DOI: 10.1002/anie.200903908

Palladium Catalysis

The Newman–Kwart Rearrangement of *O*-Aryl Thiocarbamates: Substantial Reduction in Reaction Temperatures through Palladium Catalysis**

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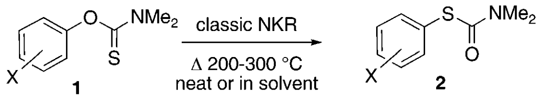
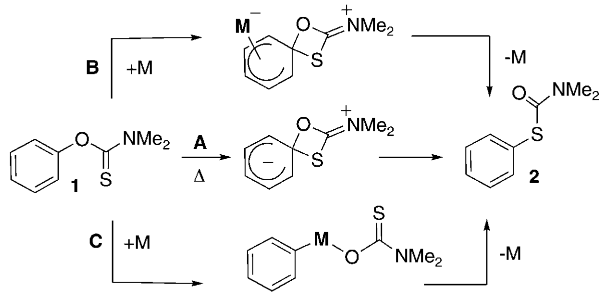
Thermally induced $O_{Ar} \rightarrow S_{Ar}$ migration in aryl thiocarbamates (**1**→**2**, Scheme 1)[1] is commonly referred to[2] as the Newman–Kwart rearrangement ("NKR")[3] and belongs to a group of rearrangements that generate Ar–S/N compounds from phenols.[4] Of these, only the NKR has been extensively utilized,[1] with applications as broad-ranging as medicinal chemistry,[5] chiral ligand synthesis,[6] supramolecular chemistry,[7] molecular switches,[8] molecular rods,[9] dendrimers,[10] organocatalysts[11] and helicenes.[12] The NKR has also been applied industrially,[1,5] more recently by applying microwave[13,14a] and flow-reactor technologies.[14]



Scheme 1. Classic thermal Newman–Kwart rearrangement (NKR).[1,2]

There are many favorable aspects to NKR,[1] including: 1) the facile generation of **1** from the corresponding phenol, a moiety that is readily accessible and is often commercially available;[15] 2) simple hydrolysis of **2** liberates the thiol, ArSH; 3) the thiocarbamate group provides both the Ar–O activation and the source of sulfur—no additional reagents are required; and 4) **1** and **2** are usually highly crystalline,[13c] aiding handling and purification.

The one major drawback to NKR is that high temperatures (200–300 °C) are required to access the strained 1,3-oxathietane transition state (see mechanism **A**,[1,16] Scheme 2). Not only do such high temperatures present issues in terms of practicality and safety, but they can also induce "charring" and other undesired side reactions, meaning that fragile substrates are not amenable to the harsh reaction conditions.[17] Clearly any significant reduction in reaction temperature would be advantageous. Herein we report on the development of the first catalyst[18,19] for the NKR **1**→**2**, facilitating rearrangement at substantially lower temperatures.



Scheme 2. Strategies for catalysis (**B**, **C**) of the thermal NKR (**A**).

We considered two distinct approaches to facilitate catalysis of the reaction. In the first (**B**, Scheme 2) a π-acid "M" could be used to increase the electrophilicity of the aryl ring, thus lowering the barrier to 1,3-oxathietane generation.[16,18] Choosing one of the most active substrates for NKR, X = p-NO_2 (**1a**) which undergoes thermal NKR at 180 °C,[3b] a range of cationic and neutral Lewis acids were explored in this regard and whilst some success was obtained with Ni and Mg complexes, the catalytic effects were specific to **1a**[20] suggesting that activation is by complexation to the NO_2 group,[21,22] not to the aromatic ring π-system.

We then explored an alternative strategy[18b] (**C**) in which the Ar–O bond is cleaved by insertion of a low-valent metal "M", with the thiocarbamate tautomer facilitating reductive elimination of M as the new Ar–S bond is formed. Given the known oxidative addition of Pd^0 complexes to arylsulfonates,[23] we tested a range of simple phosphine ligands in combination with 10 mol % Pd^0 in *N,N*-dimethylacetamide at 70 °C (P/Pd = 2). Of these ligands, $t\mathrm{Bu}_3\mathrm{P}$ was uniquely effective, giving rise to 47 % **2a** after 24 h. The effect of solvent was then explored and from *N,N*-dimethylacetamide, MeCN, CH_2Cl_2, THF, $PhCF_3$ and toluene, the latter was found to be by far the most effective, allowing quantitative conversion of **1a** at 100 °C in 2.5 h with just 2 mol % Pd (Scheme 3, and Table 1, entries 1–4). In the absence of catalyst, there was no detectable rearrangement.

