



Palladium and nickel catalyzed thio-Claisen rearrangements of chiral bicyclic thiolactams (via *N,S*-ketene acetals)

Daniel J. Watson, Paul N. Devine and A. I. Meyers *

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA

Received 17 November 1999; revised 6 December 1999; accepted 9 December 1999

Abstract

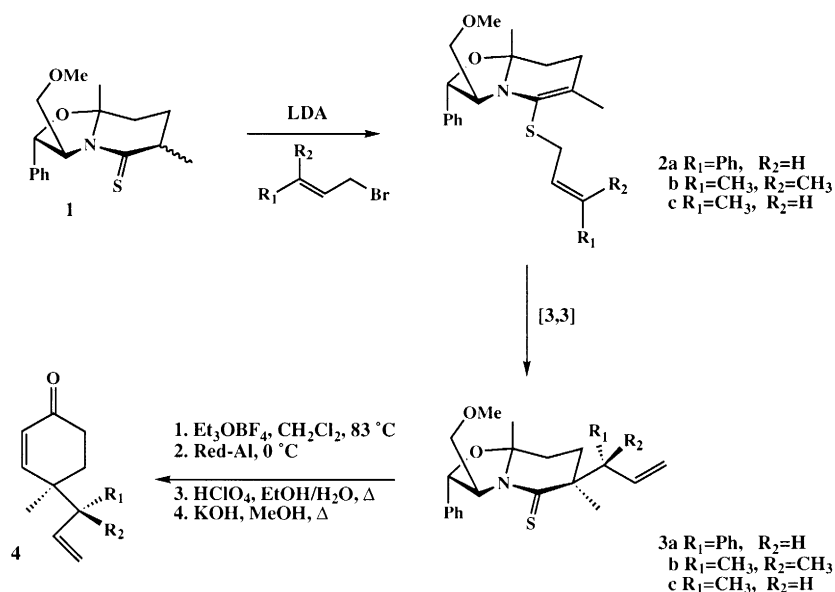
Pd, Ni, and Lewis acid catalyzed rearrangements occur under milder conditions than the thermal version of the titled rearrangements. © 2000 Elsevier Science Ltd. All rights reserved.

Recently, we reported¹ the highly stereoselective thio-Claisen rearrangement starting from **1** and a number of allylic halides to generate *N,S*-ketene acetals **2a–c** (Scheme 1). The resulting thiolactams **3a–c** bearing vicinal stereogenic quaternary centers or quaternary–tertiary centers were then transformed into 4,4-disubstituted cyclohexenones, **4**.

Further application of this thio-Claisen rearrangement has led to the first asymmetric synthesis of the sesquiterpene (–)-trichodiene,² as well as providing an asymmetric route to chiral cyclohexenones with spiro-connected cyclopentenones.³ Based upon our early work, Rawal has recently achieved highly diastereoselective thio-Claisen rearrangements employing a *C*₂-symmetric amine as the chiral auxiliary.^{4a} Apart from the classical thermal version of [3,3]-sigmatropic rearrangements^{4b–f} there has been increasing interest in the use of transition metals (Hg^{II}, Pd^{II}) to catalyze these transformations under mild conditions.⁵ Although extensive studies are known in the transition metal catalyzed [3,3]-sigmatropic rearrangements, we have found no examples of metal catalyzed thio-Claisen rearrangements. We now describe, in preliminary form, our findings that *N,S*-ketene acetals **2a** and **2b** undergo both Lewis acid and transition metal promoted [3,3]-sigmatropic rearrangements, under mild conditions, to afford thiolactams **3a** and **3b**, a process which would significantly enhance its synthetic utility.

Although Lewis acids are known to accelerate aromatic and aliphatic *O*-Claisen rearrangements,⁶ the thio-Claisen rearrangement of **2a** to **3a** has failed in our hands using common Lewis acids. TiCl₄, Bu₂BOTf and ZnCl₂ resulted in cleavage of the *S*-allylic-C bond in **2b** affording the starting α-methylated thiolactam **1**. Alkylaluminums implemented the thio-Claisen rearrangement at room temperature and although the diastereomeric ratio of the newly formed quaternary center in **3** was poor (<3:1), we obtained significantly higher yields (68–78%) than those obtained in the thermal rearrangement. When

* Corresponding author.



Scheme 1.

prenyl bromide was used to prepare the *N,S*-ketene acetal **2b**, Me_3Al provided the rearranged product **3b** in 75% yield when heated in ethylene dichloride at $83^\circ C$.

