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PAPER

Ephedrine-based diselenide: a promiscuous catalyst suitable to mimic the enzyme glutathione peroxidase (GPx) and to promote enantioselective C–C coupling reactions†

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The ephedrine-based diselenide appears as a new promiscuous catalyst, able to generate optically active alcohols by addition of organozinc to aldehydes (up to 97% ee), and shows powerful GPx like activity, reducing H_2O_2 to water in only 16.33 min (eleven times faster than PhSeSePh).

The growing field of research of selenoproteins combined with essential physicochemical properties of selenium has promoted growing interest in the chemistry and biochemistry of selenium compounds.[1] High impact studies have determined that selenium plays a pivotal role in glutathione peroxidase enzymes (GPx), which protect organisms from oxidative stress, inherent from oxygen metabolism.[2] Additionally, it has been employed as an important agent in cancer prevention, immunology, aging, male reproduction, neurodegenerative diseases, including Alzheimer's and Parkinson's disease, and other physiological processes.[3] Since the discovery that selenium plays a paramount role in GPx enzymes, synthetic developments and design of new chalcogen-based catalytic antioxidants have attracted considerable attention.[4]

Small molecule organoselenium compounds have emerged as excellent candidates to act as GPx mimics, due to their well-known ability to undergo a two-electron redox cycle between chalcogen(II) and (IV) species.[5] On the other hand, in recent years, increasing application of chiral selenium compounds as ligands in metal-catalyzed enantioselective transformations has been witnessed.[6] One of the most important challenges in this field is the development of new chiral ligands for the enantioselective addition of organozinc reagents to carbonyl compounds. This reaction is one of the most important protocols used to generate a new carbon–carbon bond in an asymmetric manner.[7] Two reactions are notable in this regard: the addition of aryl boronic acids and the addition of diethylzinc to aldehydes.[8,9] Much effort has been directed toward the design of new chiral ligands, which give access to optically active alcohols, acknowledged as important precursors for pharmacologically and biologically active compounds.[10]

Although selenium catalysts have been successfully used in the addition of diethylzinc to aldehydes, to the best of our knowledge, only a few examples have appeared in the literature describing the application of chiral selenium compounds acting as effective ligands for the addition of boronic acids to carbonyl compounds, involving the coordination of the selenium moiety with the metallic center.[11–13] Some chiral selenium compounds have shown good activity in asymmetric transformations, such as the enantioselective addition of diethylzinc to aldehydes,[14] 1,4-addition of Grignard reagents to enones[15] and asymmetric allylic substitution catalyzed by palladium.[16]

Design and screening of new ligands derived from ephedrine and its analogues have been explored in numerous asymmetric reactions.[17] The structural characteristics of ephedrine, such as the presence of two chiral centers directly attached to coordination centers and the easy introduction of new functionalities, make this chiral pool an excellent candidate for application in asymmetric transformations.

In this context, and continuing our interest in the development of chiral organochalcogen compounds with tailored biological importance and their application as ligands in asymmetric synthesis, we describe herein the preparation of a new series of selenium compound derivatives from (−)-ephedrine (Scheme 1) and their application in asymmetric carbon–carbon bond formation as well as GPx mimics.

Chiral selenium compounds **2** and **3a–d** were readily prepared, in one step, affording the ligands in satisfactory yields

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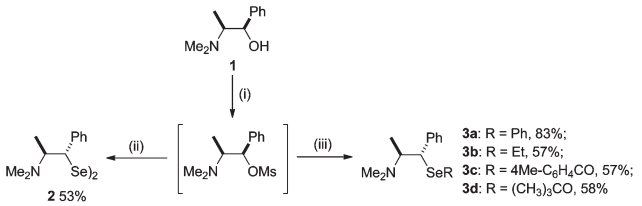


Scheme 1 *Reagents and conditions*: (i) **1** (1 mmol), THF (10 mL), Et_3N (1.2 mmol), MsCl (1 mmol), 0 °C, 30. (ii) Li_2Se_2 (2 mmol) in THF (5 mL), overnight. (iii) $Na[RSeB(OEt)_3]$ (1 mmol), in THF (5 mL), r.t. 12 h.

(Scheme 1). Mesylation of amino alcohol **1** "*in situ*", followed by subsequent reaction with Li_2Se_2 or a sodium selenolate derivative, allowed the preparation of **2** in 53% yield and **3a–d** in 56–83% isolated yields.