The $[\mathrm{Pd}(t\mathrm{Bu}_3\mathrm{P})_2]$ catalyst was tested with a small range of simple aryl thiocarbamates (**1a**–**h**, 100 °C, toluene, Table 1, entries 5–11). In all cases rearrangement was catalyzed, allowing NKR at a substantially lower temperature than

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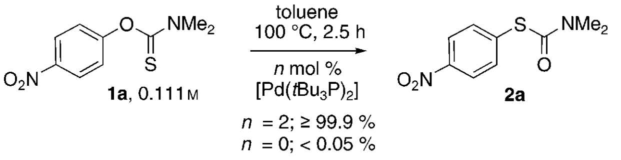
[**] We thank AstraZeneca Global PR&D for generous funding and Dr. Ross T. Burn (AZ) for assistance with MS analysis. G.C.L.-J. is a Royal Society Wolfson Research Merit awardee.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200903908.



Scheme 3. Palladium-catalyzed NKR of thiocarbamate **1a**. Conversions determined by HPLC; limits of detection 0.05%.

Table 1: Pd-catalyzed NKR versus standard thermal conditions.[3b,13a]

Entry	Ar=	Catalyzed[a]		Thermal[b]
		t [h]	Conv.,[c] T	T
1[d]	p-NO$_2$-C$_6$H$_4$ (**1a**)[e]	24	3%, 21°C	180°C
2[d]	p-NO$_2$-C$_6$H$_4$ (**1a**)[e]	24	15%, 50°C	180°C
3[d]	p-NO$_2$-C$_6$H$_4$ (**1a**)[e]	24	66%, 70°C	180°C
4[d]	p-NO$_2$-C$_6$H$_4$ (**1a**)[e]	2.5	>99%, 100°C	180°C
5[d]	p-CN-C$_6$H$_4$ (**1b**)[e]	4	>99%, 100°C	220°C
6[d]	p-CF$_3$-C$_6$H$_4$ (**1c**)[e]	4	>99%, 100°C	260°C
7[f]	p-F-C$_6$H$_4$ (**1d**)[g]	21	98%, 100°C	>295°C
8[d]	p-CO$_2$Me-C$_6$H$_4$ (**1e**)[g]	12	>99%, 100°C	240°C
9[h]	p-Me-C$_6$H$_4$ (**1f**)[g]	14	90%, 100°C	>295°C
10[i]	p-MeO-C$_6$H$_4$ (**1g**)[g]	14	92%, 100°C	>295°C
11[d]	2-C$_{10}$H$_7$ (**1h**)[e]	4	>99%, 100°C	285°C

[a] Catalyst [Pd(tBu$_3$P)$_2$], 100°C, **1a–h** in toluene. [b] Ref. [3b,13a]. [c] Conversion determined by HPLC analysis. [d] 2 mol% Pd. [e] 0.111 M. [f] 4 mol% Pd. [g] 0.221 M. [h] 6 mol% Pd. [i] 8 mol% Pd.

that required for the standard thermal conditions. Electron-rich substrates, which are less reactive in the standard NKR,[3b] were also less susceptible to catalysis. Nonetheless, in no cases were any side-products detected, and the reaction was readily scaled up. For example, 2 g of naphthyl substrate **1h** (1.8 M in toluene, 2 mol% [Pd(tBu$_3$P)$_2$], 100°C, 4 h, >99%) gave analytically pure **2h** in 90% isolated yield. In comparison, the uncatalyzed rearrangement requires heating to 285°C and affords 80% **2h**.[3b]

The mechanism of the [Pd(tBu$_3$P)$_2$]-catalyzed reaction of **1a** was investigated. Reaction rates displayed a predominantly first-order dependency on both [**1a**] and [Pd] with a slight acceleration, not inhibition, on addition of excess tBu$_3$P ligand.[24] Reaction of a mixture of [^{2}H$_2$]-**1a** and [^{18}O$_1$]-**1a**, produced not only the expected isotopologues [^{2}H$_2$]-**2a** and [^{18}O$_1$]-**2a**, but also generated unlabelled **2a** and double-labelled [^{2}H$_2$,^{18}O$_1$]-**2a** (Figure 1) through cross-over of the thiocarbamoyl moiety with the aromatic ring.[24]

