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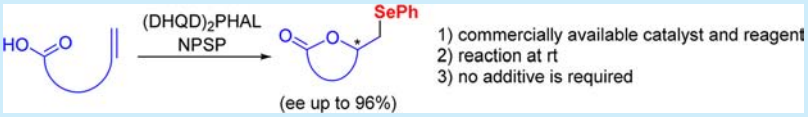
Catalytic and Highly Enantioselective Selenolactonization

Wenxue Niu and Ying-Yeung Yeung*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

Supporting Information



ABSTRACT: An enantioselective selenolactonization of olefinic acids has been developed using $(DHQD)_2PHAL$ as the catalyst. Structurally simple and commercially available *N*-phenylselenophthalimide was used as the electrophilic selenium reagent. The corresponding selenolactones could be obtained with up to 96% ee.

Electrophilic functionalization of unactivated olefins through asymmetric catalysis has been a topic of great importance in organic chemistry in the past decades. A vast amount of asymmetric catalytic systems for epoxidation, dihydroxylation, aminohydroxylation, hydrogenations, and aziridination are well-documented in the literature.[1] In the past few years, there has also been a dramatic growth of asymmetric halogenation processes using various catalytic protocols.[2] A highly relevant class of reactions is the use of chalcogen electrophiles, including sulfur and selenium, in electrophilic chalco-functionalization processes.[3] This type of reaction is also considered as a complementary tool of co-halogenation as the chalcogen-containing molecules have apparently different synthetic utilities. Chemistry using thio and seleno compounds is also well-established.[4]

Significant efforts have been devoted to the development of chiral electrophilic selenium reagents in the stoichiometric enantioselective selenofunctionalization of unactivated olefins.[5] In sharp contrast, the catalytic enantioselective variant remains very uncommon. Recent reports by Denmark demonstrated excellent control of enantioselectivity in chiral Lewis-base-catalyzed sulfenofunctionalization reactions.[6] Intramolecular selenoetherification of olefinic alcohols with up to 70% ee was achieved when a similar protocol was applied.[7] In the report, the authors found that the phenylseleniranium ion could readily be racemized by olefin-to-olefin degeneration. A structurally unique reagent, *N*-(2-nitrophenylselenenyl)succinimide, was used as the electrophilic selenium source because the corresponding 2-nitrophenylseleniranium ion was found to be configurationally stable and can avoid extensive racemization. Very recently, Jacobsen and co-workers took advantage of the rapid racemization of the seleniranium ion and developed a highly enantioselective selenoetherification of olefinic phenols using a dynamic kinetic resolution strategy. In their report, the chiral squaramide/achiral sulfide Lewis base/PyHCl cocatalyst system together with the newly designed *N*-*p*-anisylselenyl succinimide selenium reagent was employed.[8] However, to the best of our knowledge, there has been no report on the catalytic enantioselective selenolactonization. Herein, we disclose our recent finding on using a substoichiometric amount of $(DHQD)_2PHAL$ as a bifunctional organocatalyst in the enantioselective selenolactonization of unactivated olefinic acids at room temperature, giving the corresponding selenolactones with up to 96% ee. This represents the first case of catalytic, asymmetric selenolactonization at a useful level of enantioselectivity.

Development of enantioselective chalco-functionalization is challenging because there are three inherent difficulties: (1) racemization of the thiiranium or seleniranium ion through olefin-to-olefin degeneration; (2) nucleophilic partners (e.g., alcohol or carboxylic acid) may capture the thiiranium or seleniranium species and racemize it; and (3) Lewis basic chalcogen-containing products may capture the seleniranium ion and redeliver it to the olefin; this process is not necessary to be enantiospecific.[9,10] In one of the reports by Denmark and co-workers,[9a] it has been clearly demonstrated that both thiiranium and seleniranium ions could readily degenerate between olefins. When we compare thiiranium ions, seleniranium ions are far more configurationally unstable and their olefin-to-olefin transfer cannot be suppressed even at exceedingly low temperature; this might explain the extra difficulty in obtaining high enantioselectivity in catalytic enantioselective selenofunctionalization reactions.[9] In 1996, Toshimitsu and co-workers reported a potential solution to this problem in which a very bulky 2,4,6-tri-*tert*-butylphenyl group was introduced to provide steric protection to the chiral episeleniranium ion to suppress the racemization.[10] On the other hand, to avoid racemization of the chiral episeleniranium ion through the olefin-to-olefin degeneration or capturing by other nucleophiles, we decided to employ a bifunctional catalyst pocket that might potentially shield the configurationally unstable episeleniranium ion during the cyclization (Scheme 1).

