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A Simple and Efficient L-Prolinamide-Catalyzed α-Selenenylation Reaction of Aldehydes

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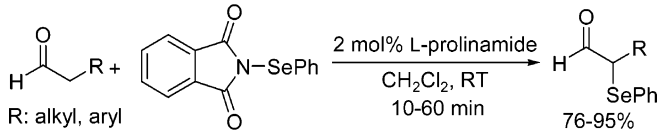
ABSTRACT



An efficient and simple L-prolinamide-catalyzed α-selenenylation reaction of aldehydes with *N*-(phenylseleno)phthalimide has been developed for the efficient preparation of α-phenylselenoaldehydes. Such compounds are versatile building blocks for the synthesis of α,β-unsaturated aldehydes, allylic alcohols, and amines.

α-Selenoaldehydes are useful synthetic intermediates.[1] The selenoxide elimination reaction of α-selenoaldehydes is a powerful, mild method for the preparation of α,β-unsaturated aldehydes.[1,2] Oxidation of these substances, followed by 2,3-sigmatropic rearrangement, serves as a versatile route to allylic alcohols[3] and amines.[4] Several methods for preparing α-selenoaldehydes have been reported, including formylation of α-lithioselenides,[5] direct selenenylation of simple aldehydes,[6] and α-selenenylation of aldehydes promoted by acid (*p*-TsOH)[7] or base (piperidine).[8] However, both methods require the use of stoichiometric amounts of acid and base, and in the latter case, the preformation of an enamine from an aldehyde with piperidine is necessary. Herein, we wish to report the first high-yielding (76−95%), catalytic α-selenenylation reaction of aldehydes, catalyzed by the L-prolinamide.

In recent years, proline-represented small organic molecule organocatalysts have emerged as a new frontier in organic synthesis.[9−19] Proline and its derivatives have been used to promote a variety of organic reactions of enolizable carbonyl

(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, 1986.

(2) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(3) (a) Lerouge, P.; Paulmier, C. *Tetrahedron Lett.* **1984**, *25*, 1983. (b) Lerouge, P.; Paulmier, C. *Tetrahedron Lett.* **1984**, *25*, 1987. (c) Lerouge, P.; Paulmier, C. *Bull. Soc. Chim. Fr.* **1985**, 1225.

(4) (a) Fitzner, J. N.; Shea, R. G.; Fankhauser, J. E.; Hopkins, P. B. *J. Org. Chem.* **1985**, *50*, 417. (b) Spaltenstein, A.; Carpino, P. A.; Hopkins, P. B. *Tetrahedron Lett.* **1986**, *27*, 147. (c) Shea, R. G.; Fitzner, J. N.; Fankhauser, J. E.; Spaltenstein, A.; Carpino, P. A.; Peevey, R. M.; Pratt, D. V.; Tenge, B. J.; Hopkins, P. B. *J. Org. Chem.* **1986**, *51*, 5243.

(5) Denis, J. N.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1976**, *17*, 453.

(6) (a) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (b) Houllemare, D.; Ponthieux, S.; Outurquin, F.; Paulmier, C. *Synthesis* **1997**, 101.

(7) Cossy, J.; Furet, N. *Tetrahedron Lett.* **1993**, *34*, 7755.

(8) Williams, D. R.; Nishitani, K. *Tetrahedron Lett.* **1980**, *21*, 4417.

(9) For reviews of proline-catalyzed reactions, see: (a) List, B. *Tetrahedron* **2002**, *58*, 5573. (b) Gröger, H.; Wilken, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 529. (c) Duthaler, R. O. *Angew. Chem., Int. Ed.* **2003**, *42*, 975.

(10) For a general review on organocatalysis, see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.

(11) For a review of amino acids and peptides as catalysts, see: Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.

(12) For a review on amine-catalyzed reactions, see: France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.

(13) For a review of asymmetric phase-transfer catalysis, see: Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, ASAP.