The cross-over is only partial (30–50% of maximum), increasing throughout reaction and becoming substantial at high conversions. This eliminates sole turnover through [Pd–S(CO)NMe$_2$] or [Pd–Ar] carriers, which would lead to full (100%) cross-over throughout the reaction. Control experiments, including labelled products, e.g. [^{2}H$_6$,^{34}S]-**2a**, showed that there is no exchange in the substrate (**1a**), and very little exchange in the product (**2a**), during the main phase of reaction. However, as **1a** becomes depleted, scrambling in **2a** begins to contribute extensively, leading to the steep upward curvature in Figure 1.[26] The extent of cross-over during productive turnover (**1a**→**2a**) increases with Pd concentration and decreases when excess tBu$_3$P ligand is added. In conjunction with the reaction kinetics, these factors suggest aggregation, for example, dimerization, of the catalyst resting state, which is attenuated by **1a** and by tBu$_3$P.

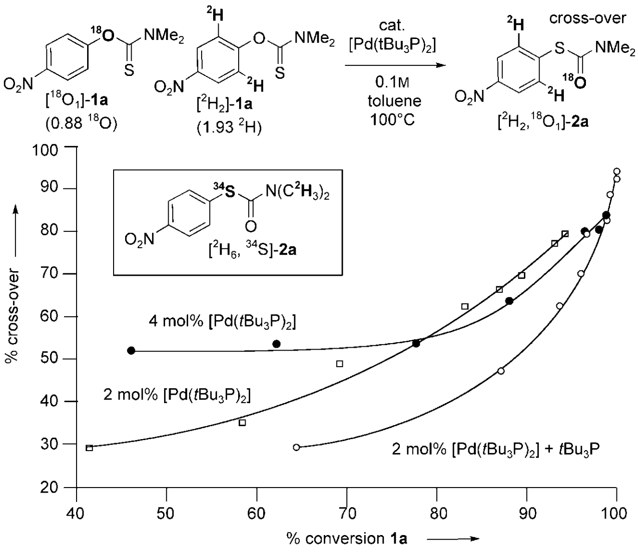
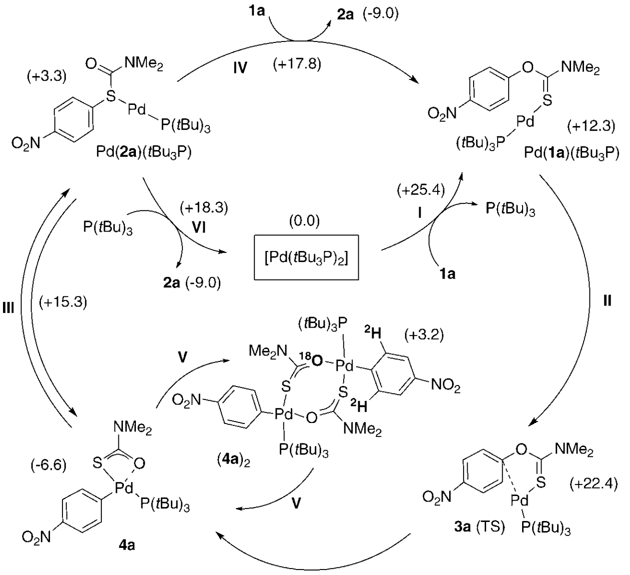


Figure 1. Effect of [Pd] and [tBu$_3$P] on the extent of maximum cross-over [%] as a function of conversion (x-axis) of [^{18}O$_1$]-**1a** and [^{2}H$_2$]-**1a**. The lines through data points are solely an aid to the eye.

Analysis of the [Pd(tBu$_3$P)$_2$]-catalyzed NKR of **1a** by DFT (B3LYP/6-31G*/lacv3p)[24] suggests that catalyst activation proceeds through associative substitution (**I**, Scheme 4) of tBu$_3$P by substrate **1a** (a dissociative mechanism may also be possible).[27] Coordination of Pd to the thiocarbonyl sulfur of **1a** in the resulting Pd^0 species [Pd(**1a**)(tBu$_3$P)] was found to facilitate oxidative insertion (**II**) into the Ar–O bond through a five-membered (-S-Pd-C$_{Ar}$-O-C(=O)-) transition state (**3a**). Extensive attempts to locate a three-membered (Pd-C$_{Ar}$-O) transition state for a conventional oxidative addition process[28] were unsuccessful; this TS may exist but would



