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ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · AUGUST 2005

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Direct, Facile Aldehyde and Ketone α-Selenenylation Reactions Promoted by L-Prolinamide and Pyrrolidine Sulfonamide Organocatalysts

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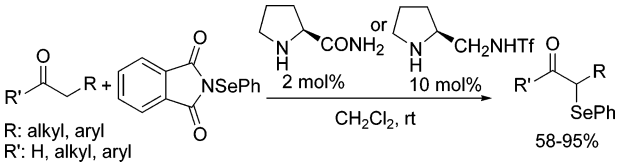
Received April 7, 2005



A new catalytic method for direct α-selenenylation reactions of aldehydes and ketones has been developed. The results of exploratory studies have demonstrated that L-prolinamide is an effective catalyst for α-selenenylation reactions of aldehydes, whereas pyrrolidine trifluoromethanesulfonamide efficiently promotes reactions of ketones. Under optimized reaction conditions, using *N*-(phenylseleno)phthalimide as the selenenylation reagent in CH_2Cl_2 in the presence of L-prolinamide (2 mol %) or pyrrolidine trifluoromethanesulfonamide (10 mol %), a variety of aldehydes and ketones undergo this process to generate α-selenenylation products in high yields. Mechanistic insight into the L-proline and L-prolinamide catalyzed α-selenenylation reactions of aldehydes with *N*-(phenylseleno)phthalimide has come from theoretical studies employing ab initio methods and density functional theory. The results reveal that (1) the rate-limiting step of the process involves attack of the enamine intermediate at selenium in *N*-(phenylseleno)phthalimide and (2) the energy of the transition state for the reaction catalyzed by prolinamide is lower than that promoted by proline. This result is consistent with experimental observations. The role of hydrogen bond interactions in stabilizing the transition states for this process is also discussed.

Introduction

Synthesis of α-phenylseleno derivatives of carbonyl compounds is of considerable importance since these substances serve as versatile intermediates in organic synthesis.[1] For example, oxidation of the α-phenylseleno derivatives by H_2O_2 or $NaIO_4$ followed by spontaneous *syn* elimination produces synthetically useful α,β-unsaturated carbonyl compounds.[2] Several methods have been developed for the preparation of α-phenylseleno aldehydes and ketones. The most widely used procedure involves reaction of the aldehyde or ketone enolate with an electrophilic selenium reagent.[2] Direct methods for α-selenenylation of aldehydes and ketones have been developed, but these reactions often proceed in low yields and lack generality.[3] Indirect approaches employing reactions of silyl enol ether with PhSeBr[4] and nucleophilic displacement of α-bromo aldehydes and ketones with PhSeLi/Na[2b] also have been described. An acid

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(1) (a) Back, T. G. *Organoselenium Chemistry*: *A Practical Approach*; Oxford University Press: New York, 1999. (b) Paulmier, C. *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, UK, 1986. (c) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

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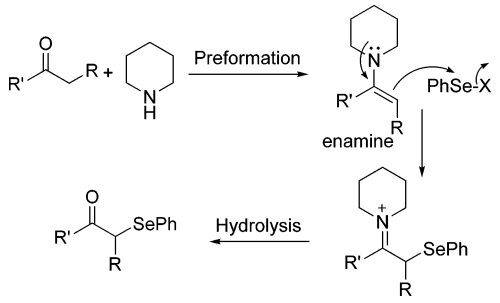
(4) Ryu, I.; Murai, S.; Niwa, I.; Sonoda, N. *Synthesis* **1977**, 874.

10.1021/jo0506940 CCC: $30.25
Published on Web 06/03/2005

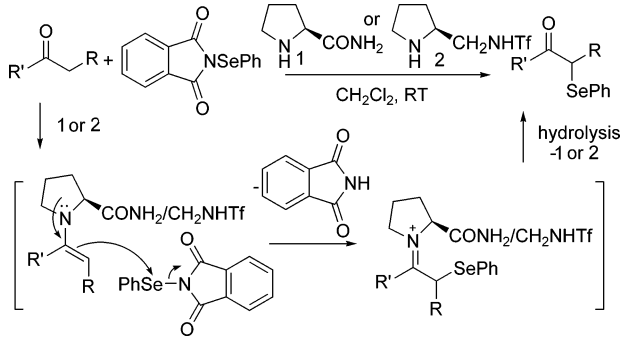
SCHEME 1. α-Selenenylation of Carbonyl Compounds by Preformation of Pyrrolidine-Based Enamines



(TsOH)[5] or base (piperidine, Scheme 1)[6] promoted process has been used to prepare α-phenylselenocarbonyl compounds, but in both cases stoichiometric amounts of acid or base are employed. Furthermore, in the latter case preformation of an enamine from piperidine and the aldehyde or ketone is required (Scheme 1).

In recent years, the use of secondary amines, such as proline and its derivatives, as organocatalysts for reactions of carbonyl compounds has become increasingly popular as a result of the operational simplicity of these processes and the fact that toxic transition metal catalysts and byproducts are not involved.[7−14] The organocatalytic processes share a common mechanistic pathway

SCHEME 2. l-Prolinamide 1/Pyrrolidine Sulfonamide 2 Catalyzed α-Selenenylation Reactions of Aldehydes and Ketones



in which electron-rich enamine intermediates are formed initially *in situ*. These intermediates then react with electrophiles to generate products. The working hypothesis for the development of the catalytic α-selenenylation reaction derives from the results of a previous study, which has shown that preformed piperidine enamines of enolizable aldehydes or ketones react with electrophilic selenium agents to generate corresponding α-selenenylation products (Scheme 2).[6] Accordingly, we anticipated that reaction of an *in situ* formed aldehyde or ketone enamine with an electrophilic selenium reagent would serve as the basis for a catalytic method for the preparation of α-seleno carbonyl compounds (Scheme 2). An investigation of this methodology has given rise to a new, direct route for the preparation of α-phenylseleno aldehydes and ketones that relies on the use of the proline derivatives, L-prolinamide (**1**; Scheme 2)[15] and organocatalyst pyrrolidine trifluoromethanesulfonamide (**2**)[16] as organocatalysts.

