Synthetic Methods

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Catalyst-Controlled Wacker-Type Oxidation of Protected Allylic Amines**

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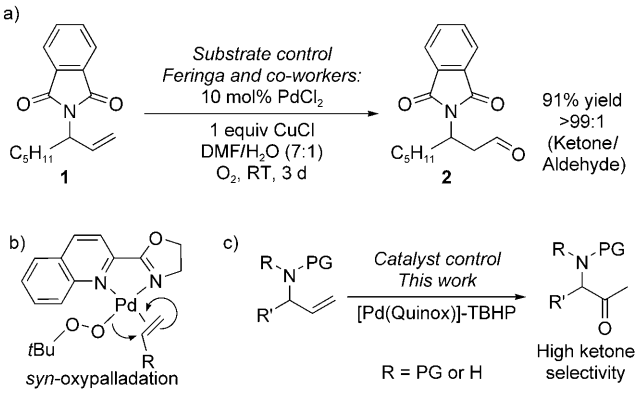
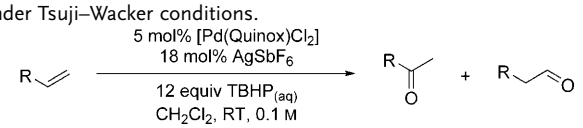
The Tsuji–Wacker oxidation provides access to methyl ketones from terminal olefins and is commonly utilized in complex molecule synthesis.[1] However, this reaction is under substrate control, which can lead to a mixture of aldehyde and ketone products, especially when the alkene bears a proximal heteroatom.[2,3] An excellent example of exploiting this was recently reported by Feringa and co-workers wherein allylic phthalimides provided high selectivity (>95:5) for anti-Markovnikov oxidation of olefins to β-amino aldehydes (Scheme 1 a).[4] In contrast, an example of an *o*-nosyl-protected allylic amine yields mainly methyl ketone product.[4] The proposed difference in selectivity between these two protecting groups is that the Lewis basic phthalimide can chelate with Pd-directing anti-Markovnikov oxidation, while the *o*-nosyl group is a relatively poor directing group. An underlying problem is the difficulty in predicting which protecting groups and which of the numerous possible variants of the Tsuji–Wacker oxidation will lead to the desired product for a given substrate.

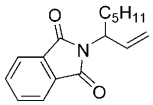
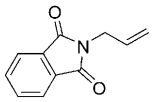
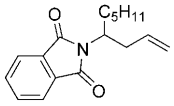


Scheme 1. a) Allylic phthalimides give high aldehyde selectivity under Tsuji–Wacker conditions, as reported by Feringa and co-workers.[4] b) Proposed intermediate in [Pd(Quinox)]–TBHP catalyst system. c) [Pd(Quinox)]–TBHP represents a catalyst-controlled oxidation system for protected allylic amines. PG = protecting group.

A goal of our research program is to use ligands on Pd^{II} to control oxidative processes.[5] In this regard, we recently reported a *tert*-butylhydroperoxide (TBHP) mediated Wacker-type oxidation, which was shown to be highly selective for the methyl ketone product in the oxidation of terminal olefins, including protected allylic alcohols.[6] The system was designed to overcome substrate control by using a bidentate ligand (Quinox) along with TBHP (Scheme 1 b). It is believed that TBHP undergoes a *syn*-oxypalladation mechanism, which would preclude the interaction of the group adjacent to the olefin with the Pd center (Scheme 1 c).[7] Therefore, using the Pd(Quinox)–TBHP catalyst system under modestly modified reaction conditions, the phthalimide substrate used by Feringa and co-workers (**1**) gives high ketone selectivity in excellent yield, overcoming the inherent substrate control (Table 1, entry 1). The crude reaction mixture was analyzed by ^{1}H NMR spectroscopy and gas chromatography (GC), which revealed the ketone was favored in a 96:4 ratio. This highlights our TBHP-mediated oxidation as a complimentary method to access α-amino ketones, which are highly versatile building blocks for targeted synthesis.

Table 1: Oxidation of allylic phthalimides and comparison to results under Tsuji–Wacker conditions.



