much higher catalytic activity (Table 1, entries 9 and 12, respectively). These findings allowed us to reduce the loading of the organocatalysts to 0.5 mol% without compromising the chemical or optical yields (Table 1, entries 13 and 14).[14]

Table 1: Selected screening results for the α-selenenylation of aldehydes.[a]



1a: R = Me
1b: R = *i*Pr
2
3a, b

Entry	1	Catalyst	Amount [mol%]	Solvent	*T* [C°]	Conversion [%][b]	*ee* [%][c]
1[d]	**a**	L-proline	10	CH_2Cl_2	RT	82	18
2	**a**	**A**·TFA	10	CH_2Cl_2	RT	>95	85
3	**a**	**B**	10	CH_2Cl_2	RT	>95	84
4	**a**	**A**·TFA	10	CH_2Cl_2	−20	44	90
5	**a**	**B**	10	CH_2Cl_2	−20	15	86
6	**a**	**C**	10	CH_2Cl_2	−20	83	78
7	**a**	**A**·*p*-NO_2PhCO_2H	10	CH_2Cl_2	−20	53	87
8	**a**	**A**·TCA	10	CH_2Cl_2	−20	64	93
9	**a**	**A**·DCA	10	CH_2Cl_2	−20	>95	94
10	**a**	**B**·$PhCO_2H$	10	CH_2Cl_2	−20	47	88
11	**a**	**B**·*o*-NO_2PhCO_2H	10	CH_2Cl_2	−20	54	91
12	**a**	**B**·*p*-NO_2PhCO_2H	10	CH_2Cl_2	−20	65	91
13[e]	**a**	**A**·DCA	0.5	CH_2Cl_2	0	>95 (96)	92
14[f]	**a**	**B**·*p*-NO_2PhCO_2H	0.5	CH_2Cl_2	0	>95 (95)	90
15[f]	**a**	**B**·*p*-NO_2PhCO_2H	5	toluene	0	>95 (99)	95
16[f]	**b**	**A**·DCA	5	CH_2Cl_2	−20	91	82
17[f]	**b**	**B**·*p*-NO_2PhCO_2H	5	toluene	0	95 (89)	99

[a] Reactions carried out on a 0.2-mmol scale with 1.5 equiv of aldehyde **1**; TFA: trifluoroacetic acid; TCA: trichloroacetic acid; DCA: dichloroacetic acid; RT: room temperature; the absolute configuration of **3a** obtained with catalysts **A**–**C** was determined to be (*S*) by comparison of its specific optical rotation with the value reported in the literature.[9] [b] Conversion determined by ^{1}H NMR spectroscopy; yield of isolated product is given in parentheses. [c] *ee* values were determined by chiral HPLC analysis of the crude mixture and confirmed after reduction of **3a**,**b** to the corresponding alcohols. [d] The opposite (*R*) enantiomer of **3a** was obtained. [e] Reaction time: 16 h; 0.4-mmol scale. [f] Reaction time: 40 h; 0.4-mmol scale.

Both the employed organocatalysts afforded the α-seleno aldehyde **3a** with an (*S*) absolute configuration, as determined by comparison of its specific optical rotation with the value reported in the literature.[9] The sense of asymmetric induction is consistent with previously reported selectivity models in which the *Re*-face of the (*E*)-configured enamine intermediate is effectively shielded by the chiral fragments.[6e,12b,13b]

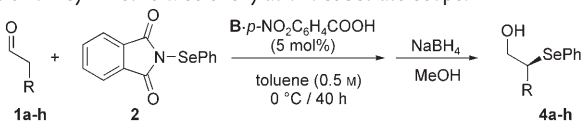
Further optimization of the standard reaction parameters[15] revealed that carrying out the reaction in toluene (0.5 M) in the presence of **B**·*p*-$NO_2C_6H_4COOH$ (5 mol%) allowed greater stereocontrol (95% *ee*; Table 1, entry 15), albeit at the expense of reactivity. On this basis, and considering the results obtained in the organocatalytic α-selenenylation of isovaleraldehyde (**1b**; Table 1, entries 16 and 17), these catalytic conditions were identified as the most consistent and general and were thus selected for further explorations.

We next examined the applicability of this enantioselective α-selenenylation strategy to various aldehydes. The reaction products were isolated as their alcohols **4** after reduction of the aldehyde moiety with $NaBH_4$ in situ to facilitate work-up.[16] Reduction of the α-seleno aldehyde **3a** to **4a** demonstrated that this process occurs without loss of optical purity (Table 2, entry 1).

The method proved successful for a wide range of aldehyde substituents, including alkyl, alkenyl, and heterosubstituted groups, the desired products **4** being isolated in excellent enantiomeric excess (95–99%) and high yields. Similarly, the sterically encumbered aldehyde **1h** was transformed smoothly into the corresponding chiral alcohol **4h** with excellent chemical and optical yields (Table 2, entry 9).[17] It is notable that no side products resulting from aldol dimerization or the formation of α,α-diseleno aldehydes were observed under these reaction conditions.