Results and Discussion

L-Prolinamide-Catalyzed α-Selenenylation Reactions of Aldehydes:[15] Catalyst Screening. As discussed above, a critical issue, which needed to be addressed in developing a catalytic method for the α-selenenylation reactions, is the identification of proper organocatalysts. Consequently, our initial studies focused on screening different amines which could be used for this purpose. First on the list was L-proline since it has been widely used for catalyzing a variety of organic transformations which take place via enamine intermediates.[9−12] We observed that reaction of isovaleraldehyde with *N*-(phenylseleno)phthalimide as the electrophilic selenium reagent occurred in the presence of 30 mol % of L-proline in CH_2Cl_2 at room temperature to afford the

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(14) Other organocatalysts have also been developed for catalysis via enamine chemistry; for selected examples, see: (a) Chiral diamine: Mase, N.; Tanaka, F.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2004**, *43*, 2420. (b) MacMillan's imidazolidinone catalyzed aldol and α-chlorination reactions: Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6722. Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (c) Chiral amine alcohol: Tang, Z.; Jiang, F.; Yu, L.-T.; Cui, X.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262. (d) Pyrrolidine tetrazole: Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 1983. (e) Pyrrolidine imide: Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84.
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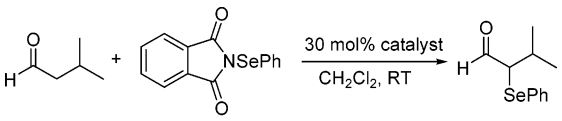
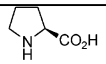
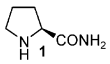
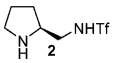
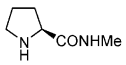
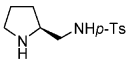
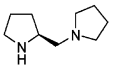
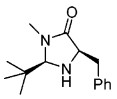
TABLE 1. Catalyst Screening for the α-Selenenylation Reaction of Isovaleraldehyde[a]



entry	catalyst	t	% yield[b]
1		30 min	82
2		<5 min	96
3		4 h	87
4		1.5 h	77
5		30 min	48
6[c]		50 min	78
7[d]		12 h	48
8		3 h	21
9		3 h	56

[a] Unless otherwise specified, the α-selenenylation reaction was performed at room temperature with isovaleraldehyde (0.25 mmol), *N*-(phenylseleno)phthalimide (0.30 mmol), and catalyst (0.075 mmol) in 0.5 mL of anhydrous CH_2Cl_2. [b] Isolated yields. [c] 5% ee observed. [d] 40% ee observed.

desired selenenylation product in 82% yield (Table 1, entry 1). Encouraged by this result, we explored reactions promoted by eight additional amine catalysts under the same conditions (Table 1, entries 2−9). The results showed that L-prolinamide (**1**) was the best catalyst out of the nine tested. The L-prolinamide (**1**) promoted reaction took place within less than 5 min in nearly quantitative yield (96%) (Table 1, entry 2). Interestingly, blocking one NH in L-prolinamide by a methyl group resulted in a considerable reduction of catalytic activity (Table 1, entry 4).

L-Proline and L-prolinamide exhibit no enantioselectivity in the α-selenenylation reaction of isovaleraldehyde.[17] However, the processes catalyzed by (*S*)-pyrrolidine trifluoromethanesulfonamide (**2**) and the analogous tosyl sulfonamide and the MacMillan's chiral imidazolidinone (Table 1, entries 3, 5, and 7) took place with 30%, 60%, and 40% ee, respectively.[18] The results indicate that the size of amide or sulfonamide moieties in the sulfonamide catalysts could be critical in affecting the enantioselectivity of the process.[19]

We also observed that pyrrolidine and piperidine, which have been used in the procedure that requires preformation of an enamine,[6] were not good catalysts for this process when 30 mol % loading was employed (Table 1, entries 8 and 9). The results suggest that the amide group in L-prolinamide or the carboxylic acid group in L-proline is essential for catalyst activity.[9c,20] The amide or carboxylic group is thought to play two roles in this process. First, they can efficiently activate amine addition to the carbonyl compound in the pathway for enamine formation. Second, hydrogen bonding between the amide or carboxylic acid groups and *N*-(phenylseleno)phthalimide can stabilize the transition state for the selenenylation step (see below).

Optimization of Reaction Conditions. On the basis of the observation described above, we chose L-prolinamide (**1**) as the catalyst used in further studies of the α-selenenylation reaction aimed at optimizing reaction conditions by varying the nature of the selenium reagents, the reaction medium, and catalyst loading.

An exploration of four commonly used selenium reagents (*N*-(phenylseleno)phthalimide, phenylselenyl chloride, phenylselenyl bromide, and diphenyl diselenide) showed that *N*-(phenylseleno)phthalimide was superior in promoting selenenylation reactions with 30 mol % of L-prolinamide (**1**) in CH_2Cl_2 (Table 2, entries 1−4). Under the identical reaction conditions, much longer times were required for reactions with phenylselenyl chloride, phenylselenyl bromide, and diphenyl diselenide and lower yields were obtained (15 h, 75%; 1 d, 24%; and 1 d, <10% yield, respectively, Table 2). The low rates of these processes resulted in recovery starting materials when bromide and diphenyl diselenide were employed. We believe that the reason *N*-(phenylseleno)phthalimide serves as the most effective selenenylation agent is that effective C═O- - -H_2N hydrogen bonding interactions take place between the carbonyl oxygen atom in *N*-(phenylseleno)phthalimide with the amide NH_2 in L-prolinamide (**1**; Scheme 3). This interaction stabilizes the transition state for enamine attack on the Se atom in the rate

(16) The (*S*) pyrrolidine trifluoromethanesulfonamide **2** has been demonstrated for the following reactions: (a) Michael addition: Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (b) α-Aminoxylation: Wang, W.; Wang, J.; Li, H.; Liao, L.-X. *Tetrahedron Lett.* **2004**, *45*, 7235. (c) Mannich reaction: Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, *45*, 7243. (d) α-Sulfenylation: Wang, W.; Li, H.; Wang, J.; Liao, L.-X. *Tetrahedron Lett.* **2004**, *45*, 8229. (e) Dehydration: Wang, W.; Mei, J.; Li, H.; Wang, J. *Org. Lett.* **2005**, *7*, 601.

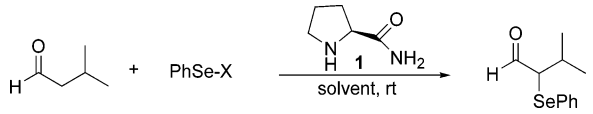
(17) Recently, Jørgensen and co-workers reported an organocatalytic asymmetric α-sulfenylation, see: Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. They tested L-proline and L-prolinamide catalyzed α-sulfenylation of isovaleraldehyde with very poor enantioselectivity (0 and 25% ee in toluene, respectively).

