Enantioselective palladium catalyzed allylic substitution of acyloxypyrrolinones by alcohols

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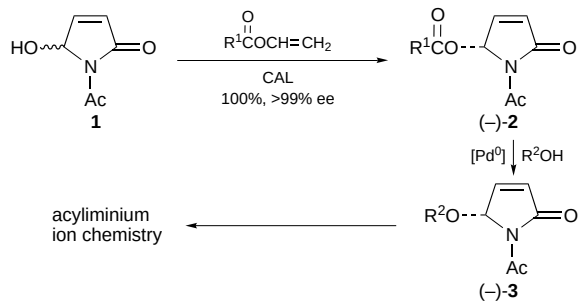
Chiral non-racemic acyloxypyrrolinones are converted into alkoxypyrrolinones with retention of configuration by a palladium catalyzed allylic substitution; this comprises a key step in a short chemo-enzymatic route to acyliminium ion precursors.

Enantiomerically pure alkoxypyrrolinones have been shown to be facile building blocks for a variety of stereoselective syntheses involving Diels–Alder cycloadditions, 1,3-dipolar reactions, conjugate additions and acyliminium ion intermediates.[1] In particular application in the asymmetric synthesis of alkaloids, based on *N*-acyliminium ion chemistry, is of great current interest.[2] For example, (*R*)-1-acetyl-5-isopropoxy-3-pyrrolin-2-one [compound (−)-**3a** (R^2 = Pr^i) in Scheme 1] has been used by Hiemstra and Speckamp as an intermediate in the synthesis of gelsemine.[3] However, the stereoselective synthesis from (*S*)-malic acid[4] is laborious and more practical routes would be desirable.

Recently we reported simple and efficient enzymatic methodology to obtain enantiomerically pure acyloxypyrrolinones **2** from hydroxypyrrolinones **1**.[5] In this process both enantiomers of an acyloxypyrrolinone can be obtained by the same enzyme (*Candida antarctica* lipase, CAL) using either an esterification (Scheme 1) or a transesterification. Although these compounds have been applied with success in various stereoselective transformations,[6] they are not suitable as acyliminium ion precursors. In order to generate an acyliminium ion the acyl group on nitrogen must be removed.[4] This is possible with an alkoxy group at the 5-position but not with a more sensitive acyloxy group. We now report that the enzymatic method can be combined with a palladium catalyzed allylic substitution to generate optically active alkoxypyrrolinones, which can readily be transformed to acyliminium ion precursors.[4]



Scheme 1

When a solution of (*R*)-(−)-**2a** (R^1 = Me) in Pr^iOH is stirred at room temperature for 7 h in the presence of 0.5 mol% $Pd(PPh_3)_4$, 5-isopropoxy derivative (*R*)-(−)-**3a** (R^2 = Pr^i) is obtained in 99% yield with 95% ee (Table 1, entry 1).‡ The optically active acyloxypyrrolinone is thus converted into optically active alkoxypyrrolinone, *via* Pd^0 catalyzed allylic substitution with Pr^iOH as the nucleophile, with nearly complete *retention of configuration*. An allyl palladium intermediate **5** (Scheme 2) is presumably involved. When the reaction was performed in the presence of $Pd(OAc)_2$ (5 mol%) and PPh_3 (20 mol%) the reaction rate was appreciably lower (90% conversion after 3 d at 20 °C, > 95% ee). An essential feature is that the nucleophile Pr^iOH is also used as a solvent (roughly 13 M). In the presence of an additional solvent like THF (Pr^iOH *ca.* 10^{-1} M) no product was obtained after 18 h at room temp. When the allylic substitution was performed at higher temperatures, the reaction was very fast, but the enantioselectivity decreased in the course of the reaction (Table 2). This depletion of ee might be due either to loss of stereochemical integrity of the allyl palladium intermediate or partial racemization of acyloxypyrrolinone **1** or alkoxypyrrolinone **3**.

