

Enantioselective Palladium(II)-Catalyzed Formal [3,3]-Sigmatropic Rearrangement of 2-Allyloxypyridines and Related Heterocycles[†]

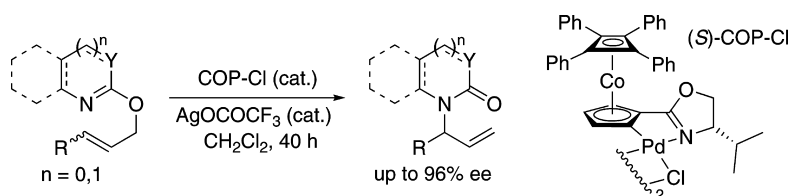
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ABSTRACT



Enantioselective palladium(II)-catalyzed formal [3,3]-sigmatropic rearrangement of (*E*)- and (*Z*)-allyloxy substituted *N*-heterocycles generates *N*-allyl *N*-heterocyclic amides in good yields and high enantioselectivities (up to 96% ee). The chiral palladacycle COP-Cl (5 mol %) is used as a catalyst with silver(I) trifluoroacetate (10 mol %) at 35–45 °C. Examples of heterocycles synthesized include 2-pyridones, quinolin-2(1*H*)-ones, and isoquinolin-1(2*H*)-ones.

Methods for the asymmetric synthesis of chiral amines, particularly those bearing a stereocenter α to the nitrogen atom, are of considerable importance due to their presence in natural products and pharmacologically active compounds. Most approaches have focused upon the asymmetric synthesis of chiral primary or secondary amines, as well as α -amino acids.¹ In contrast, direct approaches toward the enantioselective synthesis of *N*-substituted heterocycles, possessing a stereocenter α to the heterocyclic nitrogen atom, are much less well explored. Conventional approaches to chiral amine synthesis cannot often be directly applied to these *N*-heterocycles, whereas indirect approaches, involving conversion of chiral amines into the *N*-heterocycles, often lack generality or occur in poor yields. One representative class of such compounds are *N*-substituted 2-pyridones, members of which possess interesting biological and pharmacological properties, as exemplified by human rhinovirus

(HRV) protease inhibitor **1**,² glucokinase activator **2**,³ and the naturally occurring angiotension-converting enzyme inhibitors A58365A and A58365B⁴ (Figure 1). Synthetic approaches to these compounds have relied upon the indirect synthesis of the pyridone ring from chiral amines.^{2,3,5}

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[†] Dedicated to Prof. George Fleet on the occasion of his 65th birthday.

(1) (a) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290–4299. (b) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584–4671.

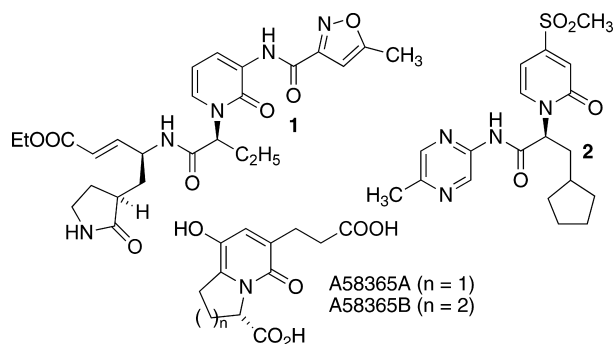
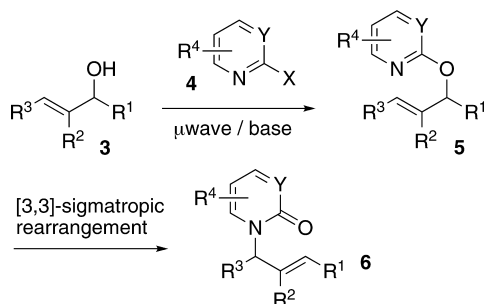


Figure 1. Examples of chiral 2-pyridones.

Direct approaches for the asymmetric synthesis of 2-pyridones and related heterocyclic compounds, therefore, constitute an important challenge. We now report an enantioselective formal [3,3]-sigmatropic rearrangement strategy for the formation of pyridones and other heterocycles using Pd(II) catalysis (Scheme 1). The approach uses readily available

Scheme 1. [3,3]-Sigmatropic Approach to Enantioselective Formation of Chiral 2-Pyridones and Related Heterocycles



allylic alcohols **3** as precursors. Nucleophilic aromatic substitution of heterocycles **4** by **3** was expected to generate allyloxy substituted N-heterocycles **5**, which could then undergo rearrangement to the product heterocycles **6**.