At the outset of our trial, 4-phenyl-4-pentenoic acid (**1a**) was used as the substrate, and the commercially available *N*-phenylselenophthalimide (NPSP) **2** was used as the electrophilic selenium source. Various bifunctional organocatalysts were subjected to the investigation. Aminothiocarbamate **4**[11] and

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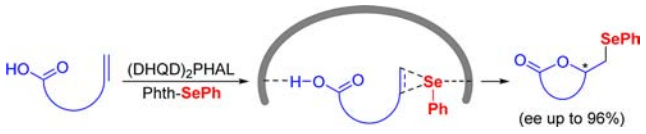
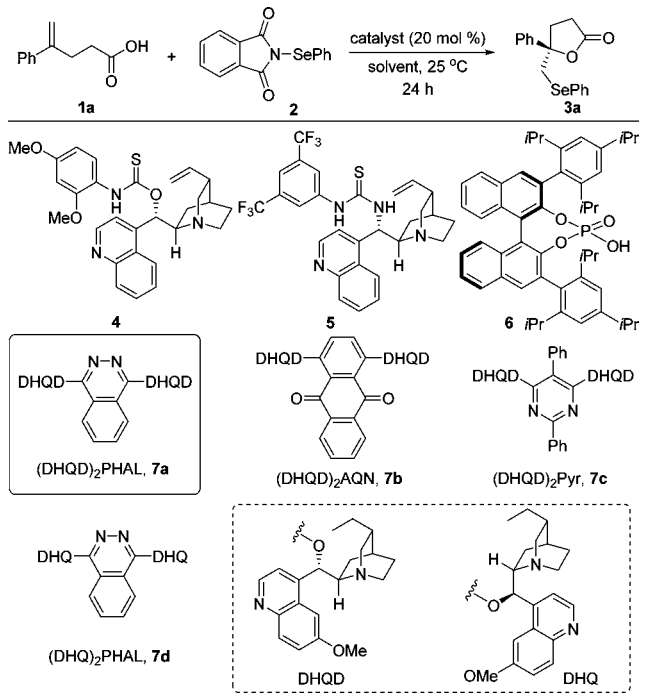
Scheme 1. Catalytic Enantioselective Selenolactonization



aminothiourea **5**,[2] which have shown excellent control in asymmetric halofunctionalization reactions, could not induce any enantioselectivity in the selenolactonization of **1a** (Table 1, entries 1 and 2). BINOL-derived phosphoric acid **6** was also examined, and the reaction was sluggish with no enantioselectivity (Table 1, entry 3). Nevertheless, to our delight, it was found that $(DHQD)_2PHAL$ **7a** could offer the desired product with an appreciable amount of ee (28%) (Table 1, entry 4). Interestingly, the ee was enhanced significantly when the solvent was changed to 1,2-dichloroethane (Table 1, entry 5).

Table 1. Reaction Optimization[a]



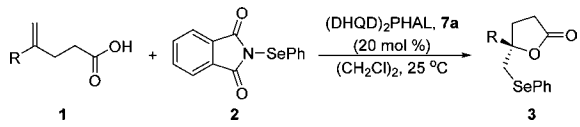
entry	cat.	solvent	concn (M)	yield (%)[b]	ee (%)
1	**4**	CH_2Cl_2	0.1	91	0
2	**5**	CH_2Cl_2	0.1	48	0
3	**6**	CH_2Cl_2	0.1	23	0
4	**7a**	CH_2Cl_2	0.1	10	28
5	**7a**	$(CH_2Cl)_2$	0.1	67	68
6	**7b**	$(CH_2Cl)_2$	0.1	33	0
7	**7c**	$(CH_2Cl)_2$	0.1	51	4
8	**7d**	$(CH_2Cl)_2$	0.1	56	−49
9[c]	**7a**	$(CH_2Cl)_2$	0.1	98	0
10[d]	**7a**	$(CH_2Cl)_2$	0.1	99	0
11	**7a**	$(CH_2Cl)_2$	0.05	73	74
12	**7a**	$(CH_2Cl)_2$	0.02	77	84
13	***7a***	***$(CH_2Cl)_2$***	***0.01***	***94***	***90***
14	**7d**	$(CH_2Cl)_2$	0.01	82	−71

