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Organocatalytic highly enantioselective α-selenenylation of aldehydes

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Abstract—The highly enantioselective organocatalytic α-selenenylation of aldehydes is presented. The reaction gives access to α-phenylselenoaldehydes and β-selenoalcohols in high yields with up to >99% ee.

α-Selenylated carbonyl compounds[1] are of great significance in organic synthesis due to the ease in which they are converted to synthetically valuable motifs such as α,β-unsaturated carbonyl compounds,[2] terminal aziridines,[3] α-hydroxy esters,[4] allylic amines,[5] and α-amino acids.[6] Thus, several methods for the preparation of racemic α-selenoaldehydes using preformed silyl ethers,[7] stoichiometric amounts of acid,[8] or preformed enamines[9] are available. In addition, the direct α-phenylselenenylation of aldehydes[10] mediated by a secondary amine has been reported.[10b] However, asymmetric α-selenenylation represents a most attractive but relatively undeveloped area of research.[11] In this context, Paulmier et al. in 1988 reported an example of a direct asymmetric α-phenylselenenylation of aldehydes.[11a] Notably, Paulmier's reaction involved in situ generated enamine intermediates derived from an unmodified aldehyde substrate and chiral proline derivatives.

Organocatalysis[12] has gained widespread attention as a result of the efficiency and selectivity of many organocatalytic reactions. In particular, amine catalysis has become tremendously important within this research area.[12] Amine catalysis relies on two fundamental mechanisms: enamine[13] and iminium activation.[14] Iminium activation, enables the incorporation of nucleophiles at the β-carbon of an α,β-unsaturated aldehyde or ketone whereas enamine catalysis is an efficient tool for the electrophilic α-functionalization of aldehydes and ketones.[13,14] For example, Jørgensen, has reported a highly enantioselective α-sulfenylation of enals using protected diarylprolinols as catalysts.[15] Moreover, chiral amines play an important role in nucleophilic organocatalysis.[12a,c]

Importantly, Wang and co-workers recently reported a catalytic protocol for the α-phenylselenenylation of aldehydes and ketones using secondary amines as catalysts.[16] Attempts were also made to develop a stereoselective reaction but almost racemic products were formed. However, three asymmetric examples were achieved with aldehydes as the nucleophiles when (*S*)-pyrrolidine tosylsulfonamide was used as the catalyst. The corresponding products were isolated with ee's ranging from 30% to 60%. Inspired by these initial attempts and our previous experience in asymmetric organocatalysis,[17] we decided to investigate the possibility of developing a highly enantioselective α-selenenylation reaction of aldehydes based on chiral pyrrolidine catalysis (Scheme 1, Eq. 1).

Herein, we report the first highly enantioselective α-selenenylation of aldehydes giving products in 63–93% yield with up to >99% ee.

In an initial experiment *iso*-valeraldehyde **2a** (0.25 mmol) and *N*-(phenylseleno)phthalimide **3**[8] (0.3 mmol), were mixed at 0 °C in the presence of a catalytic amount (20 mol %) of TMS protected α,α-diphenyl-2-pyrrolidinemethanol (TMS-DPP) **1**.[15,18] After 15 min of stirring, complete conversion had been accomplished and the resulting α-selenoaldehyde **4a** was reduced in situ with $NaBH_4$ to the corresponding alcohol **5a** with 40% ee (Table 1, entry 1).[19] Encouraged by this result we

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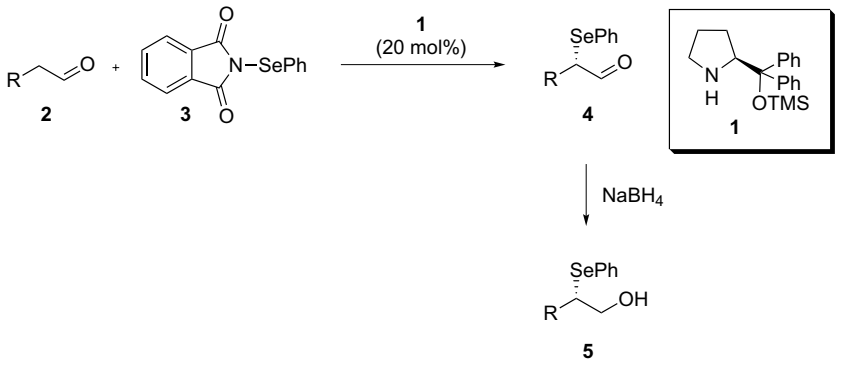
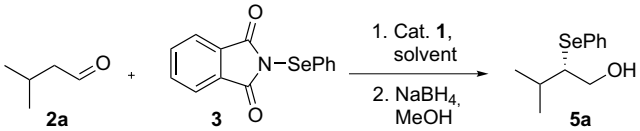