(18) As cited in ref 16d, we have reported using (*S*) pyrrolidine trifluoromethanesulfonamide **2** as catalyst for α-sulfenylation reactions of aldehydes and ketones, unfortunately no enantioselectivities were observed for the processes.

(19) As reported in ref 17, Jørgensen and co-workers found that the bulk silylated L-prolinol derivatives as catalysts afforded α-sulfenylation products with high ee.

(20) Extensive mechanistic studies of L-proline catalyzed aldol reactions have been reported, see: (a) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558. (b) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 11273. (c) Rankin, K. N.; Gauld, J. W.; Boyd, R. J. *J. Phys. Chem.* **2002**, *A106*, 5515. (d) Arnó, M.; Domingo, L. R. *Thero. Chem. Acc.* **2002**, *108*, 232. (e) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16. (f) Bahmanyar, S.; Houk, K. N.; Martin, H. J.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 2475. (g) Tang, Z.; Jiang, F.; Yu, L.-T.; Gong, L.-Z.; Mi, A.-Q.; Jian, Y.-Z.; Wu, Y.-D. *J. Am. Chem. Soc.* **2003**, *125*, 5262.

TABLE 2. Optimization of α-Selenenylation Reactions of Isovaleraldehyde Catalyzed by L-Prolinamide[a]



entry	PhSeX	solvent	catalyst loading (% mol)	*t*	yield[b] (%)
1	*N*-(phenylseleno)phthalimide	CH_2Cl_2	30	<5 min	96
2	PhSeCl	CH_2Cl_2	30	15 h	75
3	PhSeBr	CH_2Cl_2	30	1 d	24
4	PhSeSePh	CH_2Cl_2	30	1 d	<10
5	*N*-(phenylseleno)phthalimide	EtOAc	30	10 min	88
6	*N*-(phenylseleno)phthalimide	toluene	30	2 h	38
7	*N*-(phenylseleno)phthalimide	1,4-dioxane	30	15 min	93
8	*N*-(phenylseleno)phthalimide	CH_3CN	30	30 min	74
9	*N*-(phenylseleno)phthalimide	DMSO	30	1 h	83
10	*N*-(phenylseleno)phthalimide	CH_3NO_2	30	2 h	66
11	*N*-(phenylseleno)phthalimide	DMF	30	2 h	46
12	*N*-(phenylseleno)phthalimide	CH_2Cl_2	20	<5 min	94
13	*N*-(phenylseleno)phthalimide	CH_2Cl_2	10	<5 min	94
14	*N*-(phenylseleno)phthalimide	CH_2Cl_2	5	10 min	86
15	*N*-(phenylseleno)phthalimide	CH_2Cl_2	2	10 min	88
16	*N*-(phenylseleno)phthalimide	CH_2Cl_2	1	1 h	62
17	*N*-(phenylseleno)phthalimide	CH_2Cl_2	0.5	2 d	31

[a] Unless otherwise specified, for reaction conditions: see footnote *a* in Table 1. [b] Isolated yield.

determining step of the process. Indeed, the theoretical studies have shown that the hydrogen bonding interactions play a key role in involving the formation of transition states (see below). In contrast, the other selenenylation reagents provide only weak or no hydrogen bonding interactions. Furthermore, it is observed that the α-selenenylation rates are parallel to the degree of polarization of the Se−X bond in the selenium reagents: the higher the polarization (a decreasing order of polarization: Se−N, Se−Cl, Se−Br, and Se−Se), the faster the reaction.

Solvents play an important role in governing the rates of organic reactions. Therefore, we evaluated the effects of the medium on the L-prolinamide-catalyzed α-selenenylation process. We observed that solvents significantly controlled the efficiencies of these reactions (Table 2, entries 1, and 5−11). Reactions in less polar solvents, such as CH_2Cl_2, EtOAc, and 1,4-dioxane (Table 2, entries 1, 5, and 7), generally proceeded with higher yields, whereas in polar solvents (CH_3CN, DMSO, CH_3NO_2, and DMF; entries 8−11) low yields were obtained. The results show that the best yields and lowest reaction times are seen when CH_2Cl_2 was used as solvent.

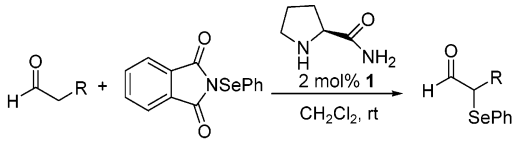
Having identified the best selenium reagent and reaction medium, we next probed the effect of catalyst loading on the reaction (Table 2, entries 12−17). Catalyst loadings, ranging from 30 to 0.5 mol %, were evaluated. The results showed that a catalyst loading as low as 1 mol % still brought about a significant reaction (Table 2, entry 16). From an operational perspective, the use of 2 mol % of L-prolinamide (**1**) was found to provide high reaction efficiency (88% yield) and maintained a reasonable reaction time (10 min, Table 2, entry 15).

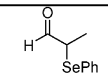
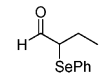
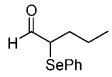
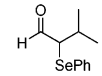
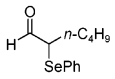
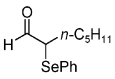
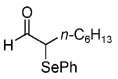
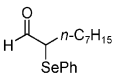
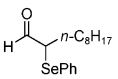
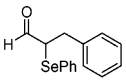
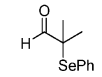
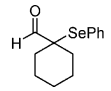
Scope of the α-Selenenylation Reactions of Aldehydes. Having uncovered the optimal reaction conditions for the α-selenenylation process, we evaluated the scope of the reactions with a variety of aldehydes. The results, summarized in Table 3, show that a variety of different aldehydes undergo this selenenylation reaction with *N*-(phenylseleno)phthalimide in the presence of L-prolinamide (**1**). Regardless of the length of the side chain (C_1−C_8) (entries 1−9, Table 3), the reactions were completed within 10 min in high yields (78−95%). Reactions of highly sterically hindered α,α-disubstituted aldehydes occurred in very poor yields (entries 11 and 12). However, addition of 4 Å molecular sieves resulted in significant enhancements of the reaction rates. Under these conditions, α,α-dialkyl α-selenenylation products were formed within 1 h in high yields (76−81%). The enhanced reaction rates caused by 4 Å molecular sieves could be due to facilitated formation of the enamine intermediate.[21]