(14) We recently developed novel pyrrolidine sulfonamides (their structures are shown in Table 1, entries 3 and 4) as organocatalysts for catalyzing asymmetric α-aminoxylation and the Mannich-type reactions: (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2004**, submitted for publication. (b) Wang, W.; Wang, J.; Li, H. *Tetrahedron Lett.* **2004**, submitted for publication.

(15) For proline-catalyzed aldol reactions, see: (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) List, B.; Pojarliev, P.; Castello, C. *Org. Lett.* **2001**, *3*, 573. (c) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (d) Northrup, A. B.; Mangion, I. K.; Hettche, F.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 2152.

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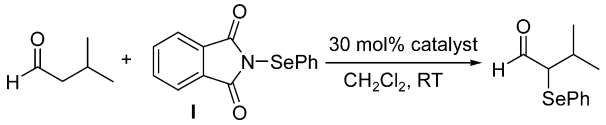
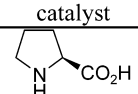
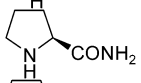
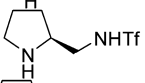
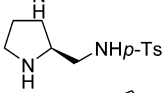
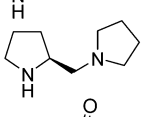
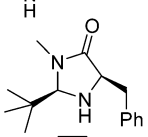
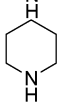
compounds.[15−19] The general mechanism for these processes involves initial formation of an electron-rich enamine, which then adds to an electrophile to give an adduct. Intrigued by the possibility that such a mechanistic scenario might be expanded to encompass electrophilic forms of selenium reagents, we have explored reactions of aldehydes with *N*-(phenylseleno)phthalimide **I** catalyzed by proline derivative L-prolinamide. The results of this effort have demonstrated that these α-selenenylation reactions proceed rapidly using 2 mol % of L-prolinamide within 10−60 min to afford α-phenylselenoaldehydes in high yields (76−95%).

In an initial study, eight organocatalysts (30 mol %) were screened for the reaction of *N*-(phenylseleno)phthalimide **I** as selenium reagent with isovaleraldehyde in CH_2Cl_2 (Table 1). It was found that L-prolinamide exhibited the most highly

Table 1. Catalyst Screening for α-Selenenylation Reaction of Isovaleraldehyde[a]



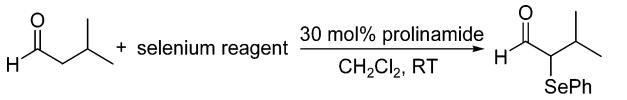
entry	catalyst	reaction time	% yield[b]
1		30 min	82
2		<5 min	96
3		4 h	87
4		30 min	48
5		50 min	78
6		12 h	48
7		3 h	21
8		3 h	56

[a] Reaction conditions: To a vial containing isovaleraldehyde (0.25 mmol), 0.5 mL of anhydrous CH_2Cl_2, and catalyst (0.075 mmol) was added *N*-(phenylseleno)phthalimide **I** (0.3 mmol) at room temperature. After a certain period of time (see Table 1), the reaction mixture was treated with water (5 mL), and 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 crude product was purified by silica gel chromatography. [b] Isolated yields.

catalytic activity (Table 1, entry 2). The reaction was completed in less than 5 min in a nearly quantitative yield (96%). L-Proline also showed good activity (Table 1, entry 1). However, it is worth noting that under the same reaction conditions, piperidine, which has been used for the reaction but with a stoichiometric amount,[8] gave only 56% yield with 30 mol % loading. The investigation promoted us to select L-prolinamide as catalyst for the further examination of the α-selenenylation reaction.