(1)

decided to optimize the reaction conditions (Table 1). A small catalyst screen revealed that TMS-DPP **1** catalyzed the formation of **4a** with the highest stereoselectivity and a temperature study in $CHCl_3$ showed that decreasing the temperature to −50 °C improved the enantiomeric excess at the expense of a prolonged reaction time (entries 1–3). The highest enantioselectivity was achieved at 0 °C in toluene and β-seleno-derivative **5a** was isolated after reduction in 95% ee. Notably, other TMS protected diaryprolinols such as Jörgensen's catalyst (Ar = 3,5-$(CF_3)_2$–C_6H_2)[15] and the dixylene derivative (Ar = 3,5-$(Me)_2$–C_6H_2) gave **5a** under these conditions in 90% yield with >99% and 81% ee, respectively. The opposite enantiomer *ent*-**5a** was isolated in 30% ee in CH_3CN. Even though the reaction media is known to influence the stereoselectivity in amine catalyzed reactions, this total switch of enantioselectivity was unexpected.[20]

Table 1. Optimization of the α-phenylselenenylation of *iso*-valeraldehyde

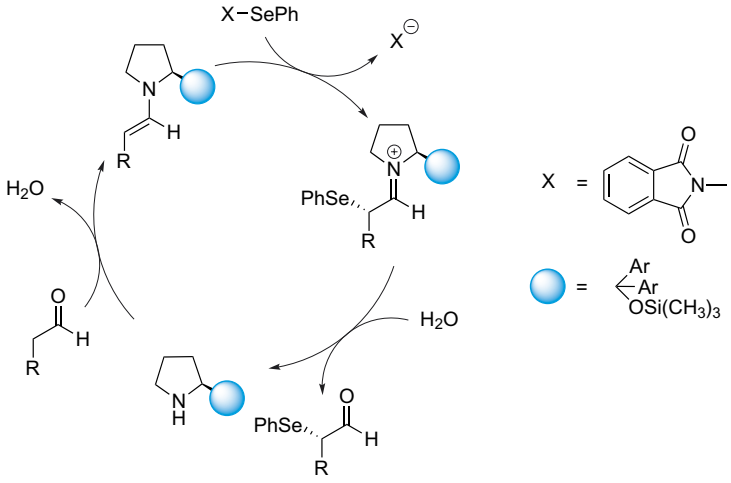


Entry	Solvent	Time (min)	Temperature (°C)	Conversion[a] (%)	ee[b] (%)
1	$CHCl_3$	15	0	100	40
2	$CHCl_3$	30	−20	100	62
3	$CHCl_3$	90	−50	100	74
4	$CHCl_3$	30	−60	<10	84
5	CH_3CN	15	0	100	−30
6	Toluene	30	0	100	95

[a] Conversion determined by NMR analyses of the crude reaction mixture.
[b] Determined by chiral-phase HPLC analyses of alcohol **4a**.

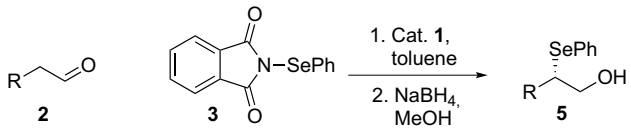
In order to probe the scope of the α-selenenylation, various aldehydes were reacted with **3** using TMS-DPP **1** as the catalyst (Table 2).

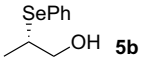
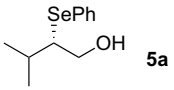
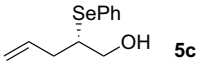
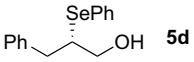
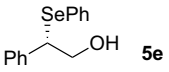
The organocatalytic α-selenenylation of aliphatic aldehydes was efficient and highly enantioselective. The corresponding β-seleno alcohols **5** were obtained in 83–93% yields with 93–96% ee. For example, the reaction between *N*-(phenylseleno)phthalimide **3** and *iso*-valeraldehyde **2a** gave the corresponding product **5a**, after in situ reduction, in 93% yield with 95% ee (entry 2). The unsaturated aldehyde 4-pentenal **2c** also successfully reacted and the corresponding β-seleno alcohol **5c** was isolated in 90% yield with 93% ee. Aromatic aldehydes such as 3-phenylpropionaldehyde were also well tolerated and



Scheme 1. Proposed catalytic cycle.