Pyrrolidine Trifluoromethanesulfonamide-Catalyzed α-Selenenylation Reactions of Ketones: Optimization of Reaction Conditions. Encouraged by the results of the studies carried out with aldehydes, we attempted to extend the methodology to ketone systems. In an exploratory investigation using cyclohexanone as a model, we found that only a moderate yield (61%) of the selenenylation product was obtained when L-prolinamide (**1**) (30 mol %) was used as the catalyst and a much longer reaction time (12 h) was required (Table 4, entry 1). Interestingly, in addition to forming the *mono* α-selenenylation adduct (**a**), bis α,α- (**b**) and α,α′- (**c**) selenenylation products were also produced (17:3:1 **a**:**b**:**c** ratio). Several different reaction conditions were tested in an attempt to minimize formation of bis-addition products. Slow addition of *N*-(phenylseleno)phthalimide to the reaction mixture over a 2 h period did not substantially affect the product ratio (15:1.4:1 of **a**:**b**:**c**) (Table 4, entry 2). Earlier studies have shown that the formation of bis-addition products can be suppressed by using polar reaction media.[14c,d] Indeed, when DMSO was employed as solvent and slow addition of the selenium

(21) Molecular sieves could retard the hydrolysis of iminium to release catalyst. However, this step is not the rate-determining step in the reaction.

TABLE 3. L-Prolinamide Catalyzed α-Selenenylation Reactions of Aldehydes[a]



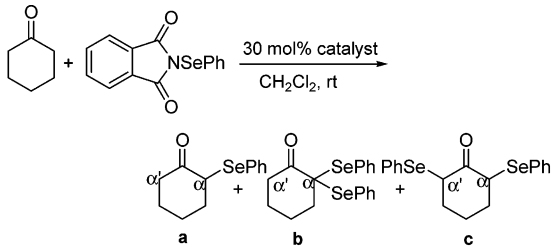
entry	product	t	% yield[b]
1		10 min	81
2		10 min	83
3		10 min	85
4		10 min	88
5		10 min	78
6		10 min	86
7		10 min	95
8		10 min	91
9		10 min	84
10		10 min	80
11[c]		1 h	76
12[c]		1 h	81

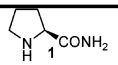
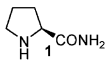
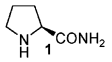
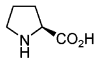
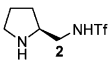
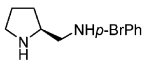
[a] Unless otherwise specified, all α-selenenylation reactions of aldehydes were performed at room temperature with an aldehyde (0.25 mmol), *N*-(phenylseleno)phthalimide (0.30 mmol), and **1** (0.005 mmol) in 0.5 mL of anhydrous CH_2Cl_2. [b] Isolated yield. [c] 4 Å molecular sieves added. In the absence of molecular sieves, the conversion was very slow and the TLC analysis showed only a small amount of product (ca. <10% yield) was formed after 3 h.

reagent was used, the **a**:**b**:**c** ratio was improved to 26:1.2:1 (Table 4, entry 3).

Our focus shifted to other organocatalysts for the selenenylation reaction of cyclohexanone (Table 4). Of the five catalysts screened (Table 4, entries 4−8), L-proline displayed a similar catalytic activity as L-prolinamide (**1**) in CH_2Cl_2, but the bis-adducts were also formed in an **a**:**b**:**c** ratio of 18:2.4:1 (Table 4, entry 4). Interestingly, the pyrrolidine trifluoromethanesulfonamide (**2**)[16] exhibited the most promising catalytic activity (Table 4, entry

TABLE 4. Catalyst Screening for α-Selenenylation Reaction of Cyclohexanone[a]



entry	catalyst	t (h)	% yield[b]	ratio of **a**:**b**:**c**[c]
1[d]		12	63	17:3:1
2[e]		12	69	15:1.4:1
3[f]		12	71	26:1.2:1
4		12	61	18:2.4:1
5		3.5	88	-[g,h]
6		24	<10	n.d.[i]
7		12	50	n.d.[i]
8		12	41	n.d.[i]

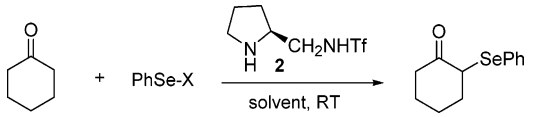
[a] Unless otherwise specified, for reaction conditions: see footnote *a* in Table 1. [b] Isolated yields. [c] Molar ratio determined by ^{1}H NMR. [d] *N*-(Phenylseleno)phthalimide was added once into a mixture of cyclohexanone and 30 mol %of L-prolinamide in CH_2Cl_2. [e] *N*-(Phenylseleno)phthalimide in CH_2Cl_2 was added dropwise over 30 min into a mixture of cyclohexanone and 30 mol % of L-prolinamide in CH_2Cl_2. [f] *N*-(Phenylseleno)phthalimide in DMSO was added dropwise over 30 min into a mixture of cyclohexanone and 30 mol % of L-prolinamide in DMSO. [g] −: Products **b** and **c** not observed by ^{1}H NMR. [h] 18% ee observed. [i] Not determined.

5). In this case, a much shorter time (3.5 h) was required to reach complete reaction and a significantly higher yield of 88% was obtained. More importantly, the *mono*-adduct was formed exclusively in this process even when slow addition of the selenium reagent was not used. Not surprisingly, low enantioselectivity (18% ee) was observed for this reaction. More sterically demanding pyrrolidine *p*-bromophenylsulfonamide (Table 4, entry 6) showed a poor catalytic activity. Again, pyrrolidine and piperidine are not effective catalysts for the α-selenenylation reaction of ketones (Table 4, entries 7 and 8).

A possible reason for why the reaction catalyzed by pyrrolidine trifluoromethanesulfonamide (**2**) affords only a *mono*-addition product is that the steric hindrance imposed by the bigger trifluoromethanesulfonamide group in **2** (vs OH in L-proline and NH_2 in L-prolinamide) could make enamine formation from the *mono*-selenenylated product more difficult.