We then examined metal salts of Pd and Ni, which have been shown to catalyze a wide variety of [3,3]-sigmatropic rearrangements. Yoshida⁷ has reported several examples of the regioselective S→N allylic rearrangement of *S*-allylthioimides into *N*-allylthioamides catalyzed by palladium(II) chloride. In addition, rearrangements such as the *O*-allyl thiocarboxylate rearrangement⁸ and the *O*-allyl phosphorothionate (C–O→C–S) rearrangement⁹ have also been reported to proceed under mild conditions. To our knowledge, none of these metals have ever been utilized in the thio-Claisen rearrangement.¹⁰

N,S-Ketene acetal **2a**, when treated with 10 mol% of the palladium(II) catalyst resulted in the rearrangement at $25^\circ C$ to produce the desired thiolactam **3a**. The rearrangement of **2a** occurred with a variety of palladium(II) catalysts at room temperature whereas the thermal rearrangement of **2a** required heating at $140^\circ C$ (Table 1). Initially, the use of $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ (Table 1, entries 2–4) provided thiolactam **3a** as a 3:1 mixture of *exo* (β) and *endo* (α) diastereoisomers, respectively. When palladium(0) was employed as a potential catalyst for this rearrangement it was found that $Pd(PPh_3)_4$ (entry 6) catalyzed the rearrangement at $25^\circ C$ and afforded a diastereomeric ratio of 3.4:1 in favor of the *exo* (β) diastereomer **3a**. However, the best result came from a $Pd_2(dba)_3$ catalyzed rearrangement of **2a** to provide **3a** in a diastereomeric ratio of 5.6:1 (entry 7). Although moderate diastereoselectivity was observed under catalytic conditions it is important to note that the isolated yield of the major *exo* diastereomer **3a** was somewhat higher than that obtained during the thermal rearrangement (entry 1).

$NiCl_2(Ph_3P)_2$ also effected the rearrangement at room temperature affording the thiolactam **3a** as a 4:1 mixture of *exo:endo* diastereoisomers, respectively, (entry 8). However, with tetrakis(triphenylphosphine)-nickel(0) reagent prepared from the treatment of a nickel(II) salt with either zinc metal or *n*BuLi,¹¹ the ratio of *exo* to *endo* diastereomers decreased (2:1 and 2.6:1, respectively, entries 9 and 10). The Lewis acid by-products, from the preparation of these catalysts were shown to render them ineffective in the thio-Claisen rearrangement and thus the $Ni(PPh_3)_4$ suffers from the same limitations as the Lewis acid catalysis. $Ni(COD)_2$ effected the rearrangement much the same as

Table 1
Thio-Claisen rearrangement of *N,S*-ketene acetal **2a** to thiolactam **3a** with palladium and nickel catalysts

Entry	Catalyst (10 mol %)	Temp (°C)	Time (h)	d.r. ^a <i>exo:endo</i> 3a	Yield ^b of 3a (%)
1	no catalyst	140		>99:1 ^c	48
2	PdCl ₂ (MeCN) ₂	25	28	3.0:1	65
3	PdCl ₂ (Ph ₃ P) ₂	25	18	3.2:1	57
4	Pd(OAc) ₂	25	18	3.3:1	54
5	PdCl ₂ (dppf)	25	17	3.0:1	64
6	Pd(Ph ₃ P) ₄	25	17	3.4:1	64
7	Pd ₂ (dba) ₃	25	15	5.6:1	58
8	NiCl ₂ (Ph ₃ P) ₂	25	16	4:1	58
9	Ni(Ph ₃ P) ₄ /LiCl	25	24	2.6:1	46
10	Ni(Ph ₃ P) ₄ /ZnCl ₂	25	24	2:1	59
11	Ni(COD) ₂	25	16	3.3:1	63

^aRatio determined by ¹H NMR, ^bIsolated Yield of the major *exo* diastereomer, ^cRatio determined by GC.

palladium to provide the thiolactam **3a** in a 3.3:1 mixture of *exo:endo* diastereomers (entry 11). Solvent changes resulted in little change in product ratios.

The prenyl bromide derived *N,S*-ketene acetal **2b** underwent a [3,3]-sigmatropic rearrangement with both palladium and nickel catalysts to afford thiolactam **3b** bearing vicinal quaternary stereogenic centers. In all the examples the rearrangement occurred with high diastereoselectivity (>20:1, *exo:endo*) and good chemical yield although heating to 65°C in THF was required (Table 2, entries 2–5 and 8). The ¹H NMR spectrum derived from the crude mixture indicated the presence of a single diastereomer corresponding to the rearrangement to the *exo* (β) face of the bicyclic system. Again, in the case of the Ni(PPh₃)₄ (entries 6 and 7), the ratio of *exo:endo* diastereomers decreased dramatically due to the presence of Lewis acid by-products. However, it is noteworthy that in entries 6 and 7 the rearrangement occurred at room temperature.