Table 2. Scope of the organocatalytic enantioselective α-phenylselenenylation of aldehydes



Entry	Product	Time (min)	Temperature (°C)	Yield[a] (%)	ee[b] (%)
1	 **5b**	30	0	83	96[c]
2	 **5a**	30	0	93	95
3	 **5c**	20	0	90	93[c]
4	 **5d**	95	−20	66	95
5	 **5e**	120	−20	63	65[c]

[a] Isolated yield of pure product **5** after silica gel chromatography.
[b] Determined by chiral-phase HPLC or GC analyses.
[c] Reaction performed with 20 mol % of benzoic acid.

compound **5d** was furnished in 66% yield and 95% ee. Even sterically demanding substrates such as 2-phenylacetaldehyde **2e** reacted and the corresponding alcohol **5e** was isolated in 63% yield with 65% ee. 2-Arylsubstituted acetaldehydes such as **2e** have previously not been used as substrates in α-selenenylation of aldehydes. The addition of benzoic acid (20 mol %) as an additive further increased the efficiency of the reaction (entries 1, 3, and 5). The absolute configuration of the α-selenylated aldehydes **4** was determined to be 2*S* after comparison of the optical rotation of alcohol **5e** with the literature data ($[\alpha]_D^{23}$ +48.9 (*c* 1.0, $CHCl_3$), lit. (**5e** $[\alpha]_D^{25}$ +130.0 (*c* 2.2, $CHCl_3$))[21]). This is also in line with the proposed catalytic cycle and the previous chiral amine **1** catalyzed α-sulfenylation reactions[15] and α-oxygenation reactions.[22] Thus, efficient shielding of the *Si*-face of the chiral enamine intermediate by the bulky aryl groups of **1** leads to stereoselective *Re*-facial addition of **3** to the activated enamine, Scheme 1. The addition of a benzoic acid derivative possibly speeds up the reaction by accelerating the iminium/enamine formation between the chiral amine and the aldehyde.

In summary, we have described a simple, highly enantioselective organocatalytic reaction between *N*-(phenylseleno)phthalimide and aldehydes. The reaction represents an asymmetric entry to valuable α-selenoaldehydes and β-selenoalcohols in high yields with up to >99% ee. These compounds create a versatile synthetic platform for construction of terminal aziridines, α-hydroxy esters, allylic amines, and α-amino acids. Mechanistic studies and synthetic applications of this transformation are ongoing in our laboratory.[23]

Note added in proof

After the submission of this manuscript on the 29th of June an elegant paper appeared on the web at the 6th of August describing the same type of reaction see Ref. 23.

Acknowledgements

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19. To a stirred solution of *iso*-valeraldehyde (0.25 mmol, 1.0 equiv) in toluene (1 mL) at 0 °C, catalyst (0.05 mmol, 0.2 equiv) and *N*-(phenylseleno)phthalimide **3** (0.28 mmol, 1.1 equiv) were added. The reaction was stirred at 0 °C until full conversion was accomplished. Then MeOH (2 mL) was added to the crude reaction mixture together with an excess of $NaBH_4$. After standard work-up, the crude product was purified by column chromatography to

afford β-phenylselenoalcohol **5a**. Compound **5a**: Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.62$–7.58 (m, 2H), 7.30–7.22 (m, 3H), 3.82–3.60 (m, 2H), 3.20–3.16 (m, 1H), 2.19 (br s, 1H), 2.06–1.99 (m, 1H), 1.08 (d, $J = 7.2$ Hz, 3H), 1.06 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 134.6, 129.1, 128.2, 127.6, 63.3, 60.1, 30.0, 21.1, 20.5. $[\alpha]_D^{23}$ −8.0 (*c* 1.0, $CHCl_3$). HRMS (ESI) (*m*/*z*): $[M+Na]^+$ calcd for $C_{11}H_{16}SeONa$, 267.0259; found, 267.0248. The enantiomeric excess was determined by HPLC with an OD-H column, (*n*-hexane–*i*-PrOH = 95:5, $\lambda = 230$ nm), 0.5 mL/min; t_R = major enantiomer 15 min, minor enantiomer 17 min.

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