Next, we probed reactions of four commonly used selenium reagents with isovaleraldehyde in the presence of 30 mol % L-prolinamide in CH_2Cl_2. The results showed that facile selenenylation occurred with *N*-(phenylseleno)phthalimide **I** (Table 2, entry 1) to produce the seleno-aldehyde

Table 2. Effect of Selenium Reagents on α-Selenenylation Reactions of Isovaleraldehyde[a]



entry	selenium reagent	reaction time	% yield[b]
1	*N*-(phenylseleno) phthalimide **I**	<5 min	96
2	PhSeCl	15 h	75
3	PhSeBr	1 d	24
4	PhSeSePh	1 d	<10

[a] Reaction conditions (see footnote in Table 1). [b] Isolated yield.

product in less than 5 min and a 96% yield. Under the same conditions, much longer times were required for reactions of phenylselenyl chloride, bromide and diphenyl diselenide, and lower yields were obtained (15 h, 75%; 1 d, 24%; and 1 d, <10% yield, respectively, Table 2). Consequently, *N*-(phenylseleno)phthalimide **I** was selected as the selenium reagent of choice for the α-selenenylation reactions of aldehydes.

A survey of media for the L-prolinamide-catalyzed α-selenenylation process revealed that solvents had a significant effect on the reaction (Table 3). Reactions in less polar solvents, such as CH_2Cl_2, EtOAc, and 1,4-dioxane (Table 2, entries 1, 2, and 4), took place in higher yields. In contrast, the use of polar solvents CH_3CN, DMSO, CH_3NO_2, and DMF (entries 5−8) resulted in low yields. Interestingly,

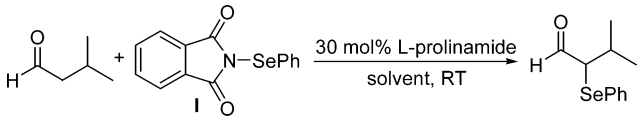
(16) For proline-catalyzed Mannich reactions, see: (a) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336. (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827. (c) Córdova, A.; Notz, W.; Zhong, G.; Betancort, J. M.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1842. (d) Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866. (e) Córdova, A.; Barbas, C. F., III. *Tetrahedron Lett.* **2003**, *44*, 1923. (f) Notz, W.; Tanaka, F.; Watanabe, S.-I.; Chowdari, N. S.; Turner, J. M.; Thayumanavan, R.; Barbas, C. F., III. *J. Org. Chem.* **2003**, *68*, 9624. (g) Hayashi, Y.; Tsuboi, W.; Ashimine, I.; Urushima, T.; Shoji, M.; Sakai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3677. (h) Hayashi, Y.; Tsuboi, W.; Shoji, M.; Suzuki, N. *J. Am. Chem. Soc.* **2003**, *125*, 11208.

(17) For proline-catalyzed α-amination reactions, see: (a) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (b) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bogevig, A.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254.

(18) For proline-catalyzed α-aminoxylation reactions, see: (a) Brown, F. J.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808. (b) Zhong, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4247. (c) Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109. (d) Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112.

(19) Recently, Jørgensen and co-workers reported L-prolinamide-catalyzed α-chlorination of ketones: Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.

Table 3. Effect of Solvents on α-Selenenylation Reaction of Isovaleraldehyde with I[a]



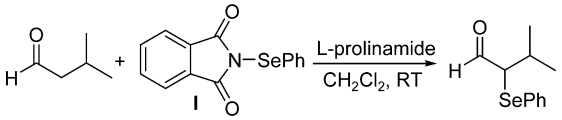
entry	solvent	reaction time	% yield[b]
1	CH_2Cl_2	<5 min	96
2	EtOAc	10 min	88
3	toluene	2 h	38
4	1,4-dioxane	15 min	93
5	CH_3CN	30 min	74
6	DMSO	1 h	83
7	CH_3NO_2	2 h	66
8	DMF	2 h	46

[a] For reaction conditions, see footnote in Table 1. [b] Isolated yield.

nonpolar toluene gave a very poor yield (38%, Table 3, entry 3), presumably as a result of the low solubility of *N*-(phenylseleno)phthalimide **I** in toluene. On the basis of these results, we selected CH_2Cl_2 as the solvent for reactions and explored testing the effect of catalyst loadings on the process.