Entry	Substrate	Yield [%][a]	*t*	Ketone/ Aldehyde[b]
1		91	19 h	96:4
2[c]		(Tsuji) 91	3 d	<1:99
3		79	18 h	>95:5
4[d]		(Tsuji) 84	3 d	40:60
5[e]		82	20 min	>95:5
6[f]		(Tsuji) 73	3 d	85:15

[a] All yields represent an average of two experiments on at least 1 mmol scale. [b] Ratios determined by GC, ^{1}H NMR integrations, and/or yields of isolated products. [c] As reported by Feringa and co-workers; see Ref. [4]. [d] Single experiment: 40 mol% $PdCl_2$, 1 equiv CuCl, DMF/H_2O (7:1), O_2, RT. [e] Reaction started at 0°C. [f] Single experiment: 30 mol% $PdCl_2$, 1 equiv CuCl, DMF/H_2O (7:1), O_2, RT.

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Using our conditions, we initially evaluated some additional allylic and homoallylic phthalimide substrates and compared the results to the Tsuji–Wacker oxidation (Table 1). In all cases, the TBHP-mediated system provided the methyl ketone product with high selectivity (Table 1, entry 3). Interestingly, under Tsuji–Wacker conditions using 40 mol% $PdCl_2$, allyl phthalimide (Table 1, entry 4) gave a mixture of ketone and aldehyde in a 40:60 ratio. This is further support for substrate control under Tsuji–Wacker conditions, as the selectivity is diminished in a substrate which does not have assistance from a Thorpe–Ingold effect. The homoallylic phthalimide is oxidized rapidly to the methyl ketone using 5 mol% [Pd(Quinox)] in high yield (Table 1, entry 5). The Tsuji–Wacker conditions also provide the ketone, albeit in an 85:15 ratio, where a substantially higher loading of Pd (30 mol%) and extended reaction times are required (Table 1, entry 6).

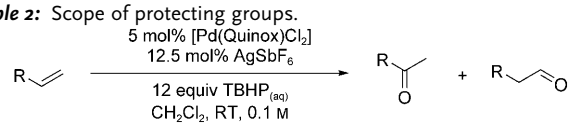
As a result of the successful oxidation of phthalimide substrates, the scope of the protecting group on the allylic amine was evaluated. Due to ease of synthesis, a number of protected allyl amine substrates were subjected to oxidation. Substrates singly protected with either benzyl carbamate (Cbz) or *tert*-butyl carbamate (Boc) were oxidized to the methyl ketone products in good yields (Table 2, entries 1 and 2), and substrates with two protecting groups on the nitrogen provided the ketone products in excellent yields (Table 2, entries 3 and 5). To emphasize the selectivity of the [Pd(Quinox)]–TBHP system, the *N*-Cbz-*N*-Boc allyl amine was evaluated under Tsuji–Wacker conditions. Using 20 mol% of $PdCl_2$ and extended reaction times, nearly full conversion (6% recovered starting material) was observed to provide a 57:43 mixture of ketone to aldehyde products.

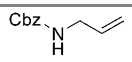
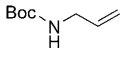
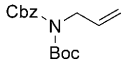
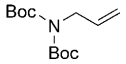
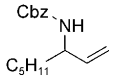
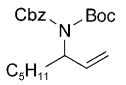
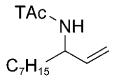
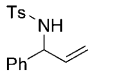
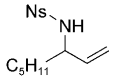
Allylic carbamates with additional substitution at the allylic position were prepared to investigate whether this would affect ketone selectivity. While a degradation in selectivity is observed with the Cbz-protected substrate (Table 2, entry 6), the ketone is still favored in a synthetically useful ratio. High ketone selectivity is regained with the doubly and orthogonally protected substrate (Table 2, entry 7). Somewhat surprisingly, the labile trichloracetamide (TAc) protecting group remained intact and provided only the ketone product; however, some starting material was recovered from the reaction mixture (Table 2, entry 8). Allylic sulfonamides were oxidized cleanly and with short reaction times in high yields (Table 2, entries 9 and 10).