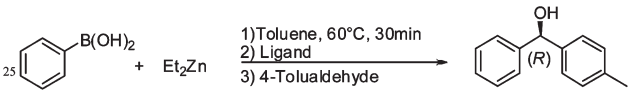
The ability of the synthesized catalysts to promote carbon–carbon bond formation in an enantioselective manner was evaluated firstly with the addition of boronic acids to aldehydes. To this aim, phenyl boronic acid was used, as a source of nucleophilic aryl species, along with 4-tolualdehyde in the presence of 10 mol% of ligands **3a–d** or **2** (Table 1). The initial experiments were carried out using the compounds **3a** and **3b** as chiral inductors. Although the product was obtained in 85 and 90% yield, respectively, after 1.5 h at r.t., in both experiments no enantiomeric excess was observed (entries 1 and 2). Interestingly, selenoester **3c**, under the same conditions, provided the product in 91% yield and with 51% of ee (entry 3).

A detailed analysis of Table 1 shows that the enantioselectivity was influenced by the temperature. For instance, using ligand **3c** at 0 °C the enantiomeric excess reached 70% with a slight increase in the yield (entry 4). On the other hand, when the reaction temperature was decreased to −20 °C, the product was achieved in 96% yield and the selectivity was decreased to 59% (entry 5). Thus, the reaction carried out at 0 °C was established as the optimal condition for this protocol.

Following these observations and in view of obtaining a more effective catalyst, the use of other synthesized ligands was tested. Analyzing Table 1, it is possible to verify that compound **3d** showed higher selectivity compared to selenoester **3c**, affording the desired product in near quantitative yield and with 85% of enantiomeric excess (entries 6 and 4). Furthermore, improved results in this testing reaction were obtained using the diselenide **2**. This compound showed excellent catalyst activity for this reaction, affording the desired product in 94% yield and with 92% ee (entry 7). A direct comparison between our designed catalyst **2** and alkylated ephedrine **1** was also performed and, encouragingly, the diselenide **2** was a much more effective catalyst for this transformation (entries 7 and 8).

Another set of experiments was also performed to optimize the amount of ligand **2** necessary to accomplish the reaction efficiently. An increase in the amount of **2** to up to 20 mol% proved to be ineffective, since the enantiomeric excess observed was at the same level obtained for the reaction using 10 mol% of **2** (entry 9). Some success was obtained by decreasing the catalyst loading to 5 and 2.5 mol%. While the yields were not affected, there was a slight decrease in the ee (entries 10 and 11). With these results it was possible to determine the optimal catalyst load as 10 mol%.

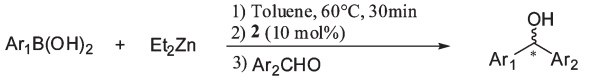
Table 1 Optimization of reaction conditions.



Entry	Ligand (load)	Time (h)	T (°C)	Yield[a] (%)	ee[b] (%)
1	**3a** (10 mol%)	1.5	25	85	—
2	**3b** (10 mol%)	1.5	25	90	—
3	**3c** (10 mol%)	1.5	25	91	51
4	**3c** (10 mol%)	1.5	0	93	70
5	**3c** (10 mol%)	1.5	−20	96	59
6	**3d** (10 mol%)	1.5	0	98	85
7	**2** (10 mol%)	1.5	0	94	92
8	**1** (10 mol%)	1.5	0	89	40
9	**2** (20 mol%)	1.5	0	99	93
10	**2** (5 mol%)	1.5	0	99	86
11	**2** (2.5 mol%)	1.5	0	93	80

[a] Yields for pure isolated products. [b] Calculated by HPLC analysis.

Table 2 Boronic acid addition to aldehydes catalyzed by **2**.

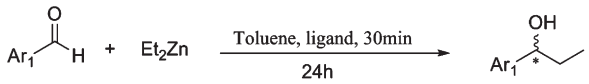


Entry	Ar_1	Ar_2	Yield[a] (%)	ee[b,c] (%)
1	C_6H_5	2-MeC_6H_4	91	97(*R*)
2	C_6H_5	4-MeC_6H_4	93	91(*R*)
3	C_6H_5	2-ClC_6H_4	85	89(*R*)
4	C_6H_5	4-ClC_6H_4	74	90(*R*)
5	C_6H_5	2-$OMeC_6H_4$	97	88(*S*)
6	C_6H_5	4-$OMeC_6H_4$	84	87(*R*)
7	2-MeC_6H_4	C_6H_5	80	75(*S*)
8	4-MeC_6H_4	C_6H_5	70	85(*S*)
9	2-$OMeC_6H_4$	C_6H_5	60	45(*R*)
10	4-$OMeC_6H_4$	C_6H_5	98	83(*S*)
11	2-ClC_6H_4	C_6H_5	50	77(*S*)
12	4-ClC_6H_4	C_6H_5	76	71(*S*)