The studies of catalyst loadings on the α-selenenylation reactions revealed that, remarkably, a catalyst loading as low as 1 mol % still afforded significant reaction activity (Table 4, entry 6). From an operational perspective, use of 2 mol

Table 4. Effect of Catalyst Loadings on α-Selenenylation Reactions of Isovaleraldehyde[a]



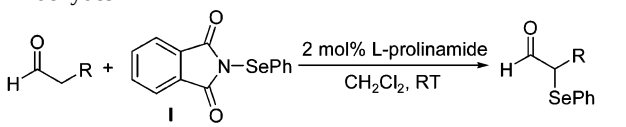
entry	mol % catalyst	reaction time	% yield[b]
1	30	<5 min	96
2	20	<5 min	94
3	10	<5 min	94
4	5	10 min	86
5	2	10 min	88
6	1	1 h	62
7	0.5	2 d	31

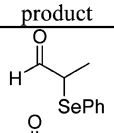
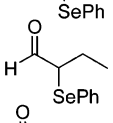
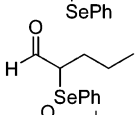
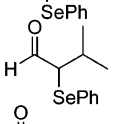
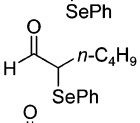
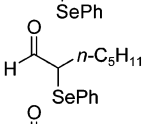
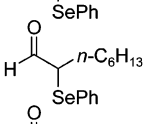
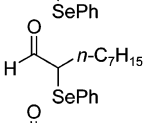
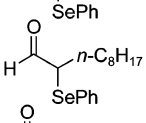
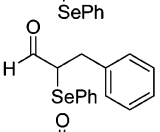
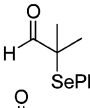
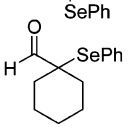
[a] For reaction conditions, see footnote in Table 1. [b] Isolated yield.

% of L-prolinamide is optimal to ensure high reaction efficiency (88% yield) while maintaining a reasonable reaction time (10 min, Table 4, entry 5).

Having established optimal reaction conditions for the selenation process, we next probed reactions with a variety of aldehydes (Table 5). The results show that considerable variation in the steric demand of the aldehyde is possible without loss in efficiency. Independent of the length of the side chains (C1−C8) (entries 1−9, Table 5), aldehydes reacted within a 10 min period in high yields (78−95%).

Table 5. L-Prolinamide-Catalyzed α-Selenenylation Reactions of Aldehydes[a]



entry	product	reaction time	% 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		1 h	76
12		1 h	81

[a] For reaction conditions, see footnote in Table 1. [b] Isolated yield.

Reaction proceeded rapidly (10 min, 88% yield) even with the more hindered isovaleraldehyde (entry 4). However, under these conditions, highly sterically crowded α,α-disubstituted aldehydes (entries 11 and 12) only slowly reacted with *N*-(phenylseleno)phthalimide **I** to give very low yields of the selenation products. Importantly, addition of 4 Å molecular sieves resulted in significant enhancements of the reaction rates. In these cases, reactions of α,α-disubstituted aldehydes were complete within 1 h and took place in high yields (76−81%). The possible reason for the enhanced reaction rate could be due to facilitated formation of the enamine intermediate in the presence of molecular sieves.

In summary, an efficient L-prolinamide-catalyzed α-selenenylation reaction of aldehydes with *N*-(phenylseleno)-

phthalimide **I** has been developed. The process is general for a variety of aldehyde substrates, and high yields (76−95%) are observed. To our knowledge, this is the first study in which an organocatalyst has been used to catalyze this type of the reaction. The results of investigation of the reaction mechanism and the asymmetric version of the α-selenenylation process will be reported in due course.[20]

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Supporting Information Available: Experimental procedures and spectra data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) L-Proline and L-prolinamide exhibited no enantioselectivity on the α-selenenylation of isovaleraldehyde. However, our pyrrolidine tosyl sulfonamide (its structure is shown in Table 1, entry 4) provided 60% ee.