This organocatalytic enantioselective α-selenenylation reaction of aldehydes provides highly versatile chiral building blocks for different synthetic transformations that lead to valuable optically active compounds. Scheme 2 shows two examples. The β-phenylseleno alcohol **4b**, for example, which was generated by direct reduction of the aldehyde **3b**, was converted into the corresponding carbamate and then oxidized in situ to generate a selenonyl group. The stereospecific intramolecular nucleophilic substitution of this excellent leaving group by the nitrogen atom of the carbamate gave rise to a ring closing reaction that afforded the highly enantioenriched 4-substituted 1,3-oxazolidinone **5**.[18] The (*R*) absolute configuration of **5**, as determined by comparison of its specific optical rotation with the value reported in the literature,[19] indicates that the substitution occurs with inversion of configuration. α-Selenenylated aldehydes can also undergo in situ reductive

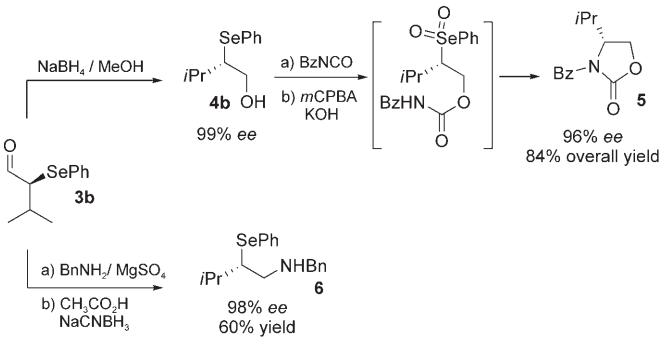
Table 2: Asymmetric α-selenenylation: substrate scope.[a]



1a-h
2
4a-h

Entry	R (aldehyde)	Yield [%][b] (alcohol)	*ee* [%][c]
1	Me (**1a**)	99 (**4a**)	95
2	*i*Pr (**1b**)	89 (**4b**)	99
3	*i*Pr (**1b**)	94 (*ent*-**4b**)	99[d]
4	Et (**1c**)	84 (**4c**)	97
5	Bu (**1d**)	99 (**4d**)	98
6	$PhCH_2$ (**1e**)	81 (**4e**)	97
7	allyl (**1f**)	91 (**4f**)	98
8	CH_2SCH_3 (**1g**)	94 (**4g**)	98
9	*t*Bu (**1h**)	99 (**4h**)	99

[a] Reactions performed on a 0.4-mmol scale with 1.5 equiv of aldehyde **1**. [b] Yield of isolated product. [c] Determined by HPLC analysis. [d] (*R*)-**B** was used as the catalyst to afford the (*R*) enantiomer of **4b**.



Scheme 2. Synthetic transformations of α-seleno aldehydes.

amination upon treatment with benzylamine and $NaCNBH_3$ without loss of enantiomeric purity.[20] Interestingly, the phenylseleno amine **6**, which can be generated in good yield and high enantioselectivity, is a useful intermediate for the preparation of several compounds.[8]

In summary, we have reported an organocatalytic asymmetric α-selenenylation of aldehydes that employs unmodified and commercially available starting materials and catalysts under mild reaction conditions. Besides expanding the scope of asymmetric aminocatalysis, this transformation provides the first catalytic access to highly enantioenriched (ee values ranging from 95 to 99%) α-seleno aldehydes, which are versatile chiral intermediates that lead to valuable, optically active compounds. A full account of the scope of this methodology will be reported in due course.

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[15] Solvent screening for α-selenenylation of **3a** (10 mol% catalyst, −20°C, 1 h reaction time): catalyst **A**·DCA: CH_2Cl_2: >95% conversion, 94% *ee*; toluene: 47% conversion, 90% *ee*; THF: 50% conversion, 70% *ee*; acetone: 85% conversion, 87% *ee*. Catalyst **B**·*p*-$NO_2C_6H_4COOH$: CH_2Cl_2: 65% conversion, 91% *ee*; toluene: 20% conversion, 95% *ee*; EtOAc: 15% conversion, 90% *ee*; Et_2O: 23% conversion, 94% *ee*; acetone: 29% conversion, 80% *ee*; EtOH: no reaction; $CHCl_3$: 17% conversion, 90% *ee*.

[16] The optically active α-seleno aldehyde **3a** slowly racemizes during column chromatography on silica gel; see the Supporting Information for details.

[17] α,α-Disubstituted aldehydes such as 2-phenylpropanal react smoothly under our α-selenenylation conditions to form quaternary stereocenters, albeit with low enantioselectivity (−20°C, 10 mol% catalyst **B**·*p*-$NO_2C_6H_4COOH$, 24 h, >95% conversion, 34% *ee*).

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