[a]Reactions were carried out with olefinic acid **1a** (0.1 mmol), catalyst (0.02 mmol), and NPSP (**2**) (0.1 mmol) at 25 °C for 24 h. [b]Isolated yield. [c]PhSeCl was used as the selenylating agent. [d]PhSeBr was used as the selenylating agent.

A brief survey of other structural analogues, including $(DHQD)_2AQN$ and $(DHQD)_2Pyr$, revealed that $(DHQD)_2PHAL$ **7a** remained a better catalyst for this reaction (Table 1, entries 5−8). The antipode of **3a** could be obtained in 49% ee when the pseudoenantiomeric catalyst **7d** was employed. Other commercially available reagents, including PhSeCl and PhSeBr, were also examined, but no ee was obtained (Table 1, entries 9 and 10). The ee could be increased when the reaction was conducted at a lower concentration environment; 90% ee of **3a** could be obtained at 0.01 M (Table 1, entries 11−13).

With the optimized conditions, we then expanded the substrate scope, and the results are shown in Table 2. In general,

Table 2. Asymmetric Selenolactonization of 1[a]



entry	**3**, R	time (days)	yield % (ee %)
1	**3b**, 2-naphthyl	3	76 (86)
2	**3c**, 4-CH_3-C_6H_4	3	87 (83)
3	**3d**, 4-CH_3O-C_6H_4	1	89 (61)
4	**3e**, 4-Cl-C_6H_4	3	85 (90)
5	**3f**, 4-F-C_6H_4	5	72 (93)
6	**3g**, 4-CF_3-C_6H_4	5	65 (94)
7	**3h**, 3-CH_3-C_6H_4	3	79 (91)
8	**3i**, 3-CH_3O-C_6H_4	3	64 (91)
9	**3j**, 3-Cl-C_6H_4	5	85 (92)
10	**3k**, 3,5-$(CF_3)_2$-C_6H_3	5	45 (96)
11	**3l**, 2-CH_3-C_6H_4	3	23 (47)
12	**3m**, 3-thienyl	3	83 (81)
13	**3n**, cyclohexyl	3	89 (16)

[a]Reactions were carried out with olefinic acid **1** (0.1 mmol), catalyst **7a** (0.02 mmol), and NPSP **2** (0.1 mmol) in 1,2-dichloroethane (10 mL). The yields were isolated yields.

the reactions were all performed smoothly with good yields and ee values. Aromatic-substituted acid substrates bearing electron-withdrawing chloro, fluoro, trifluoromethyl, and 3,5-bistrifluoromethyl substituents gave excellent ee (Table 2, entries 4−6, 9, and 10). The relatively low conversion in the formation of **3k** (55% of **1k** was recovered) could be attributed to the deactivated olefinic system. On the other hand, moderate ee values were obtained for the electron-donating *p*-methoxyphenyl- and *p*-methylphenyl-substituted substrates **1c** and **1d**, presumably due to the destruction of the episeleniranium ion through resonance (Table 2, entries 2 and 3). Nevertheless, the electron-rich *m*-methoxyphenyl and *m*-methylphenyl substrates **1h** and **1i** returned high enantioselectivity (Table 2, entries 7 and 8). Additionally, heteroaromatic substrate **1m** was found to be amenable to the catalytic asymmetric protocol and gave **3m** in good yield and ee (Table 2, entry 12). The *ortho*-methyl substrate **1l** gave low yield and ee of **3l**, probably due to the combination of adverse steric and electronic effects (Table 2, entry 11). While excellent yield of **3n** was obtained with the cyclohexyl substrate **1n**, the ee was undesirable under this catalytic protocol (Table 2, entry 13).