Table 2
Thio-Claisen rearrangement of *N,S*-ketene acetal **2b** to thiolactam **3b** with palladium and nickel catalysts

Entry	Catalyst (10 mol %)	Temp (°C)	Time (h)	d.r. ^a (<i>exo:endo</i>) 3b	Yield ^b of 3b (%)
1	no catalyst	140		>99:1 ^c	68
2	PdCl ₂ (MeCN) ₂	65	36	>20:1	65
3	PdCl ₂ (dppf)	65	48	>20:1	66
4	Pd ₂ (dba) ₃	65	36	>20:1	50
5	NiCl ₂ (Ph ₃ P) ₂	65	37	>20:1	62
6	Ni(Ph ₃ P) ₄ /LiCl	65	24	2.2:1	40
7	Ni(Ph ₃ P) ₄ /ZnCl ₂	65	24	3:1	63
8	Ni(COD) ₂	65	44	>20:1	70

^aRatio determined by ¹H NMR, ^bIsolated yield of major *exo* diastereomer, ^cRatio determined by GC.

The stereochemistry of products **3a** was shown to be identical to that observed from the thermal [3,3]-sigmatropic rearrangement indicating palladium(II) most likely catalyzes the rearrangement through a chair transition state.¹² Rationale for the stereoselective outcomes is presented below (Figs. 1 and 2). The palladium(II) pathway⁵ (Fig. 1) coordinates to the double bond of **2a** and subsequent nucleophilic attack of the thioenol ether provides a six-membered palladated intermediate **5** which undergoes elimination

of Pd(II) to afford the [3,3] rearranged thiocarbonyl **3a**. The palladium(0) pathway (Table 1, entry 6) is shown in Fig. 2. The low selectivity shown by *N,S*-ketene acetal **2a** may be due to the proximity of Pd and the phenyl group in **5** (Fig. 1), or the regioselectivity in thioenolate addition to the π -allyl complex in **6** (Fig. 2).¹³

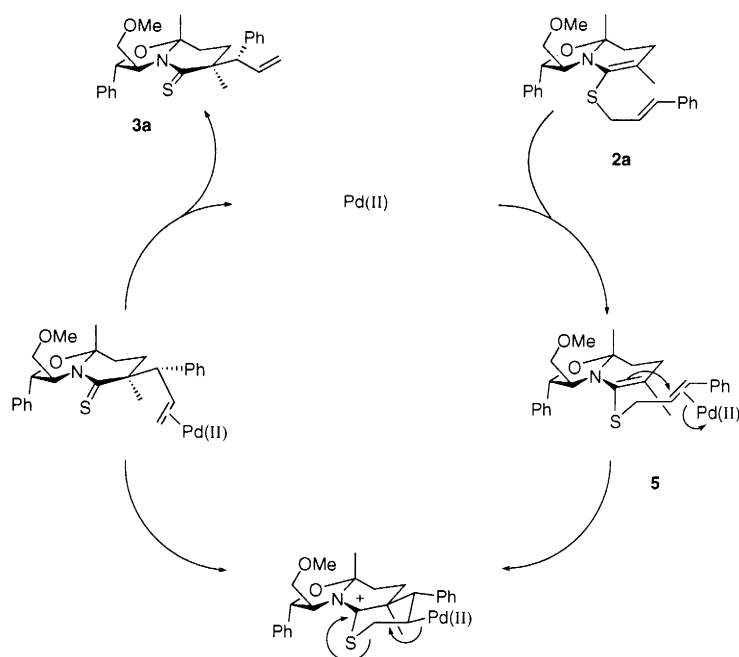


Fig. 1.

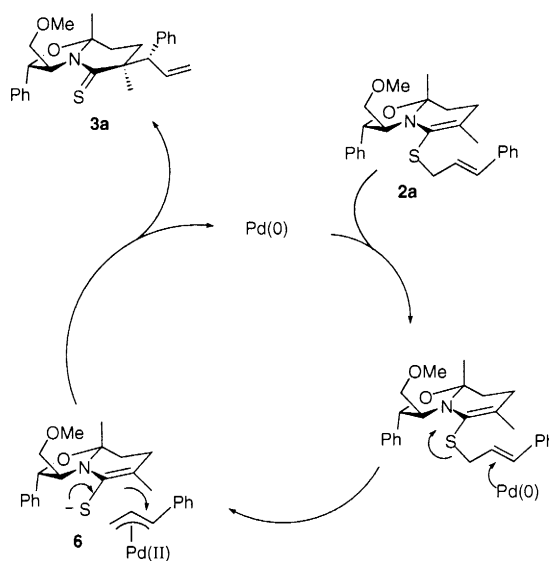
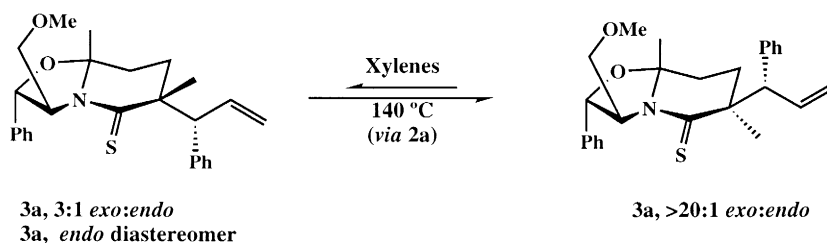