Early studies by Moffett demonstrated thermal [3,3]-sigmatropic rearrangement of 2-allyloxypyridine into *N*-allyl 2-pyridone at 245 °C.⁶ Unfortunately, the high temperature required for this reaction led to competing Cope rearrangement to 3-allylpyridone. Moreover, in the case of thermal rearrangement of *E*-crotyloxypyridine (*R* = Me), a mixture of products arising from [3,3]-sigmatropic rearrangement, Cope rearrangement, and formal [1,3]-sigmatropic rearrangement was observed.^{7,8}

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(8) Similar problems and low yields have been reported in the rearrangements of other 2-allyloxy N-heterocycles, such as tetrachloropyridines, quinolines, isoquinolines, benzoxazoles, benzthiazoles, and tetrazoles. See: (a) Iddon, B.; Hans, S.; Taylor, J. A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2756–2761. (b) Makisumi, Y. *Tetrahedron Lett.* **1964**, *5*, 3822–3838. (c) Win, H.; Tieckelmann, H. *J. Org. Chem.* **1967**, *32*, 59–61. (d) Elwood, J. K.; Gates, J. W., Jr. *J. Org. Chem.* **1967**, *32*, 2956–2959.

The goal of our study was to establish whether enantioselective formal [3,3]-sigmatropic rearrangement of allyloxy substituted N-heterocycles **5** could be achieved using metal catalysis (Scheme 1). Venkataratnam demonstrated that Pd(II)-catalyzed rearrangement of 2-allyloxypyridines at room temperature proceeds cleanly to provide only the desired [3,3]-aza-oxa-Cope products.^{9–11} Furthermore, chiral Pd(II) catalysts have been demonstrated in other enantioselective 3-aza-1-oxa-Cope rearrangements. Overman first demonstrated this strategy in rearrangements of allylic imidates to allylic amides.^{12,13} The strategy was also extended to related reactions, such as the enantioselective rearrangements of *O*-allyl carbamothioates to *S*-allyl carbamothioates¹⁴ and of allyloxy iminophospholindines to allyl phosphoramides.^{15,16} These enantioselective variants have mainly used the commercially available palladacyclic Pd(II) catalyst COP–Cl¹⁷ and related chiral palladacycle catalysts (Figure 2).

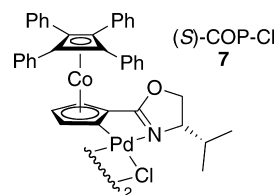


Figure 2. Planar chiral Pd(II) complex (*S*)-COP–Cl **7**.

Allyloxypyridine (*E*)-**8a** was chosen as a test substrate for the rearrangements and was accessed through a nucleophilic

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(10) Pd(0)-catalyzed rearrangement of *E*-crotyloxypyridine leads to a mixture of both formal [1,3]- and [3,3]-sigmatropic rearranged products, whereas Pd(II) leads to clean [3,3]-rearrangement: Itami, K.; Yamazaki, D.; Yoshida, J. *Org. Lett.* **2003**, *5*, 2161–2164.

(11) Limited success was found using Lewis acid and transition metal catalyzed reactions, such as with SnCl₄, BF₃·OEt₂, H₂PtCl₆, and Pt(PPh₃)₄. See: (a) Stewart, H. F.; Seibert, R. P. *J. Org. Chem.* **1968**, *33*, 4560–4561. (b) Balavoine, G.; Guibe, F. *Tetrahedron Lett.* **1979**, *41*, 3949–3952.

(12) For a general overview of the Overman rearrangement, see: Overman, L. E.; Carpenter, N. E. *The Allylic Trichloroacetimidate Rearrangement*. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: Hoboken, NJ, 2005; Vol. 66, pp 1–107. See also: Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597–643.

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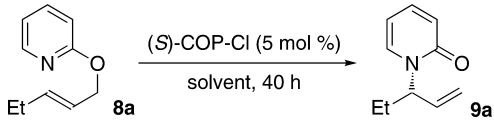
(15) Lee, E. E.; Batey, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 14887–14893.

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aromatic substitution reaction of the corresponding allylic alcohol on 2-bromopyridine. Deprotonation of (*E*)-2-penten-1-ol using NaH and subsequent microwave heating of the alkoxide at 160 °C with 2-bromopyridine led to the desired product in good yield. Initial attempts for the rearrangement of (*E*)-**8a** in CH₂Cl₂ (0.2 M solution) with 5 mol % (*S*)-COP-Cl at room temperature provided the desired product **9a** in low conversion (23%) but good enantioselectivity (90% ee) (Table 1). The rearrangement proved to be clean, with

Table 1. Enantioselective Palladium(II)-Catalyzed Rearrangement of 2-Allyloxypyridine **8a** into **9a**