More importantly, we were delighted to realize that the catalytic protocol could also be applied in the desymmetrization−asymmetric selenolactonization of diene carboxylic acid **1o**,

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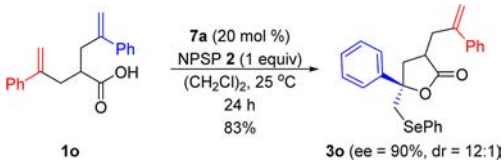
Org. Lett. 2015, 17, 1660−1663

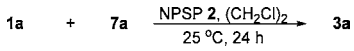
affording **3o** in 90% ee with 12:1 dr (Scheme 2). The absolute configuration of lactones **3** was assigned to be *R* based on an X-ray crystallographic study of **3a**.

Scheme 2. Catalytic Enantioselective Selenolactonization and Desymmetrization of 1o



After the substrate scope expansion, the effect of catalyst loading on the reaction was investigated. It was found that 10 mol % of $(DHQD)_2PHAL$ could also promote the selenolactonization with 86% ee (Table 3, entry 1). Unexpectedly, increasing the

Table 3. Catalyst Loading Study[a]



entry	**7a** (mol %)	yield (%)	ee (%)
1	10	91	86
2	20	94	90
3	50	79	90
4	100	60	90

[a]Reactions were carried out with olefinic acid **1a** (0.1 mmol), catalyst **7a**, and NPSP **2** (0.1 mmol) in 1,2-dichloroethane (10 mL). The yields were isolated yields.

catalyst loading to 50 mol % suppressed the reaction rate, while the enantioselectivity was maintained (Table 3, entry 2 vs 3). The reaction efficiency was further suppressed in the presence of 1 equiv of $(DHQD)_2PHAL$ (Table 3, entry 4).

These unusual phenomena prompted us to further examine the interactions among substrate **1**, NPSP **2**, and catalyst **7a** using ^1H NMR.[12] The results are summarized as follows: (1) Upon mixing 1:1 of acid substrate **1a** and $(DHQD)_2PHAL$ **7a** in CD_2Cl_2, the protons H_a-H_d in **1a** shifted upfield while the methylene protons adjacent to the N atom of quinuclidine in **7a** exhibited a slight downfield shift (~0.1 ppm), which could be the result of the formation of a hydrogen-bonding complex between **1a** and **7a**. Since H_g also exhibited a downfield shift, an interaction between the phthalazine and the proton might be present (Figure 1, **7a-H**).[13] (2) The shift pattern of H_a-H_f has no significant change for the **1a**/**2**/**7a** (1:1:1) mixture. In

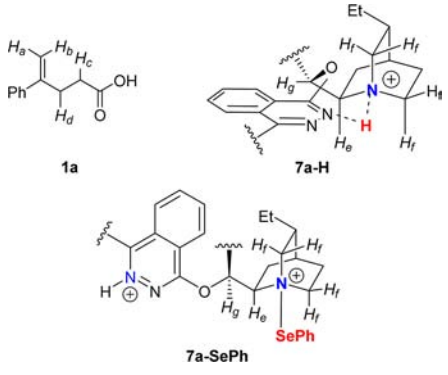
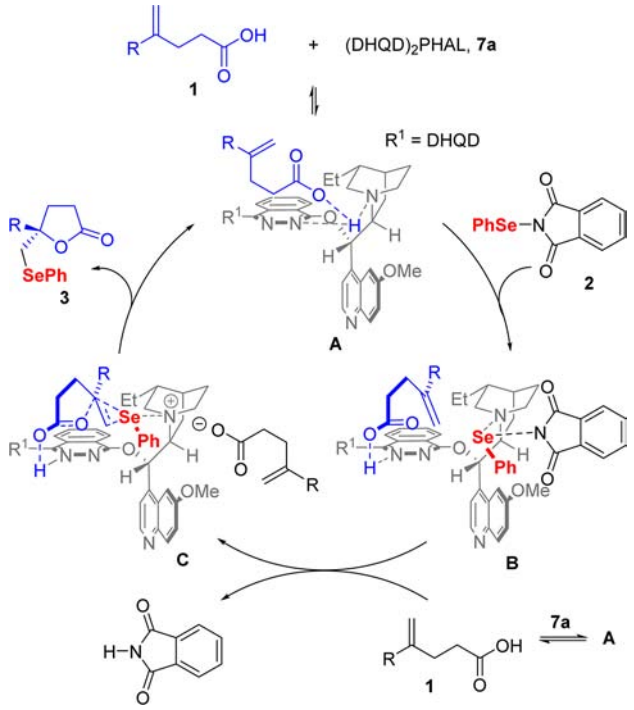