Fig. 2.

Thio-Claisen rearrangements derived from a thio ketone have been reported to be reversible.¹⁴ However, [3,3]-sigmatropic rearrangements from thioamides are rarely reversible.² When we subjected both the 3:1 mixture and the pure *endo* diastereomer **3a** to thermal conditions (xylenes, 140°C, 12 h), we

observed excellent conversion via *N,S*-ketene acetal **2a**, providing >95% of the major *exo* diastereomer **3a** (Scheme 2). This further supports the reversibility of the thio-Claisen rearrangement,² and the thermodynamic preference of the *exo* diastereomer **3a**.



Scheme 2.

In summary, we have shown that the thio-Claisen, [3,3]-rearrangement proceeds efficiently, with moderate stereoselectivity in the presence of Lewis acids, Pd, and Ni catalysts. The mild conditions required to bring this about may find broad applications for thermally sensitive compounds.

Acknowledgements

The authors are grateful to the National Institutes of Health for support of this work. A postdoctoral fellowship from Merck is gratefully acknowledged (PND).

References

- (a) Devine, P. N.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 2633. For reviews of the chemistry of bicyclic lactams, see: (b) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (c) Meyers, A. I.; Brengal, G. P. *J. Chem. Soc., Chem. Commun.* **1997**, 1.
- Lemieux, R. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1998**, *120*, 5453.
- Lemieux, R. M.; Devine, P. N.; Mechelke, M. F.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 3585.
- (a) Shuwen, H.; Kozmin, S. A.; Rawal, V. H., submitted for publication in *J. Am. Chem. Soc.* (b) Jain, S.; Sinha, N.; Dikshit, D. K.; Anand, N. *Tetrahedron Lett.* **1995**, *36*, 8467. (c) Reddy, K. V.; Rajappa, S. *Tetrahedron Lett.* **1992**, *33*, 7957. (d) Welch, J. T.; Eswarakrishnan, S. *J. Am. Chem. Soc.* **1987**, *109*, 6716. (e) Tamaru, Y.; Furukawa, Y.; Mizutani, M.; Kitao, O.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 3631. (f) Takano, S.; Hirama, M.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 881.
- (a) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579. (b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.
- (a) Sonnenberg, F. M. *J. Org. Chem.* **1970**, *35*, 3166. (b) Narasaka, K.; Bald, E.; Mukaiyama, T. *Chem. Lett.* **1975**, 1041. (c) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 446.
- (a) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *J. Org. Chem.* **1980**, *45*, 5221. (b) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *Tetrahedron Lett.* **1981**, *22*, 4245.
- Auburn, P. R.; Whelan, J.; Bosnich, B. *Organometallics* **1986**, *5*, 1533.
- Tamaru, Y.; Yoshida, Z.; Yamada, Y.; Mukai, K.; Yoshioka, H. *J. Org. Chem.* **1983**, *48*, 1293.
- Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.
- (a) Sasaki, K.; Nakao, K.; Kobayashi, Y.; Sakai, M.; Uchino, N.; Sakakibara, Y.; Takagi, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2446. (b) Henningsen, M. C.; Jeropoulos, S.; Smith, E. H. *J. Org. Chem.* **1989**, *54*, 3015.
- (a) Schenk, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058. (b) Trost, B. M.; Runge, T. A.; Jungheim, L. M. *J. Am. Chem. Soc.* **1980**, *102*, 2840.
- For a discussion on nucleophilic attack on η^3 -allyl complexes, e.g. **6**, see: Harrington, P. J. In *Comprehensive Organometallic Chemistry*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds. Transition metal allyl complexes. Hegedus, L. S., Ed.; Pergamon, Elsevier Science Ltd: New York, 1995; Vol. 12.
- (a) Beslin, P.; Lagain, D.; Vialle, J. *J. Org. Chem.* **1980**, *45*, 2517. (b) Metzner, P.; Pham, T. N.; Vialle, J. *J. Chem. Res.* **1978**, 478.