The results of the preliminary studies prompted us to carry out a more thorough investigation of pyrrolidine

TABLE 5. Optimization of Reaction Conditions for α-Selenenylation Reactions of Cyclohexanone[a]



entry	selenium reagent	solvent	catalyst loading (% mol)	*t* (h)	yield[b] (%)
1	*N*-(phenylseleno)phthalimide	CH_2Cl_2	30	3.5	88
2	PhSeCl	CH_2Cl_2	30	24	57
3	PhSeBr	CH_2Cl_2	30	24	<10
4	*N*-(phenylseleno)phthalimide	THF	30	10	73
5	*N*-(phenylseleno)phthalimide	1,4-dioxane	30	6	82
6	*N*-(phenylseleno)phthalimide	DMSO	30	6	47
7	*N*-(phenylseleno)phthalimide	DMF	30	12	41
8	*N*-(phenylseleno)phthalimide	CH_2Cl_2	20	8	86
9	*N*-(phenylseleno)phthalimide	CH_2Cl_2	10	16	80
10	*N*-(phenylseleno)phthalimide	CH_2Cl_2	5	48	62

[a] Unless otherwise specified, for reaction conditions: see footnote *a* in Table 1. [b] Isolated yield.

trifluoromethanesulfonamide (**2**) catalyzed ketone α-selenenylation reactions. A similar strategy was used to uncover optimal reaction conditions for the process. First, we evaluated other selenium reagents, phenylselenyl chloride and bromide, to determine selenenylation efficiencies. Again it was found that the rates of reactions with phenylselenyl chloride and bromide were much smaller than that when *N*-(phenylseleno)phthalimide was employed and 57% and <10% product yields, respectively, were observed (Table 5, entries 2 and 3). As a result, *N*-(phenylseleno)phthalimide is the choice, used as the selenium reagent for subsequent studies.

As the data in Table 5 demonstrate, in a manner similar to α-selenenylation reactions of aldehydes, the reaction medium has a significant impact on ketone α-selenenylation processes. Reactions in less polar solvents, such as CH_2Cl_2, THF, and 1,4-dioxane (Table 5, entries 1, 4, and 5) generally took place with higher yields, whereas low yields were obtained when more polar solvents (DMSO and DMF) were employed (entries 6 and 7). Finally, an evaluation of the effect of catalyst loading on the reaction (Table 5, entries 8−10) showed that the use of 10 mol % of pyrrolidine sulfonamide **2** was sufficient to maintain a high reaction rate without sacrificing the reaction yield (80% yield, Table 5, entry 9).

Scope of the α-Selenenylation Reactions of Ketones. Under the optimized reaction conditions, a series of ketones smoothly undergo the pyrrolidine trifluoromethanesulfonamide (**2**) catalyzed α-selenenylation reactions (Table 6). Generally, *mono*-addition products were formed in moderate to high yields. A wide range of acyclic (entries 1−6) and cyclic ketones (entries 7−14) participate in this process. The mild reaction conditions tolerate a variety of other functional groups (Table 6, entries 5, 12, and 13). We also observed that **2** catalyzed reactions of various ring-sized cyclic ketones (Table 6, entries 7−14). Importantly, we found that α-selenenylation reactions of unsymmetric ketones proceeded preferentially at the less substituted α-sites presumably because of sterically guided preferences in enamine forming steps of the process (Table 6, entries 4 and 5). This trend parallels those seen in LDA promoted α-selenenylations, which are governed by kinetically controlled α-deprotonation[2a] and contrast with acid promoted α-selenenylations, which are controlled by thermodynamically controlled enolization.[5]

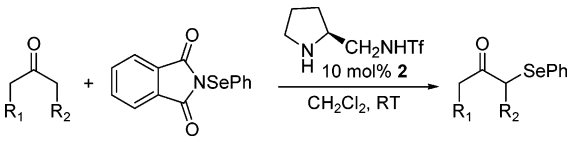
Theoretical Analysis of L-Proline and L-Polinamide Catalyzed α-Selenenylation Reactions of Aldehydes. The significant difference observed in the activities of L-proline and L-prolinamide in catalyzing α-selenenylation reactions of aldehydes promoted us to explore these processes by using ab initio and density functional theoretical (DFT) methods. A reaction mechanism similar to that proposed for the L-proline promoted aldol reaction (Scheme 3) was presumed to be operating in the selenenylation reactions.[20] The initial step of the sequence involves formation of an enamine intermediate which then undergoes rate-limiting attack at the electrophilic selenium (Se) atom of *N*-(phenylseleno)phthalimide. Formation of the Se−C bond takes place in concert with departure of phthalimide anion to produce the α-selenoiminium ion intermediate **A**. Hydroxide ion, formed by water protonation of the phthalimide nitrogen, then adds to the iminium carbon to produce a carbinolamine **B**, the precursor of the α-selenoaldehyde product.

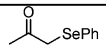
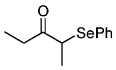
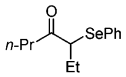
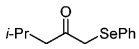
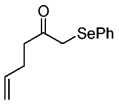
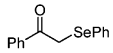
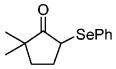
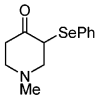
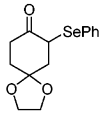
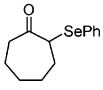
On the basis of this mechanistic scenario, the computational studies were designed to gain an insight into the factors that govern the energies of stationary points along the reaction coordinates involved in rate determining reactions of L-prolinamide and L-proline enamine with *N*-(phenylseleno)phthalimide. Energies of stationary points obtained by using different levels of theory and some important atom−atom distances and angles and energies of reaction intermediates and TSs are listed in the Table 7.

The reactant complex (**RC**), containing the enamine, *N*-(phenylseleno)phthalimide, and a water molecule (Figure 1), is held together largely by hydrogen bonds. For the complex with prolinamide catalyst **1** (**RC**), two presumably cooperative hydrogen bonds ($r_{O\cdots HN}$ = 2.74 and 2.83 Å) exist between the amide NH and a carbonyl oxygen of *N*-(phenylseleno)phthalimide. For the proline catalyst derived complex (**RC′**), a hydrogen bond exists ($r_{O\cdots HO}$ = 1.89 Å) between the carboxylate OH and a carbonyl oxygen of the phthalimide.

As the data in Table 7 suggest, the barrier for the rate-limiting prolinamide−enamine attack on the electrophilic

TABLE 6. Pyrrolidine Trifluoromethanesulfonamide 2 Catalyzed α-Selenenylation Reactions of Ketones[a]



entry	product	t (h)	% yield[b]
1		24	69
2		24	61
3		48	58
4		17	62
5[c]		24	63
6		24	81
7		24	78
8		24	67
9		16	80
10		24	79
11		24	76
12		26	85
13		24	72
14		48	59

[a] Unless otherwise specified, all α-selenenylation reactions of ketones were performed at room temperature with a ketone (0.25 mmol), *N*-(phenylseleno)phthalimide (0.30 mmol), and **2** (0.025 mmol) in 0.5 mL of anhydrous CH_2Cl_2. [b] Isolated yield. [c] Two regioisomers at less substituted (structure shown) and more substituted site with a 10:1 ratio (observed by ^1H NMR).