Figure 1. ^1H NMR study of the reaction mixture.

addition, the solution remained clear, and the selenolactonization was sluggish after 12 h in CD_2Cl_2, indicating that the reaction was suppressed. (3) For the ^1H NMR study of a mixture of **1a**/**2**/**7a** at a 1:1:0.2 ratio, which mimics the catalytic protocol, H_e and H_f demonstrated an appreciable downfield shift (~0.4 ppm) while the chemical shift of H_a-H_d was similar to that of the 1:1:1 mixture of **1a**/**2**/**7a**. In addition, a white precipitate of phthalimide was formed gradually, and the selenolactonization proceeded smoothly. These observations could be attributed to a change in the environment close to the quinuclidine. A possible explanation is that the quinuclidine's basic nitrogen might coordinate to the selenium reagent while the acid substrate might interact with the phthalazine's nitrogen (Figure 1, **7a-SePh**). Precipitation of phthalimide suggested that the counteranion might be the carboxylate of **1a**.

Consolidating these results, we attempted to establish a plausible mechanistic picture, as depicted in Scheme 3. We

Scheme 3. Plausible Mechanism of the $(DHQD)_2PHAL$-Catalyzed Asymmetric Selenolactonization



speculate that olefinic acid **1** might interact with **7a** to form the hydrogen-bonding complex **A**. Subsequent interaction of **A** with NPSP **2** could give the quinuclidine−NPSP complex **B**. Since no ee was observed when $(DHQD)_2AQN$ **7b** was used, the phthalazine's nitrogen might play a key role in the reaction, potentially interacting with the carboxylic acid moiety.[13] As shown in the above-mentioned results, the 1:1:1 mixture of **1a**/**2**/**7a** (a mimic of species **B**) could not undergo the selenolactonization smoothly, indicating that the selenium in **B** might not be electrophilic enough to drive the reaction. Thus, we suspect that species **B** might be further activated with another carboxylic acid **1** to give ionic species **C**, together with the elimination of a molecule of phthalimide, which might be the reason for the gradual generation of phthalimide precipitate in the 1:1:0.2 mixture of **1a**/**2**/**7a**. Species **C**, which contains a more electrophilic selenium, could then trigger the cyclization to give the desired product **3**.[6d] On the other hand, excess **7a** (under a

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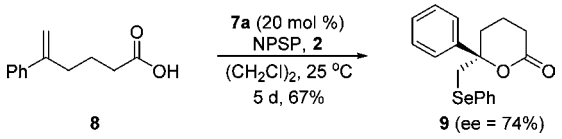
high catalyst loading condition) would trap acid **1** and slow the formation of species **C**, hence suppressing the reaction while the enantioselectivity could be maintained. It appears that a large catalyst pocket was required for this transformation to induce high enantioselectivity (Table 1); a possible explanation is that the catalyst might shield the seleniranium ion from racemization through the olefin-to-olefin degeneration.[10] Alternatively, the seleniranium ion could racemize rapidly, and intermediate **C** could be energetically more favorable through a dynamic kinetic resolution pathway.[8] A more detailed study is underway to further elucidate the whole reaction mechanism.

To further extend the scope, we examined the selenolactonization of **8**. Preliminary unoptimized results indicate that this catalytic protocol is potentially applicable to other skeletons in which **9** could be obtained in 74% ee (Scheme 4).

Scheme 4. Preliminary Study on the Selenolactonization of 8



8 **9** (ee = 74%)

In summary, we have developed a catalytic and highly enantioselective selenolactonization reaction. Further optimization of this catalytic protocol to other substrates with different skeletons is in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all new compounds, and CIF file of the X-ray structure. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chmyyy@nus.edu.sg.

Notes

The authors declare no competing financial interest.

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(12) Details appear in Supporting Information.

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