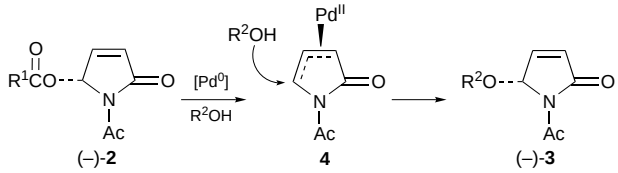
The substitution using $Pd(PPh_3)_4$ can easily be performed on a gram scale with equal efficiency (99%) and selectivity (94% ee). A lower rate was observed in the presence of additional PPh_3, probably because the equilibrium for the oxidative addition of the palladium complex is shifted to the left (Scheme 2).[7] The effect on the enantioselectivity is negligible.

When EtOH was used instead of Pr^iOH as a nucleophile the reaction was much faster, probably because of the higher

Table 1 Pd catalyzed nucleophilic substitution of (−)-**2** (> 99% ee)

Entry	R^1	R^2	*T*/°C	Catalyst	*t*/h	Conversion[a] (%)	Ee[b] (%)
1[c]	Me	Pr^i	25	$Pd(PPh_3)_4$ (0.5%)	7	99	95
2[c]	Me	Pr^i	25	$Pd(PPh_3)_4$ (0.5%)	5.5	72	97
3[c]	Me	Et	18	$Pd(PPh_3)_4$ (5%)	1	100	93
4[d]	Allyl	Pr^i	20	$Pd(OAc)_2 + PPh_3$ (5%)	63	100	83
5[d]	C_9H_{19}	Pr^i	20	$Pd(OAc)_2 + PPh_3$ (10%)	63	40	84
6[d]	Bu^t	Pr^i	20	$Pd(OAc)_2 + PPh_3$ (5%)	48	29	95
7[d]	Ph	Pr^i	20	$Pd(OAc)_2 + PPh_3$ (5%)	18	33	93
8	Me	Pr^i	25	$Pd(MeCN)_2Cl_2 + PPh_3$ (5%)	21	100	89
9	Me	Pr^i	25	$Pd(MeCN)_2Cl_2$ (5%)	3	99	> 99
10	Me	Et	25	$Pd(MeCN)_2Cl_2$ (5%)	3	94	99

[a] The conversion was determined by GC. [b] The ee of **3** was determined by chiral GC; > 99% indicates that the other enantiomer could not be detected. [c] (+)-**2** (> 99% ee) was used as starting material. [d] The ee of starting material **2** is unknown.



Scheme 2

Table 2 Pd catalyzed nucleophilic substitution of (+)-**2a** (R^1 = Me) at 70 °C[a]

Entry	*t*/min	Conversion[b] (%)	Ee[c] (%)
1	5	43	90
2	25	91	79
3	40	100	75

[a] $Pd(OAc)_2$ + PPh_3 (5%) was used as catalyst, Pr^iOH was used as solvent. [b] The conversion was determined by GC. [c] The ee of (+)-**3a** (R^2 = Pr^i) was determined by chiral GC.

solubility of the substrate in this solvent. A slight decrease in selectivity (93% ee) was observed (Table 1, entry 3).

This reaction can also be performed with acyloxypyrrolinones with other acyl groups (Table 1, entry 4–7). The optically active starting materials were obtained *via* enzymatic esterification, analogously to our reported procedure.[5] Because a method for direct ee determination of these 5-acyloxypyrrolinones has not yet been found, the palladium catalyzed allylic substitution and subsequent ee determination of the 5-isopropoxy pyrrolinone provides a useful alternative for determination of the ee of the starting materials.

Other palladium catalysts were also examined as the use of $Pd(PPh_3)_4$ did not result in complete stereoselectivity (95–97% ee). $PdBn(PPh_3)_2Cl$ gave, under the same conditions in Pr^iOH, less than 5% conversion in 23 h (71% ee), whereas with $Pd(dppe)_2$ no product was obtained. Palladium(II) complexes such as $Pd(OAc)_2$ were also tested without PPh_3. In this case the reaction did not proceed, but surprisingly when LiCl was added 22% conversion was found after 23 h (42% ee). A mixture of $Pd(MeCN)_2Cl_2$ (5 mol%) and PPh_3 (20 mol%) was also used, but although this reaction was faster than with $Pd(OAc)_2$ and PPh_3 (100% conversion in 21 h), the selectivity was not improved (Table 1, entry 8). A remarkable improvement was achieved when $Pd(MeCN)_2Cl_2$ (5 mol%) was used without PPh_3. With this catalyst the reaction is fast, quantitative and proceeds with complete stereoselectivity (Table 1, entries 9, 10). On 0.5 g scale with 5 mol% Pd^{II} catalyst, 96% yield of (*S*)-**3a** (R^2 = Pr^i, 99% ee) was obtained.