Scheme 4. Working model for Pd-catalyzed NKR of **1a** to **2a**. Numbers in parenthesis are DFT-derived ZPE corrected energies in kcal mol^{-1}.

certainly lie at higher energy. The predicted on-cycle resting state is a κ^2-S(CO)NMe$_2$ intermediate (**4a**), which can undergo reversible reductive elimination (**III**) to give a [Pd(**2a**)(tBu$_3$P)] complex through a more conventional three-membered TS. Substitution of **2a** by **1a** leads, in the predicted turnover-limiting step (**IV**), to product (**2a**) with the regeneration of [Pd(**1a**)(tBu$_3$P)]. Intermediate **4a** can also cross-over (**V**) through the corresponding μ-O,S-bound dimer (**4**)$_2$. The equilibration of the resting state between (**4a**)$_2$ and [Pd(**2a**)(tBu$_3$P)] accounts for the extent of cross-over increasing with both conversion (decreasing [**1a**]) and catalyst loading (increasing [**4**]). The TS for substitution of product (**2a**) in [Pd(**2a**)(tBu$_3$P)] by tBu$_3$P (**VI**) is only 4 kcal mol^{-1} higher in energy than that involving **1a** (**IV**). The extent of cross-over, particularly at high conversions of **1a**, can thus be attenuated by added tBu$_3$P.

In summary, we report the first catalyst for the Newman–Kwart rearrangement (**1**→**2**),[1] an efficient reaction for generation of Ar–S compounds from phenols. This reaction normally requires high temperatures (200–300 °C), but in the presence of [Pd(tBu$_3$P)$_2$] proceeds smoothly at 100 °C with a range of substrates (Table 1, entries 4–11). Substrates such as **1a** which bear activating electron-withdrawing substituents, rearrange, albeit inefficiently, at temperatures as low as 21 °C (entry 1). Preliminary investigations suggest that a thio-coordinated monophosphine–palladium complex, [Pd(**1**)(tBu$_3$P)], engages in an oxidative addition/tautomerisation/reductive elimination sequence,[18,29] and that the latter parts of the cycle are readily accessible through re-insertion of Pd into the C$_{\mathrm{Ar}}$–S bond of **2a**.[26] The steric bulk in tBu$_3$P appears to favour loss of one phosphine from [Pd(tBu$_3$P)$_2$]; nonetheless other ligands, and indeed metals, may be more effective. The thiocarbamate moiety, although readily installed and inexpensive,[15] is not the ideal partner for the catalytic events; other Ar-OC(X)-R species may undergo catalyzed rearrangement at much lower temperatures.[30] We are currently exploring these aspects in detail.

Received: July 16, 2009

Keywords: homogeneous catalysis · palladium · reaction mechanism · rearrangement · sulfur compounds

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[25] An empirical rate equation $-d[\mathbf{1a}]/dt = k_{obs}[\mathbf{1a}]$ satisfied most of the data ($k_{obs} = k\{[Pd(tBu_3P)_2]-n\}$; $k = 0.53\,\text{M}^{-1}\,s^{-1}$, $n = 1.1\,\text{mM}$), with slight upward curvature in plots of k_{obs} vs $[Pd(tBu_3P)_2]$ and in $\ln([\mathbf{1a}]_0/[\mathbf{1a}]_t)$ vs t, particularly with excess tBu_3P ligand.

[26] Control experiments with a 1:1 mixture of [$^2H_2$]-**2a**/[$^{18}O_1$]-**2a** (0.111 M in toluene) confirmed that $[Pd(tBu_3P)_2]$ (2 mol%) catalyzed exchange, with equilibrium (equimolar [$^2H_2$]-**2a**/[$^{18}O_1$]-**2a**/**2a**/[$^{18}O_1$,$^2H_2$]-**2a**) being attained in less than 600 s at 100 °C. Cross-over or post-turnover exchange is degenerate in the absence of isotopic labelling and should not affect synthetic utility unless mixtures of dialkyl thiocarbamates ($R_2NC(S){-}OAr$ + $R'_2NC(S){-}OAr$) are employed. Under such circumstances, reactions run to ca. 90% conversion, using low catalyst loadings, with a large excess of tBu_3P ligand, would minimise cross-over.

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