Highlighting the utility to prepare optically active α-amino ketones, an enantiomerically enriched substrate **4** (>99% *ee*) derived from L-serine[8] was oxidized to give the methyl ketone product **5** in high selectivity and good yield, and with no erosion of enantiomeric excess (Scheme 2). The same substrate was evaluated under Tsuji–Wacker conditions. Again, high loadings of $PdCl_2$ and extended reaction times were required to achieve 56% yield (32% recovered starting material) of an inseparable mixture of **5** and **6** in a 60:40 ratio.[9]

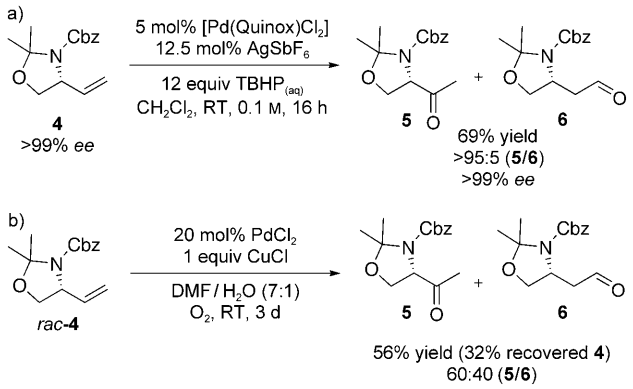
When *N*-methyl-*N*-benzoyl allyl amine **7a** was subjected to the reaction conditions an inseparable mixture of the formal deallylation product **10a**, in addition to ketone **8a**, and aldehyde **9a** was observed (Scheme 3). It is not evident whether the deallylation is a result of Pd–allyl chemistry or an E_{1CB} elimination from the aldehyde. An electrophilic palladium species has been reported to catalytically deallylate the same substrate;[10] however, the aldehyde **9a** was observed to decompose to **10a** on silica and during gas chromatography. Regardless of the mechanism, it is likely that the poor

Table 2: Scope of protecting groups.

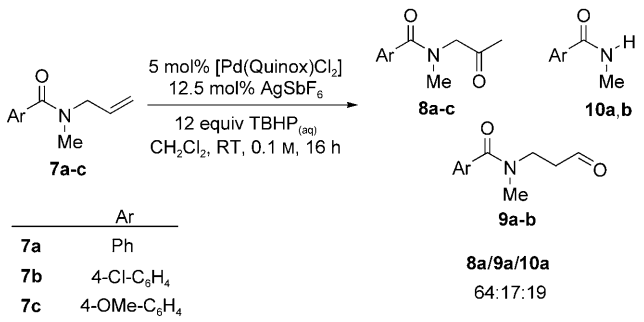


Entry	Substrate	Yield [%][a]	*t*	Ketone/ Aldehyde[b]
1[c]		81	50 min	>95:5
2[c]		74	2.5 h	>95:5
3		95	2.5 h	>95:5
4[d]		(Tsuji) 85	3 d	57:43
5		93	2.5 h	>95:5
6		74[e]	12 h	90:10
7		76	14 h	>95:5
8[f]		67[g]	23 h	>95:5
9		90	2 h	>95:5
10[f]		88	4 h	>95:5

[a] All yields represent an average of two experiments on at least 1 mmol scale. [b] Ratios determined by GC, ^{1}H NMR integrations, and/or yields of isolated products. [c] Reactions started at 0°C. [d] 20 mol% $PdCl_2$, 1 equiv CuCl, DMF/H_2O (7:1), O_2, RT. [e] Yield represents both ketone and aldehyde. [f] Reaction performed on 0.5 mmol scale. [g] An average of 12% starting material was recovered.



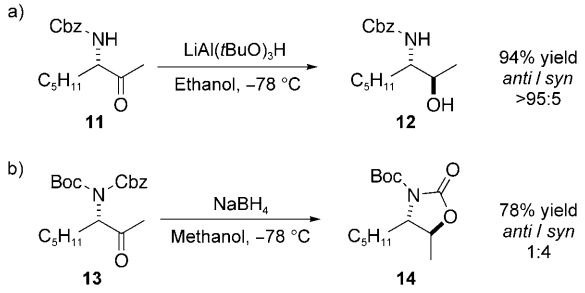
Scheme 2. a) Examination of the retention of enantiomeric excess and b) comparison to the Tsuji–Wacker oxidation.



