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Lewis Acid Promoted Phenylseleno Group Transfer Tandem Radical Cyclization Reactions

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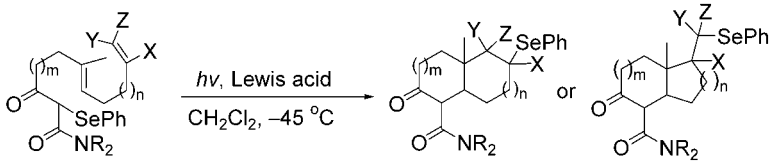
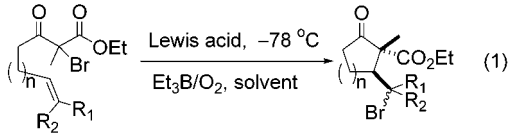
ABSTRACT



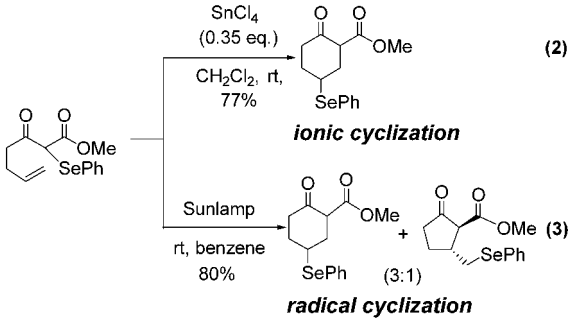
A new Lewis acid promoted phenylseleno group transfer tandem radical cyclization method was developed. In the presence of Lewis acids such as $Yb(OTf)_3$ or $Mg(ClO_4)_2$, under photolysis condition at low temperature (–45 °C), various unsaturated α-phenylseleno β-keto amides underwent radical cyclization reactions to give monocyclic or bicyclic products in a highly efficient, regioselective, and stereoselective manner.

Since its discovery more than a decade ago, atom or group transfer radical cyclization has become a powerful tool for the synthesis of cyclic compounds.[1] Recently we discovered a chiral Lewis acid catalyzed bromo atom-transfer radical cyclization method for the synthesis of 2,3-disubstituted cyclic ketones (eq 1).[2] Here we report a new Lewis acid



promoted phenylseleno group transfer radical cyclization method[3] and its successful application to tandem cyclization reactions for the construction of various bicyclic ring skeletons.[4]

There are two known pathways for the cyclization of α-phenylseleno 1,3-dicarbonyl compounds: the ionic pathway promoted by Lewis acids (eq 2),[5] and the radical pathway under photolysis condition (eq 3).[6] After screening



several 1,3-dicarbonyl compounds and heteroatom/group combinations, we found unsaturated α-phenylseleno β-keto

(1) (a) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489−2490. (b) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140−3157. (c) Curran, D. P.; Chen, M.-S.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265−6276. (d) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872−8878. (e) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746−2750. (f) For a recent review, see: Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, Chapter 1.5.

(2) Yang. D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheung, K.-K. *J. Am. Chem. Soc.* **2001**, *123*, 8612−8613.

(3) For an recent review on the use of Lewis acids in free radical reactions, see: (a) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562−2579. For recent examples of Lewis acid promoted atom transfer radical reactions, see: (b) Mero, C. L.; Porter, N. A. *J. Am. Chem. Soc.* **1999**, *121*, 5155−5160. (c) Clark, A. J.; Campo, F. D.; Deeth, R. J.; Filik, R. P.; Gatard, S.; Hunt, N. A.; Lastecoueres, D.; Thomas, G. H.; Verlhac, J.-B.; Wongtap, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 671−680. (d) Kitagawa, O.; Yamada, Y.; Fujiwara, H.; Taguchi, T. *J. Org. Chem.* **2002**, *67*, 922−927.