[a] Yields for pure isolated products. [b] Calculated by HPLC analysis. [c] The relative configuration was determined by literature comparison.[12b]

Given that diselenide **2** proved to be the most effective catalyst for the addition of phenyl boronic acid to 4-tolualdehyde, we next examined the scope of addition of boronic acids to different aldehydes using diselenide **2**. Initially, phenyl boronic acid was employed as a source of aryl species and substituted aldehydes (Table 2). Our results showed that electronic and steric effects in the tested aldehydes have only a slight influence on the course of this reaction. It was found that all substituted aldehydes afforded products in the same range of yields and with high levels of enantioselectivity (entries 1–6). The best result was obtained for 2-tolualdehyde, affording the respective product in 91% yield and 97% ee (entry 1). Next, we investigated the aryl transference of different aryl boronic acids to benzaldehyde (entries 7–12). A small decrease in terms of the yield and enantioselectivity was observed employing *para*-substituted boronic acids in comparison with the first set of experiments. Moreover, the reactions were strongly affected by the use of *ortho*-substituted boronic

Table 3 Asymmetric addition of diethylzinc to benzaldehyde.



Entry	Ligand (mol%)	T (°C)	Yield[a] (%)	ee[b] (%)
1	**3c** (10)	25	57	91
2	**3d** (10)	25	82	92
3	**2** (10)	25	71	86
4	**3d** (10)	0	68	89
5	**3d** (10)	−20	66	93
6	**3d** (5)	−20	61	90
7	**3d** (2.5)	−20	64	89

[a] Yields for pure isolated products. [b] Calculated by HPLC analysis.

acids. In most cases a decrease in the yield was observed. This pattern could be attributed to ineffective transmetalation between Et_2Zn and substituted phenyl boronic acid due to the steric and electronic effects of the substituent.

Encouraged by these results, we also evaluated the efficiency of the most effective ligands in the addition of diethylzinc to aldehydes. Different reaction conditions were screened in a view to improve the efficiency of the system (Table 3). Reactions carried out with 10 mol% of ligands **3c**, **3d** and **2** were tested and all of them showed good results for the addition of diethylzinc to benzaldehyde (entries 1–3). To the compounds tested, catalyst **3d** showed improved efficiency, furnishing 1-phenyl-1-propanol in 82% yield and 92% ee at 25 °C (entry 2). Other reaction conditions, such as the temperature and the amount of **3d**, were analyzed in order to establish the best protocol for this reaction.

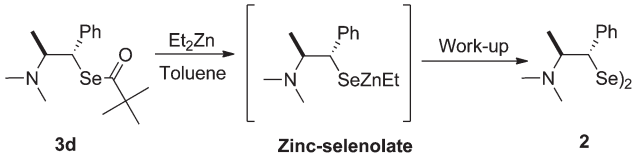
As shown in Table 3, a decrease from 10 to 5 and 2.5 mol% at −20 °C caused just a slight decrease in terms of enantiomeric excess, however, the reaction yields were significantly affected (entries 5, 6 and 7).

The mechanism for this reaction is similar to that described in the literature involving selenium compounds, where the active species is a selenolate generated in the reaction medium. In fact, we postulated that diselenide can be cleaved in the presence of diethylzinc leading to the formation of a selenolate (active species) and a selenoether.[13]

Indeed, this hypothesis was confirmed by performing a reaction involving the ligand **3d** in the presence of diethylzinc, under the same conditions employed in our methodology (Scheme 2).

As expected, after completion of the experiment, it was possible to obtain the diselenide **2**, which was derived from the oxidation of active species. The compound **2** was purified and identified by nuclear magnetic resonance of ^{1}H, ^{13}C and ^{77}Se. The importance of formation of selenolate in the addition of organometallic species to aldehydes explains the lack of activity shown by the respective selenides **3a** and **3b**. These catalysts cannot coordinate effectively with Zn due to the lower Lewis basicity character of the Se atom compared to the diselenide catalyst **2** or its precursor **3d**.