Scheme 3. *N*-Methyl benzoyl protected allylic amines proved to be a limitation and a mechanistic tool.

outcome of this reaction is due to coordination of the electron-rich benzoyl group to the palladium center. Qualitative examination of electronically disparate benzoyl groups supports this hypothesis as 4-Cl benzoyl **7b** provided a greater ratio of ketone **8b** to a mixture of **9b** and **10b**. Conversely, a more electron-rich substrate, 4-OMe benzoyl **7c**, led to less **8c** than **9c** and **10c**.[11]

To further emphasize the utility of the α-amino ketones produced using this method, the corresponding β-amino alcohols with either a 1,2-*syn* or 1,2-*anti* relationship were accessed. By using $LiAl(tBuO)_3H$ to reduce the Cbz-protected α-amino ketone **11**, the chelation-controlled reduction product **12** (*anti*) was obtained with excellent diastereoselectivity (Scheme 4a).[12] With the addition of a Boc group and

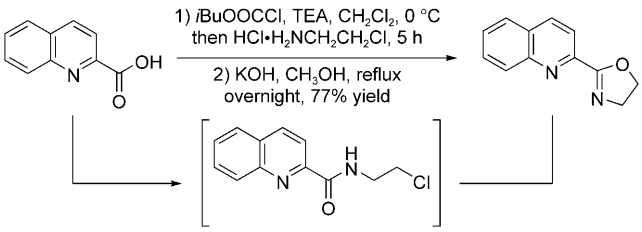


Scheme 4. Diastereoselective reductions to provide both a) *anti* and b) *syn* β-amino alcohols.

use of $NaBH_4$, **13** was reduced predominately to the Felkin–Anh product, which undergoes a concomitant cyclization on the benzyl carbamate to give **14** (*syn*) (Scheme 4b).

Finally, we would like to report an improved one-pot synthesis of the Quinox ligand, which utilizes the commercially available HCl salt of 2-chloroethylamine (Scheme 5). Following the standard amide coupling procedure, the solvent is switched to methanol and addition of KOH promotes the cyclization to the oxazoline ring. The $[Pd(Quinox)Cl_2]$ complex can then be prepared quantitatively by stirring Quinox with $[Pd(CH_3CN)_2Cl_2]$.[13]

In conclusion, we have reported the [Pd(Quinox)]–TBHP catalyst system as providing a catalyst-controlled oxidation of protected allylic amines. The methyl ketone is provided with high selectivity and good to excellent yields for substrates,



Scheme 5. Improved one-pot synthesis of the Quinox ligand.

which either provide substrate-controlled anti-Markovnikov oxidation or incomplete oxidation under Tsuji–Wacker conditions. This is further support for the mechanistic hypothesis that coordination sites on Pd^{II} are blocked with a bidentate ligand and an oxidant, which promotes *syn*-oxypalladation of the substrate. Enantiomerically pure substrates do not undergo racemization under the reaction conditions. This provides facile access to the α-amino ketone synthon, which can be diastereoselectively reduced to give a *syn* or *anti* β-amino alcohol by proper selection of reducing conditions and protecting groups. Finally, a one-pot synthesis of the Quinox ligand was reported, which makes this chemistry more accessible for use in targeted synthesis. Future work is ongoing to further extend the applications of this catalyst system and to gain a more precise understanding of the factors resulting in catalyst control.

Experimental Section

General procedure for [Pd(Quinox)]–TBHP oxidation: In the dark, $AgSbF_6$ (43 mg, 0.125 mmol, 0.125 equiv) and $[Pd(Quinox)Cl_2]$ (19 mg, 0.05 mmol, 0.05 equiv) were added to a 25 mL round-bottomed flask equipped with a magnetic stir bar. The flask was charged with CH_2Cl_2 (3.3 mL) and the mixture was stirred for 10 min, after which aqueous 70% wt/wt TBHP (1.7 mL, 12 mmol, 12 equiv) and remaining CH_2Cl_2 (5.0 mL) were added. The mixture, which turned a deep orange, was stirred for 10 min before the substrate (1.0 mmol, 1 equiv) was added. Once thin-layer chromatography (TLC) indicated complete consumption of starting material, the reaction was cooled to 0°C and quenched with saturated aqueous Na_2SO_3 (15 mL) to consume excess TBHP. The mixture was transferred to a separatory funnel and diluted with hexanes (25 mL). The aqueous layer was extracted with hexanes (25 mL). Note: For polar substrates ($R_f = 0.25$, ≥40% EtOAc in hexanes needed) the aqueous portion was extracted with EtOAc (25 mL). The combined organics were washed with H_2O (4×10 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by silica gel flash chromatography and the product containing fractions were combined and concentrated under reduced pressure.

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[13] For preparation of the [Pd(Quinox)Cl_2] complex and full analytical data see Ref. [6]. See the Supporting Information for the one-pot synthesis procedure.