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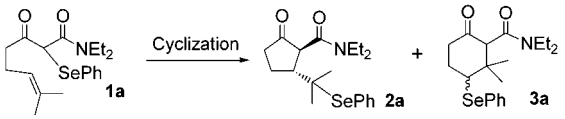
amides suitable radical precursors since they are stable and easy to prepare and purify.[7] For compound **1a**, several reaction conditions were examined (Table 1). At 6 °C and

Table 1. Effect of Lewis Acids on the Phenylseleno Group Transfer Radical Cyclization Reaction of **1a**[a]



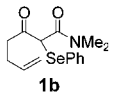
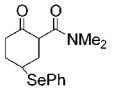
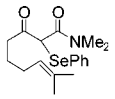
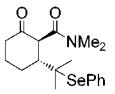
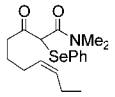
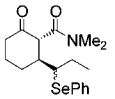
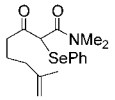
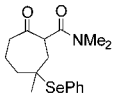
entry	Lewis acid	solvent	initiating condition	temp (°C)	time (h)	product	yield[b]
1	$Mg(ClO_4)_2$	CH_2Cl_2		6	1	**3a**	70%
2		CH_2Cl_2	*hν*	−45	5	nr	
3	$Mg(ClO_4)_2$	CH_2Cl_2	*hν*	−45	4.5	**2a**	53%
4	$Mg(ClO_4)_2$	toluene	Et_3B/O_2	−78 to 0	10	**2a**	40%
5	$Mg(ClO_4)_2$	toluene	*hν*	−50	9	**2a**	74%
6	$Yb(OTf)_3$[c]	CH_2Cl_2	*hν*	−45	2	**2a**	80%

[a] Unless otherwise indicated, 1.0 equiv of Lewis acid was used. [b] Isolated yield. [c] 0.6 equiv.

in the presence of $Mg(ClO_4)_2$ (1 equiv), only the six-membered-ring compound **3a** was formed in 70% yield (entry 1), which is believed to be the ionic cyclization product.[5] No reaction took place at −45 °C when the reaction mixture was irradiated with UV light in the absence of Lewis acid (entry 2). In contrast, with the addition of 1 equiv of $Yb(OTf)_3$ or $Mg(ClO_4)_2$, the desired product **2a** could be obtained by using either UV light or Et_3B/O_2 to initiate the radical reaction (entries 3−6). It was noteworthy that at lower temperatures (−50 or −45 °C), the ionic side reactions were effectively suppressed and no compound **3a** was formed. With a catalytic amount of $Yb(OTf)_3$ (0.6 equiv) as catalyst (entry 6), the best yield (80%) was achieved under photolysis condition at −45 °C in CH_2Cl_2. Clearly Lewis acids promoted this phenylseleno group transfer radical cyclization reaction. By complexation with 1,3-dicarbonyl groups, Lewis acids can make the α-radical more electron-deficient and therefore activate it toward addition to unactivated alkenes.

Various unsaturated α-phenylseleno *β*-keto amide substrates (**1b**−**e**) were then tested under the above radical cyclization condition (Table 2). Cyclization of **1b** gave exclusively the 6-*endo* product **2b** as a mixture of epimers in 68% yield (entry 1). In contrast, Byers and co-workers

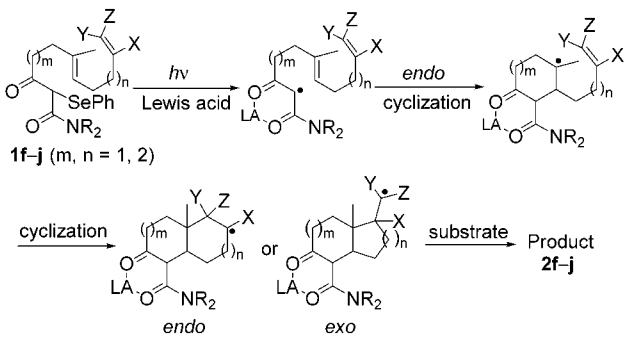
Table 2. Lewis Acid Promoted Phenylseleno Group Transfer Monocyclization Reactions[a]

Entry	Substrate	Lewis Acid	Time	Product	Yield
1	 **1b**	$Yb(OTf)_3$	1.5 h	 **2b**	68 % (1:1)[b]
2	 **1c**	$Yb(OTf)_3$[c,d]	1 h	 **2c**	56 %
3	 **1d**	$Yb(OTf)_3$[c]	2.3 h	 **2d**	80 % (1.3:1)[b]
4	 **1e**	$Mg(ClO_4)_2$[e]	4 h	 **2e**	70 % (2.4:1)[b]

[a] Unless otherwise indicated, the reaction was irradiated with UV light at −45 °C in CH_2Cl_2 and 1 equiv of Lewis acid was added. [b] Ratio of epimers. [c] 0.6 equiv. [d] Et_2O was used as the solvent. [e] 4 Å molecular sieves was added.