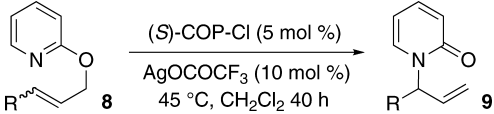
entry	solvent	AgOCOCF ₃	[8a] (M)	temp ^b (°C)	convn (%) ^a	ee (%)
1	CH ₂ Cl ₂	-	0.2	rt	23	90
2	CH ₂ Cl ₂	10 mol %	0.2	rt	31	90
3	CH ₂ Cl ₂	-	1.0	45	92	86
4	CH ₂ Cl ₂	10 mol %	1.0	45	≥98	87
5	MeCN	10 mol %	1.0	45	67	87
6	benzene	10 mol %	1.0	45	≥98	88
7	toluene	10 mol %	1.0	45	88	82

^a Conversion measured by ¹H NMR. ^b Reactions carried out in sealed vessels.

only unreacted starting material observed by ¹H NMR spectroscopy of the reaction mixture. Dechlorination of the (*S*)-COP-Cl catalyst with 10 mol % AgOCOCF₃ under the same conditions afforded a small improvement in conversion (31%) with no change in enantioselectivity (90% ee). Increasing the reaction temperature to 45 °C and substrate concentration to 1.0 M greatly improved the conversions for both rearrangements with (*S*)-COP-Cl and the (*S*)-COP-Cl/AgOCOCF₃ combination (92% and ≥98%, respectively). The increase in temperature also resulted in a slight decrease in enantioselectivity (86% and 87% ee). Rearrangement of (*E*)-**8a** with 5 mol % (*S*)-COP-Cl and 10 mol % AgOCOCF₃ at 45 °C in MeCN resulted in lower conversion (67%), while reaction in toluene provided **9a** in slightly lower enantioselectivity (82% ee). Reaction in benzene provided nearly identical results to that obtained in CH₂Cl₂, and as a result CH₂Cl₂ was selected as the optimal solvent.

The optimized conditions of (*S*)-COP-Cl (5 mol %) and AgOCOCF₃ (10 mol %) at 45 °C in CH₂Cl₂ were applied toward the rearrangement of a variety of allyloxypyridine substrates **8** (Table 2). The requisite substrates **8** were obtained using microwave-assisted nucleophilic aromatic substitution reactions.¹⁸ The (*E*)- and (*Z*)-pyridine substrates **8a** both rearranged with good yield and enantioselectivity at 45 °C (Table 2, entries 1 and 2). The product **9a** was obtained in 83% yield and with 86% ee from (*E*)-**8a**, while

Table 2. Variation in the Rearrangement of Substituted 2-Allyloxypyridines **8** into Chiral 2-Pyridones **9**



entry	substrate	R	product	yield ^a (%)	ee (%) (config)
1	(<i>E</i>)- 8a	Et	9a	83	86 (<i>S</i>)
2	(<i>Z</i>)- 8a	Et	9a	87	96 (<i>R</i>)
3	(<i>E</i>)- 8b	ⁿ Pr	9b	91	85 (<i>S</i>)
4	(<i>Z</i>)- 8b	ⁿ Pr	9b	88	88 (<i>R</i>)
5	(<i>Z</i>)- 8c	ⁿ Hex	9c	92	90 (<i>R</i>)
6	(<i>Z</i>)- 8d	Chx	9d	0	-
7	(<i>E</i>)- 8e	Ph	9e	33	47 (<i>R</i>)
8	(<i>Z</i>)- 8f	CH ₂ OTBDMS	9f	90	88 (<i>S</i>)
9	(<i>Z</i>)- 8g	CH ₂ OTBDPS	9g	88	85 (<i>S</i>)
10	(<i>Z</i>)- 8h	(CH ₂) ₂ OTBDMS	9h	61	83 (<i>R</i>)
11	(<i>Z</i>)- 8i	(CH ₂) ₃ OBn	9i	87	87 (<i>R</i>)
12	(<i>Z</i>)- 8j	(CH ₂) ₂ Ph	9j	93	83 (<i>R</i>)

^a Isolated yields. ^b Reactions carried out in sealed vessels.

the enantiomer was obtained in 87% yield and with 96% ee from substrate (*Z*)-**8a**. Similar results were obtained for the other straight chain aliphatic derived substrates **8b–8c** (Table 2, entries 3–5). The rearrangement reaction is however sensitive to steric effects, and for the more sterically hindered substrate **8d**, bearing a cyclohexyl group, rearrangement did not occur and only starting material was recovered (Table 2, entry 6). The cinnamyl alcohol derived substrate **8e** reacted sluggishly, providing the product **9e** in low yield (33%) and enantioselectivity (47%). The reaction occurred in good yields and enantioselectivities for the TBDMS, TBDPS, and benzyl ether substituted precursors **8f–i** and for the phenylethyl-substituted precursor **8j** (Table 2, entries 8–12). Removal of the TBDMS group from **9f** provided the corresponding alcohol **10**, the absolute configuration of which was determined as (*S*) by X-ray crystallographic analysis (Figure 3). The absolute