From a biological point of view, the structural feature of our designed compounds became attractive. Numerous reports have described the positive influence in the GPx like activity of



Scheme 2

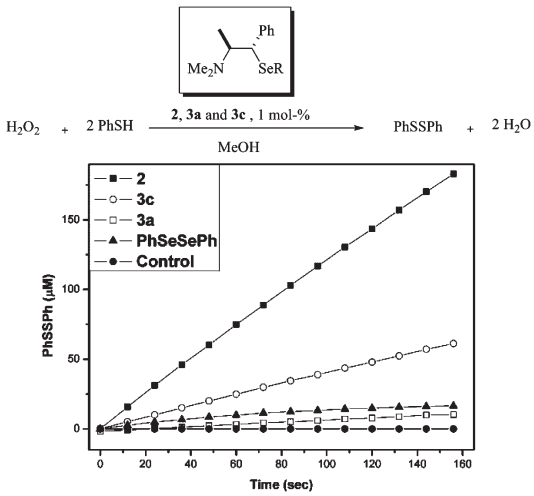


Fig. 1 GPx like behavior of catalysts **2**, **3a**, **3c** and PhSeSePh.

Table 4 GPx like activity of organoselenium catalysts **2**, **3a**, **3c** and PhSeSePh.

Entry	Catalyst[a,b]	T_{50} [c] (min)	Relative activity
1	PhSeSePh	187.28 (±7.53)	1.0
2	**2**	16.33 (±1.30)[d]	11.5
3	**3a**	244.27 (±25.05)	0.8
4	**3c**	48.75 (±5.47)	3.8

[a] Values of T_{50} were corrected for the uncatalyzed background reaction. [b] MeOH (1 mL); catalyst (0.05 mM); PhSH (5 mM); H_2O_2 (10 mM). [c] T_{50} is the time required, in minutes, to reduce the thiol concentration by 50% after the addition of H_2O_2. [d] Data in parentheses: experimental error.

compounds carrying chelating groups such as amines, amides or alcohols near to selenium.[18] According to this, we decided to investigate the GPx like activity of the new ephedrine derivatives **2**, **3a** and **3c**.

The GPx like activity of the synthesized compounds was monitored according to the method reported by Iwaoka and Tomoda.[19] In this method, the reduction of hydrogen peroxide, using PhSH as the thiol cofactor, is followed spectrophotometrically due to the increase in the absorbance at 305 nm relative to the formation of diphenyl disulfide (Fig. 1).

All tested compounds showed catalytic activity in this screening, promoting the oxidation of thiophenol as compared to the control reaction in the absence of a catalyst. The time required to reduce the concentration of the thiol to a half (T_{50}) is depicted in Table 4. For comparison purposes, diphenyl diselenide (PhSeSePh), a well known GPx like mimic,[18a] was used as a

standard catalyst in our study and its activity was arbitrarily ascribed as 1.0 (entry 1).

Not surprisingly, selenide **3a** was the poorer catalyst in this set of experiments (entry 3). The lower catalytic activity of this compound, T_{50} of 244 min, is the result of the sluggish oxidation of the selenide with H_2O_2. Conversely, a different scenario is observed for catalysts **2** and **3c**. Ephedrine derivative **3c** with a labile selenoester functionality allows the formation *in situ* of the correspondent selenolate, which impacts substantially its activity. Compared to the standard PhSeSePh, catalyst **3c** showed catalytic performance aproximately 4-fold higher. Moreover, diselenide **2** promoted the reduction of the concentration of PhSH to a half in just 16.3 min (entry 2). The increased activity of this compound, 11.5-fold higher than PhSeSePh, is attributed to the beneficial interactions between selenium and the nitrogen moiety in the course of the reaction.[20]

In summary, we have described in this paper the preparation of new chiral selenium ligands derived from (−)-ephedrine in only one step in good yields. The ephedrine-based diselenide was revealed to be an important example of a synthesized promiscuous catalyst, with activity as GPx mimics and the enantioselective addition of organozinc to aldehydes, acting as a redox element or a metal ligand.

In a comparison study, diselenide **2** proved to be a much better catalyst than the parent aminoalcohol ephedrine **1** for enantioselective carbon–carbon bond formations. Our designed catalysts were found to be convenient for use in the enantioselective aryl transfer addition of boronic acids to aldehydes, as well as the addition of diethylzinc to aldehydes, allowing the preparation of the desired chiral alcohols in good to excellent yields and high enantiomeric excess.

The ephedrine-based diselenide was also efficiently used as a GPx mimic, catalyzing the reduction of H_2O_2 to water at the expense of thiophenol using as little as 1 mol%. This diselenide significantly accelerated the reaction exhibiting a T_{50} of 16.33 min, while only a marginal accelerating effect was observed for the already known GPx mimic, PhSeSePh, which showed a T_{50} of 187.28 min. This opens a new perspective of using this kind of compound in medicine, since it could act as a redox element or a metal ligand with potential application as mimics or inhibitors of enzymes.

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