obtained a 3:1 mixture of 6-*endo* and 5-*exo* products for the cyclization of the corresponding *β*-keto ester under sunlamp irradiation without the addition of Lewis acids (eq 3).[6a] Substrate **1c** failed to cyclize when treated under the standard photolysis condition (1.0 equiv of $Yb(OTf)_3$ or $Mg(ClO_4)_2$ in CH_2Cl_2). When the solvent was changed to Et_2O and 0.6 equiv of $Yb(OTf)_3$ was added, the 6-*exo* cyclization product **2c** was formed in 56% yield (entry 2). Substrate **1d** has two cyclization modes, i.e., 6-*exo* and 7-*endo*, but only the 6-*exo* product was isolated in 80% yield (entry 3). For the cyclization of **1e**, the α-radical intermediate attacked the less substituted side of the alkene to form the seven-membered-ring amide **2e** exclusively (entry 4).[8] These results demonstrate that excellent regioselectivity can be achieved for the Lewis acid promoted phenylseleno group transfer radical cyclization reactions.

It is known in the literature that the phenylseleno group transfer is slower than the I or Br atom transfer, and this feature makes the phenylseleno group transfer especially suitable for tandem cyclization reactions.[1f,9] By applying the above monocyclization method to a series of diene substrates (**1f**−**j**), we expected to obtain various bicyclic phenylseleno



(4) For recent reviews on radical tandem cyclization reactions, see: (a) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224−2248. (b) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306.

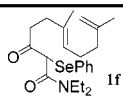
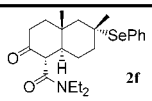
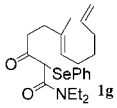
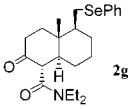
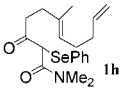
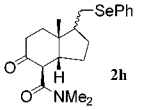
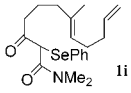
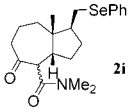
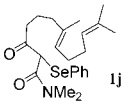
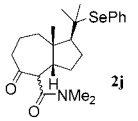
(5) Jackson, W. P.; Ley, S. V.; Morton, J. A. *Tetrahedron Lett.* **1981**, *22*, 2601−2604.

(6) (a) Byers, J. H.; Gleason, T. G.; Knight, K. S. *J. Chem. Soc., Chem. Commun.* **1991**, 354−356. For examples of phenylseleno group transfer radical cyclization reactions, see: (b) Back, T. G.; Gladstone, P. L. *Synlett* **1993**, 699−700. (c) Ryu, I.; Muraoka, H.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1996**, *61*, 6396−6403. (d) Pandey, G.; Rao, K. S. S. P.; Rao, K. V. N. *J. Org. Chem.* **1996**, *61*, 6799−6804. (e) Abazi, S.; Rapado, L. P.; Schenk, K.; Renaud, P. *Eur. J. Org. Chem.* **1999**, 477−483. For a recent review, see: (f) Renaud, P. In *Organoselenium Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Springer: Berlin, 2000; pp 81−112.

(7) Rosenstein, I. J.; Tynan, T. A. *Tetrahedron Lett.* **1998**, *39*, 8429−8432.

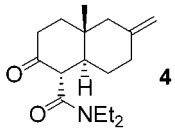
group transfer products. Once generated, the α-radicals of *β*-keto amides would undergo *endo*-cyclization to attack the less substituted side of the internal alkene group, yielding cyclic tertiary alkyl radical intermediates. At this stage, the slow rate of phenylseleno group transfer would allow enough time for the formation of the second carbon−carbon bond before the radical chain is terminated. Subsequent group transfer would be accomplished when the bicyclic alkyl radical abstracts the phenylseleno group from another substrate. This was indeed the case for the tandem cyclization reactions of substrates **1f**−**j** (Table 3). Despite the difference

Table 3. Lewis Acid Promoted Tandem Phenylseleno Group Transfer Reactions[a]

Entry	Substrate	Lewis Acid	Time	Product	Yield
1	 **1f**	$Mg(ClO_4)_2$	3 h	 **2f**	61 %
2		$Yb(OTf)_3$	3 h		68 %
3	 **1g**	$Mg(ClO_4)_2$[b]	4 h	 **2g**	67 %
4		$Yb(OTf)_3$[c]	6 h		62 %
5	 **1h**	$Mg(ClO_4)_2$[b,d]	2.5 h	 **2h**	80 % (1:3.6)[e]
6	 **1i**	$Yb(OTf)_3$	3.5 h	 **2i**	78% (1:2.4)[e]
7	 **1j**	$Yb(OTf)_3$	2 h	 **2j**	71% (1:2.7)[e]