Se atom (**TS1**) is 26.00 kcal/mol at the HF level. As expected, the inclusion of electron correlation significantly lowers this barrier. The MP2 barrier height of 6.74 kcal/mol is close to that obtained from a B3LYP calculation (8.82 kcal/mol). The corresponding barrier heights for reaction of the proline−enamine are consistently higher (27.63, 9.44, and 9.80 kcal at the HF, MP2, and B3LYP levels of theory, respectively).

TS1 is characterized by an elongated Se−N bond and a shorter distance between Se and the C=C bond. This concerted, electrophilic substitution reaction is accompanied by an increase in the hydrogen bond strength between the phthalimide carbonyl oxygen and both the OH and NH_2 groups in the respective proline− and prolinamide−enamines. For the proline−enamine derived **TS1′**, $r_{O\cdots HO}$ is reduced to 1.75 Å, whereas for the prolinamide−enamine **TS1**, the $r_{O\cdots HN}$ distances are 2.45 and 2.67 Å. The strengthening of the hydrogen bonds, as evidenced by reduced hydrogen bond lengths, can be attributed to the increase of the negative charge on carbonyl oxygen as selenium departs from the phthalimide nitrogen. It is clear that these hydrogen bonds are essential for the catalytic activity in the selenenylation reaction. The role of hydrogen bond interactions in stabilizing proline-catalyzed aldol reactions has been extensively discussed in the literature.[20] It is also obvious by comparing barrier heights that the two hydrogen bonds in the **TS1** of the prolinamide−enamine reaction have a larger stabilizing effect on the transition state than the lone hydrogen bond in the proline−enamine process.

The inclusion of solvent (CH_2Cl_2) does not qualitatively change the theoretically derived conclusion that the rate-limiting **TS1** is lower for reaction of the prolinamide−enamine (23.27 kcal/mol at the HF/6-31G(d) level) than that for the proline analogue (24.20 kcal/mol). The ca. 3 kcal/mol lower **TS1** energy relative to **RC** can be attributed to the charge separation that develops between Se and the phthalimide nitrogen. Importantly, the results from the theoretical calculations are consistent with the experimental observations,

The calculations indicate that reaction of the prolinamide−enamine with *N*-(phenylseleno)phthalimide to produce the intermediate (**INT**) has energies of 3.25, −5.27, and −6.33 kcal/mol relative to **RC** at the HF, MP2, and B3LYP levels, respectively. Similar results, 12.90, 4.48, and 6.25 kcal/mol, were found for proline−enamine reaction. Interestingly, only one, shorter ($r_{O\cdots HN}$ = 1.85 Å) hydrogen bond is preserved between the phthalimide anion and the NH_2 group of the prolinamide catalyst. In contrast, the hydrogen bond between the phthalimide anion and the proline OH is also shorter ($r_{O\cdots HO}$ = 1.61 Å). These phenomena are almost certainly due to negative charges developed in the carbonyl oxygen atoms in the phthalimide anion. In both cases, water is hydrogen bonded with the nitrogen in the phthalimide anion with the oxygen pointing toward the α-carbon of the iminium ion **A**. Like **TS1**, there is a significant solvent effect on complex **INT** because of its zwitterionic nature.

Deprotonation of water by the phthalimide anion seems to take place in concert with nucleophilic addition of hydroxide to the iminium carbon. The transition state for this general base-catalyzed process is labeled **TS2**. In this process, the hydrogen bonds between the phthalimide anion and proline OH or prolinamide NH_2 groups are weaken, as evidenced by larger OH···O and NH_2···O distances in **TS2** and **TS2′**, respectively. **TS2** is much

SCHEME 3. Proposed Enamine Mechanism of the Prolinamide-Catalyzed α-Selenenylation Reaction of *N*-(Phenylseleno)phthalimide with Propionaldehyde

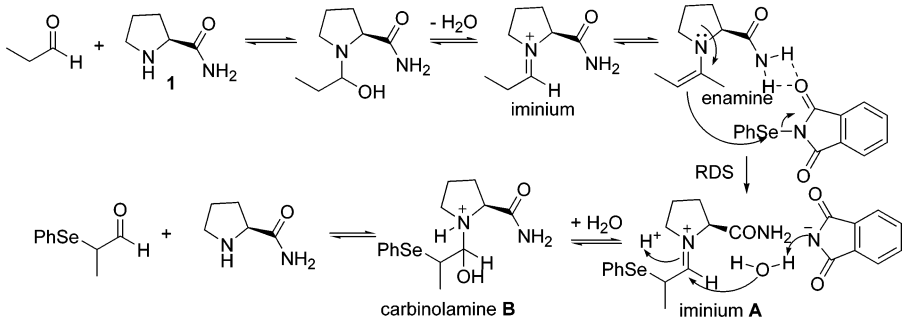


TABLE 7. Ab Initio and DFT Results for the Selenenylation Reaction between Enamine and *N*-(Phenylseleno)phthalimide with Two Different Organocatalysts: L-Prolinamide (NH_2) and L-Proline (OH)

	reactant complex		transition state 1		intermediate	
	NH_2	OH	NH_2	OH	NH_2	OH
energy (kcal/mol)						
HF/6-31G* Opt	0	0	26.00	27.63	3.25	12.90
B3LYP/6-31G* SP	0	0	8.82	9.80	−5.27	4.48
MP2 SP	0	0	6.74	9.44	−6.33	6.25
HF/6-31G* PCM/SP	0	0	23.27	24.20	0.74	7.63
distances (Å)						
NH_2···O=C	2.74/2.83		2.45/2.67		1.85/3.24	
OH···O=C	-	1.89		1.75		1.61
Se···C=C	4.12	5.08	2.24	2.30	2.02	2.02
Se···N	1.87	1.88	2.42	2.40	6.09	5.76
C=C=N	1.33/1.39	1.33/1.38	1.42/1.30	1.41/1.31	1.49/1.27	1.49/1.27
OH_2···N	4.30/4.09	3.75/4.12	2.21/3.37	2.31/3.23	1.94/3.09	1.89/2.99
H_2O···C=C	4.80	3.55	4.83	4.83	4.52	3.64
H−O−H	0.95/0.95	0.95/0.95	0.95/0.95	0.95/0.95	0.96/0.95	0.97/0.95
dihedral angles (deg)						
N−C−C−Se	−88.41	−127.14	−80.34	−84.21	−124.17	−123.15
C−C−Se−N	3.86	−54.81	−101.24	−99.83	−74.70	−72.43