Palladium catalyzed nucleophilic substitution reactions of allylic substrates have found widespread use in organic synthesis and although a variety of nucleophiles has been employed emphasis has been on carbon–carbon bond formation.[8] On the contrary the use of alcohols as nucleophiles in Pd catalyzed allylic substitution is rare, because alcohols are generally considered poor nucleophiles. The few reported examples[9] are often either intramolecular substitutions or make use of derivatives of alcohols. The quantitative and stereoselective Pd catalyzed allylic substitution of 5-acyloxypyrrolinones by alcohols provides a key step in the new catalytic enantioselective, lipase and palladium based methodology for the preparation of enantiopure alkoxypyrrolinones.

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Notes and References

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‡ Ee's were determined with a Hewlett Packard 5890 GC, equipped with a capillary column coated with CP cyclodextrin B-2,3,6-M-19 (for **3a**, R = Pr^i) or with a 30 m × 0.25 mm capillary column (ASTEC G9409-15) coated with B-TA (β-cyclodextrin, trifluoroacetyl) (for **3b**, R = Et).

Selected data for **3a**: $[\alpha]_D^{25}$ −149 (*c* 0.5, $CHCl_3$); $\delta_H(CDCl_3)$ 1.15 (d, 3 H, *J* 8.8), 1.18 (d, 3 H, *J* 8.8), 2.49 (s, 3 H), 4.23 (sept, 1 H, *J* 6.1), 5.92 (d, 1 H, *J* 2.0), 6.06 (d, 1 H, *J* 6.1), 6.97 (dd, 1 H, *J* 2.0, 6.1); $\delta_C(CDCl_3)$ 22.8 (q), 23.0 (q), 24.9 (q), 73.0 (d), 86.3 (d), 126.8 (d), 147.7 (d), 168.7 (s), 170.0 (s).

1 D. Romo and A. I. Meyers, *Tetrahedron*, 1991, **47**, 9503; A. H. Fray and A. I. Meyers, *Tetrahedron Lett.*, 1992, **33**, 3575; A. I. Meyers and L. Snyder, *J. Org. Chem.*, 1992, **57**, 3814; W.-J. Koot, H. Hiemstra and W. N. Speckamp, *Tetrahedron: Asymmetry*, 1993, **4**, 1941; W.-J. Koot, R. van Ginkel, M. Kranenburg, H. Hiemstra and W. N. Speckamp, *Tetrahedron Lett.*, 1991, **32**, 401.
2 P. Renaud and D. Seebach, *Helv. Chim. Acta*, 1986, **69**, 1704; M.-P. Heitz and L. E. Overman, *J. Org. Chem.*, 1989, **54**, 2591; M. Thaning and L.-G. Wistrand, *J. Org. Chem.*, 1990, **55**, 1406.
3 N. J. Newcombe, F. Ya, R. J. Vijn, H. Hiemstra and W. N. Speckamp, *J. Chem. Soc., Chem. Commun.*, 1994, 767.
4 W.-J. Koot, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.*, 1992, **57**, 1059.
5 H. van der Deen, A. D. Cuiper, R. P. Hof, A. van Oeveren, B. L. Feringa and R. M. Kellogg, *J. Am. Chem. Soc.*, 1996, **118**, 3801.
6 A. D. Cuiper, R. M. Kellogg and B. L. Feringa, unpublished work.
7 B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1980, **102**, 4730.
8 J. Tsuji, in *Palladium Reagents and Catalysts*, Wiley, Chichester, 1995, ch. 4.
9 B. M. Trost and A. Tenaglia, *Tetrahedron Lett.*, 1988, **29**, 2927; R. C. Larock and N. H. Lee, *J. Org. Chem.*, 1991, **56**, 6253; F. Guibe and Y. Saint M'Leux, *Tetrahedron Lett.*, 1981, **22**, 3591; R. Lakhmiri, P. Lhoste and D. Sinou, *Synth. Commun.*, 1990, **20**, 1551; A. P. Davis, B. J. Dorgan and E. R. Mageean, *J. Chem. Soc., Chem. Commun.*, 1993, 492.

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