[a] Reaction conditions: 1 equiv of Lewis acid, *hν*, −45 °C, CH_2Cl_2. [b] 4 Å MS was added. [c] 0.6 equiv. [d] In the absence of MS, the reaction took 5 h to complete and the yield was 74%. [e] Ratio of epimers (α:*β*).

in the second ring formation, i.e., 6-*endo* for **1f** and 6-*exo* for **1g**, both cyclization products **2f** and **2g** possessed the *trans*-decalin skeleton with four stereocenters set up in one step (entries 1−4). Slightly better yield of **2f** was obtained when $Yb(OTf)_3$ was used as the Lewis acid instead of $Mg(ClO_4)_2$ (entry 1 vs entry 2). Oxidative elimination of PhSe group from **2f** provided the exocyclic olefinic compound **4**, a core structure found in many naturally occurring bioactive terpenoids, such as andrographolide,[10a] subglutinol,[10b] and the candelalides.[10c] A notable feature of this reaction is the highly regioselective formation of the exocyclic C=C bond. In contrast, oxidative radical cyclization of similar unsaturated *β*-keto esters without α-SePh group using $Mn(OAc)_3$ and $Cu(OAc)_2$ resulted in a mixture of *exo*- and *endo*-cyclic olefinic products.[11] After the cyclization of **1h** (entry 5), *cis*-6,5-fused ring product **2h** was isolated in high yield (80%) as a mixture of epimers (α:*β* = 1:3.6). In addition, *cis*-7,5-fused ring skeleton was constructed in good yield as a pair of epimers (entries 6 and 7). A small amount of alkene **5** (7%), arising from elimination of bicylic alkyl radical intermediate, was also formed in the cyclization reaction of **1j** (entry 7). Presumably the bulky geminal methyl groups of **1j** hindered the abstraction of the PhSe group from another substrate molecule. Oxidative elimination of selenide **2j** afforded **5**, a potential intermediate for the total synthesis of the potent antibacterial agent guanacastepene.[12]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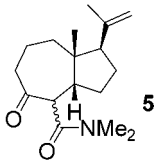
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In conclusion, the Lewis acid promoted phenylseleno group transfer radical cyclization represents an efficient, regioselective, and stereoselective tool for the formation of monocyclic and bicyclic compounds that are important core structures of many biologically interesting natural products. Future efforts will be directed at developing the enantioselective version of these reactions.[13]

Acknowledgment. This work was supported by The University of Hong Kong and Hong Kong Research Grants Council. We thank Dr. N.-Y. Zhu for X-ray analysis. D.Y. acknowledges the Bristol-Myers Squibb Foundation for an Unrestricted Grant in Synthetic Organic Chemistry and the Croucher Foundation for a Croucher Senior Research Fellowship.

Supporting Information Available: Experimental details and X-ray data of compounds **2f** and *β*-**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) When $Mg(ClO_4)_2$ was used as the Lewis acid, the addition of 4 Å molecular sieves led to faster reaction and higher yield

(9) Curran, D. P.; Martin-Esker, A. A.; Ko, S.-B.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4691−4695.

(10) (a) Puri, A.; Saxena, R.; Saxena, R. P.; Saxena, K. C.; Srivastava, V.; Tandon, J. S. *J. Nat. Prod.* **1993**, *56*, 995−999. (b) Lee, J. C.; Lobkovsky, E.; Pliam, N. B.; Strobel, G.; Clardy, J. *J. Org. Chem.* **1995**, *60*, 7076−7077. (c) Singh, S. B.; Zink, D. L.; Dombrowski, A. W.; Dezeny, G.; Bills, G. F.; Felix, J. P.; Slaughter, R. S.; Goetz, M. A. *Org. Lett.* **2001**, *3*, 247−250.

(11) (a) Snider, B. B.; Mohan, R.; Kates, S. A. *Tetrahedron Lett.* **1987**, *28*, 841−844. (b) Yang, D.; Xu, M. *Org. Lett.* **2001**, *3*, 1785−1788.

(12) (a) Snider, B. B.; Hawryluk, N. A. *Org. Lett.* **2001**, *3*, 569−572. (b) Dudley, G. B.; Danishefsky, S. J. *Org. Lett.* **2001**, *3*, 2399−2402.

(13) For an excellent review on enantioselective radical reactions, see: Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163−171.