	transition state 2		product complex	
	NH_2	OH	NH_2	OH
energy (kcal/mol)				
HF/6-31G* Opt	10.45	19.30	−26.45	−18.36
B3LYP/6-31G* SP	−2.37	6.30	−26.70	−18.04
MP2 SP	−2.18	8.34	−27.56	−17.02
HF/6-31G* PCM/SP	9.32	16.29	−25.52	−20.32
distances (Å)				
NH_2···O=C	2.29/3.59	-	2.19/3.61	-
OH···O=C	-	1.73	-	1.95
Se···C=C	2.01	2.01	2.02	2.02
Se···N	5.26	5.46	6.22	6.23
C=C=N	1.51/1.32	1.52/1.34	1.53/1.44	1.53/1.44
OH_2···N	1.63/3.08	1.69/3.19	1.00/3.70	1.01/3.70
H_2O···C=C	1.86	1.77	1.40	1.40
H−O−H	1.01/0.96	1.00/0.96	1.98/0.95	2.00/0.95
dihedral angles (deg)				
N−C−C−Se	−77.21	−78.62	−53.16	−53.76
C−C−Se−N	148.11	146.32	−166.36	−162.22

lower in energy than **TS1** and, as a result, it is kinetically insignificant. However, the HF, MP2, and B3LYP results show that here again the energy barrier is lower for the prolinamide−iminum hydrolysis reaction. This provides further support for the hypothesis that hydrogen bond interactions are responsible for the stabilization of the transition state.

Finally, the product complex (**PC**), comprised of phthalimide and carbinolamine **B**, is of much lower energy than the reactants, roughly 26 and 18 kcal/mol for the two reactions. The hydrogen bonds between the carbonyl of phthalimide and the OH of proline or the NH_2 of prolinamide still exist, but they are weak ($r_{O\cdots HO}$ = 1.95 Å and $r_{O\cdots HN}$ = 2.19 Å). In addition, hydrogen bonds between the NH of phthalimide and the OH group of the carbinolamine ion **B** exist with a NH···O distance of 2.00 and 1.98 Å for the proline and prolinamide catalysts, respectively. Since the two products are neutral, solvation has a relatively small effect.

To investigate the effect of water on the rate-limiting step of the α-selenenylation reaction, we calculated the optimized gas phase structures of the reactant complex and first transition state. The energy barriers are calculated to be 34.24, 18.38, and 18.26 kcal/mol for the

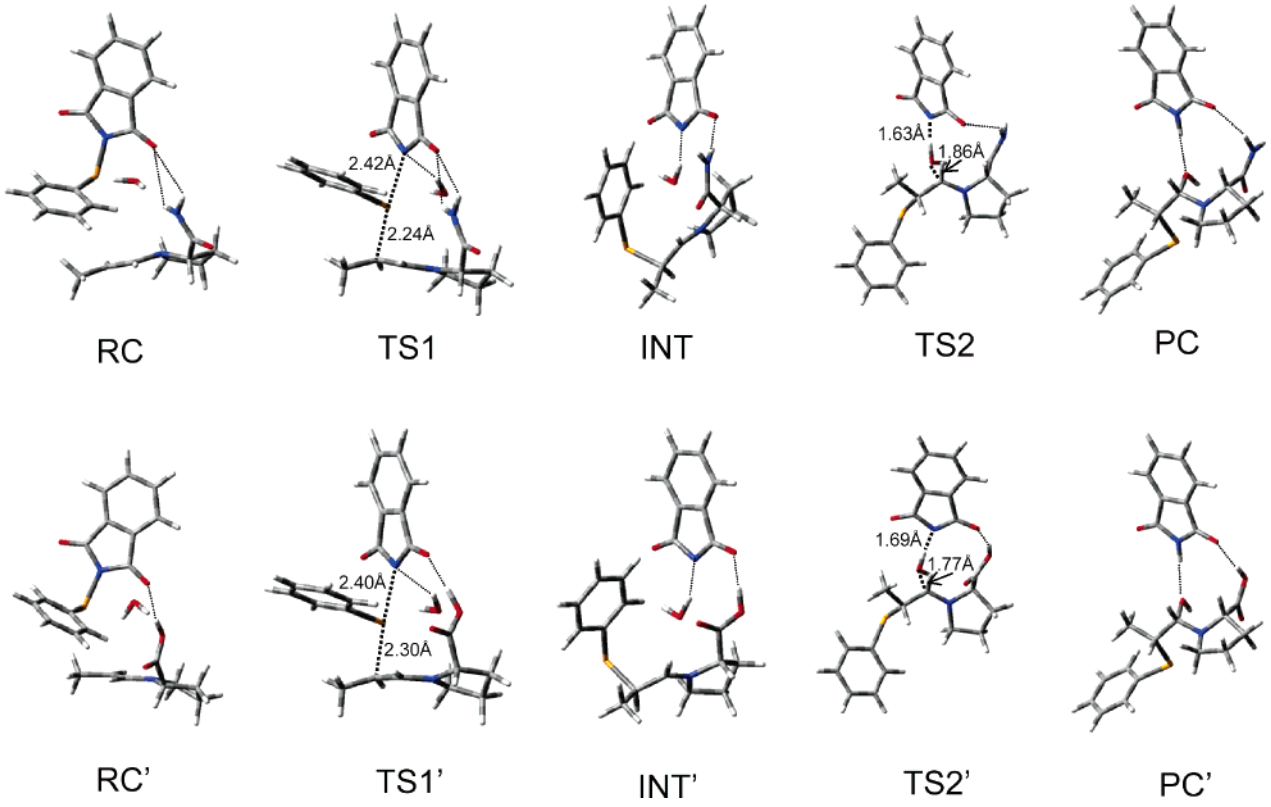


FIGURE 1. Geometries of stationary points along the reaction pathways. (Hydrogen bonds are represented by thin dashed lines, while the partial bonds at transition states are represented by thick dashed lines.)

prolinamide−enamine reaction at the HF, B3LYP, and MP2 levels of theory, respectively. The corresponding values for the proline−enamine reaction are 37.13, 19.72, and 20.79 kcal/mol. The higher barriers found for the latter process, as compared with those calculated for the transition state incorporating a water molecule, indicate that the water plays an important role in the first reaction step, via hydrogen bond interaction with the phthalimide nitrogen. Although the barriers are larger in the absence of water, the trend is the same, namely the two hydrogen bonds between the carbonyl oxygen in phthalimide and the prolinamide NH_2 group provide more stabilization of the rate-limiting transition state than the single hydrogen bond existing between the carbonyl oxygen in phthalimide and the proline OH group.