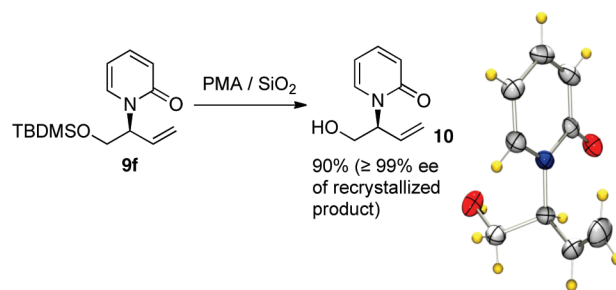


Figure 3. Formation and X-ray crystal structure determination of pyridone **10** to establish (*S*)-absolute stereochemistry of **9f**.

configuration of the other products was assigned by analogy. The absolute sense of stereoinduction matches that observed in previous COP-Cl-based rearrangements.

(18) See the Supporting Information for details.

The success of the enantioselective rearrangement of **8** prompted us to investigate related formal [3,3]-sigmatropic rearrangements of other nitrogen heterocycles (Table 3). In

Table 3. Rearrangement of 2-Allyloxy N-Heterocycles **11** into **12**

$n = 0, 1$ **11** **12**

substrate	<i>E/Z</i>	temp (°C)	product (config)	yield ^a (%)	ee (%)
	(<i>Z</i>)- 11a	35	(<i>R</i>)- 12a	87	91
	(<i>E</i>)- 11b	35	(<i>S</i>)- 12b	75	86
	(<i>Z</i>)- 11b	35	(<i>R</i>)- 12b	85	95
	(<i>E</i>)- 11c	35	(<i>S</i>)- 12c	89	89
	(<i>Z</i>)- 11c	35	(<i>R</i>)- 12c	95	92
	(<i>E</i>)- 11d	45	(<i>S</i>)- 12d	80	83
	(<i>Z</i>)- 11d	45	(<i>R</i>)- 12d	85	92
	(<i>E</i>)- 11e	45	—	— ^b	—
	(<i>Z</i>)- 11e	45	—	— ^b	—

^a Isolated yields ^b No reaction, only starting material observed by ¹H NMR.

the presence of 5 mol % (*S*)-COP-Cl/10 mol % AgOCOCF₃ at 35 °C, pyridine **11a** rearranged to **12a** in good yield and enantioselectivity. Rearrangement of the (*E*)- and (*Z*)-quinoline substrates¹⁹ both occurred in good yields (Table 3). The (*E*)-substrate **11b** produced **12b** in 86% ee, while (*Z*)-**11b** rearranged to the enantiomer in 95% ee. In the case of the isoquinoline substrates **11c**, better reactivity was

(19) Substrates **11a–e** were prepared in a similar fashion to substrate **8** with conventional heating at 50 °C over 40 h instead of microwave heating.

observed for the rearrangement of the (*Z*)-isomer (95% yield, 92% ee) than for the (*E*)-isomer (89% yield, 89% ee). A similar trend in selectivity was observed for the benzothiazole substrates (*E*)- and (*Z*)-**11d** which rearranged in good yield (80% and 85%) and good enantioselectivity (83% and 92% ee, respectively). More electron-deficient heterocycles such as pyrimidine substrates **11e** did not react under the optimal conditions, and only starting material was recovered in these reactions.²⁰

The observation that the rearrangements of **8** and **11** occurred with better selectivity and yield for (*Z*)-substrates than for (*E*)-substrates contrasts those obtained for the Pd(II)-catalyzed rearrangements of allylic trichloroacetimidates^{13f} but is similar to that found for rearrangements of allyloxy iminodiazaphospholidines¹⁵ and allylic *N*-(*p*-methoxyphenyl)benzimidates.²¹

In summary, enantioselective formal [3,3]-rearrangement of 2-allyloxy N-heterocycles occurs in good yields and high enantioselectivities (up to 96% ee) using the commercially available chiral palladacycle COP-Cl. The (*Z*)-substrates show greater reactivity than the (*E*)-substrates, and the control of absolute stereochemistry in the products is analogous to that obtained for other COP-Cl-based formal [3,3]-sigmatropic rearrangements. Further applications of these methods and related chemistry will be reported in due course.

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Supporting Information Available: Detailed descriptions of experimental procedures. Spectroscopic data of all new compounds, chiral HPLC data, and an X-ray crystallographic information file for **10** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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