Conclusions

We have uncovered direct, mild methods for the preparation of α-phenylseleno aldehydes and ketones, important intermediates in the synthesis of α,β-unsaturated aldehydes and ketones. These processes are efficiently promoted by the organocatalysts, L-prolinamide (**1**) and pyrrolidine trifluoromethanesulfonamide (**2**). Unlike other existing methods, the operational procedure for these processes is simple and economic. The studies have demonstrated that the methodology is applicable to a wide range of aldehydes and ketones, having a broad spectrum of structural features. In addition, we have found that L-prolinamide (**1**) efficiently catalyzes aldehyde α-selenenylation reactions, whereas pyrrolidine trifluoromethanesulfonamide (**2**) serves as the most active catalyst for selenenylation of ketones. Moreover, the investigation reveals that the reactions of unsymmetric ketones take place preferentially at the least substituted α-sites. Theoretical studies with ab initio and DFT methods have been carried out to understand why L-prolinamide is the most effective oragnocatalyst for α-selenenylation reactions of aldehydes. Energy barriers for rate limiting formation of Se−C bond, through enamine attack of the Se atom in *N*-(phenylseleno)phthalimide, are calculated for the L-prolinamide and L-proline catalyzed processes. The results show that the transition state energy is lower for the prolinamide−enamine reaction than for the proline−enamine process. Moreover, the calculations demonstrate that hydrogen bonding plays an important role in stabilizing the transition states for the rate-limiting step of the selenenylation reaction.

Experimental Sections

General Procedure A for α-Selenenylation of Aldehydes (Table 3, Entries 1−10). To a vial containing aldehyde (0.25 mmol), 0.5 mL of anhydrous CH_2Cl_2, and catalyst l-prolinamide (**1**) (0.005 mmol) was added *N*-(phenylseleno)-phthalimide (0.3 mmol) at room temperature. After 10 min, the reaction mixture was treated with water (5 mL), then the solution was extracted with ethyl acetate (3 × 5 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was then purified by silica gel chromatography, eluting with EtOAC/hexane to afford a clear oil.

2-(Phenylseleno)propanal (Table 3, entry 1). The reaction was carried out following the general procedure A to provide a clear oil (45 mg, 81%). ^1H NMR (500 MHz, $CDCl_3$) δ 9.45 (d, 1H, J = 3.0 Hz), 7.51 (d, 2H, J = 7.0 Hz), 7.35 (t, 1H,

J = 7.5 Hz), 7.29 (t, 2H, J = 7.5 Hz), 3.71 (dq, 1H, J = 7.0, 3.0 Hz), 1.46 (d, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 136.3, 129.5, 129.1, 125.9, 46.8, 13.6; HRMS (EI) calcd for $C_9H_{10}OSe$ (M^+) 213.9891, obsd 213.9909.

General Procedure B for α-Selenenylation of Aldehydes (Table 3, Entries 11 and 12). To a vial containing an aldehyde (0.25 mmol) and 0.5 mL of anhydrous CH_2Cl_2 was added catalyst L-prolinamide (**1**) (0.005 mmol) at room temperature. The mixture was vigorously stirred for 0.5 h in the presence of 4 Å molecule sieves (40 mg). Then *N*-(phenylseleno)phthalimide (0.3 mmol) was added. After 0.5 h, the molecule sieves were removed by filtrating paper and then the filtrate was treated with water (5 mL), the solution was extracted with ethyl acetate (3 × 5 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was then purified by silica gel chromatography, eluting with EtOAc/hexane (1/40) to provide a clear oil.

2-Methyl-2-(Phenylseleno)propionaldehyde (Table 3, Entry 11). The reaction was carried out following the general procedure B to provide a clear oil (45 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.49 (d, 2H, J = 7.0 Hz), 7.39 (t, 1H, J = 7.5 Hz), 7.30 (t, 2H, J = 8.0 Hz), 1.44 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.7, 138.0, 129.7, 129.3, 126.3, 53.6, 21.7; HRMS (EI) calcd for $C_{10}H_{12}OSe$ (M^+) 228.0048, obsd 228.0065.

General Procedure for α-Selenenylation of Ketones (Table 6, Entries 1−14). To a vial containing ketone (0.3 mmol) and 1.0 mL of anhydrous CH_2Cl_2 was added catalyst pyrrolidine trifluoromethanesulfonamide (**2**) (0.03 mmol) at room temperature. The mixture was vigorously stirred for 0.5 h before *N*-(phenylseleno)phthalimide (0.3 mmol) was added. After 16−48 h, the reaction mixture was treated with water (10 mL), and then the solution was extracted with ethyl acetate (3 × 10 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was then purified by silica gel chromatography (EtOAc/hexanes) and fractions were collected and concentrated in vacuo to provide a clear oil.

1-(Phenylselanyl)propan-2-one (Table 6, Entry 1). The title compound was prepared according to the general procedure in 69% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55−7.50 (m, 2H), 7.26−7.31 (m, 3H), 3.59 (s, 2H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.7, 33.5, 129.6, 128.9, 128.2, 37.0, 28.2; HRMS (EI) calcd for $C_9H_{10}OSe$ (M^+) 213.9891, obsd 213.9909.

Computational Methods. All the calculations, including Hartree−Fock (HF), Møller−Plesset (MP2), and density functional theory (DFT), were carried out with the Gaussian 03 package.[22] Molecular geometries of all the stationary points, including the enamine reactant complex (**RC**), the first transition state (**TS1**), the intermediate (**INT**), the second transition state (**TS2**), and product complex (**PC**), were optimized in vacuo at the HF/6-31G(d) level of theory. The standard effective core potentials (ECP) were used for the selenium atom with the LANL2DZ basis set.[23] The stationary points were confirmed by frequency calculations. To include the electron correlations, single-point energy calculations were performed at these geometries at the MP2[24] and B3LYP[25] levels of theory with the same basis set.

The solvent effect on the reaction pathway was estimated by using the polarizable continuum model (PCM),[26] as implemented in Guassian 03. PCM calculations were performed at both the HF and DFT levels with the 6-31G(d) basis set. Calculations were performed with the dielectric constant corresponding to CH_2Cl_2 at 25 °C: ϵ = 8, as in the experiment.

Acknowledgment. Support for this research was provided by the Department of Chemistry and the Research Allocations Committee, the University of New Mexico. We thank Professor Patrick S. Mariano for making critical editorial comments about the manuscript.

Supporting Information Available: The ^{1}H and ^{13}C NMR and HRMS spectral characterization data for all α-selenenylation products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0506940

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