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Aldehyde Selective Wacker Oxidations of Phthalimide Protected Allylic Amines: A New Catalytic Route to β^3-Amino Acids

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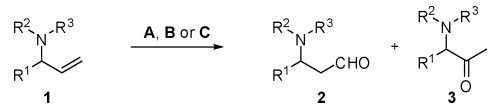
β-Amino acids are key structural elements of peptides, peptidomimetics, and natural products.[1] β^3-Amino acids are also found in their free form in nature, and they are essential chiral building blocks for the synthesis of pharmaceuticals. We present here a new catalytic method that allows the synthesis of β^3-amino acids employing palladium-catalyzed oxidation as a key step. To date, the palladium-catalyzed anti-Markovnikov Wacker oxidation of olefins remains a major challenge. The Wacker oxidation is an important industrial and synthetic catalytic process for the conversion of olefins.[2] Usually the oxidation of terminal alkenes yields selectively methylketones; however, in some cases a preference for aldehyde formation is seen.[3] Aldehydes have especially been observed in the presence of directing functional groups[4] or by using a palladium-nitro-nitroso redox couple.[5] Notably, Dai and coworkers found that the Wacker-type reaction of allylic and homoallylic amines affords terminal acetals in 45−85% yield.[6] The new methodology presented here involves the selective anti-Markovnikov oxidation of various phthalimide protected allylic amines to amino aldehydes in excellent yields. No formation of side products and no olefin isomerization or allylic exchange is observed. We also demonstrate that this method can be combined with asymmetric allylic amination to be applied in the synthesis of an optically active β^3-amino acid.

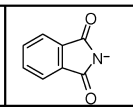
We employed three catalytic systems in our initial screening for protecting groups for the allylic amine. Method A is based on the palladium-nitro-nitroso redox couple and copper(II) chloride. The catalyst is activated under O_2 for 2 h at 55 °C. The reaction is performed at 30 °C in *tert*-butanol which is the best solvent for aldehyde selectivity previously shown by us.[5] Method B and related method C employ palladium(II) chloride as catalyst and either copper(I) or copper(II) chloride and O_2 as oxidant.

The allylic amine **1a** with the electron-donating *p*-methoxy phenyl (PMP) protecting group did not show conversion with both catalytic systems (Table 1, entries 1−2). Substrate **1b** with the carboxybenzyl (Cbz) protection gave full conversion in both cases, with a slightly better selectivity of 70:30 for the aldehyde with catalyst B (Table 1, entry 4). The tosyl (Ts) protected amine **1c** gave full conversion, an aldehyde/ketone ratio of 45:55 with catalyst A, and high selectivity for the ketone with catalyst B (Table 1, entries 5−6). The *tert*-butoxycarbonyl (Boc) amine **1d** gave only low conversion in 2 days with catalyst A and an undesired aldehyde/ketone ratio of 35:65 (Table 1, entry 7), whereas no conversion was seen with catalyst B (Table 1, entry 8). The oxidation of benzoyl (Bz) amine **1e** gave full conversion and a promising aldehyde selectivity of 3:1 in the case of catalyst A and 4:1 for catalyst B (Table 1, entry 9−10). The *o*-nosyl (Ns) amine **1f** shows high but undesired selectivity for the ketone (Table 1, entry 11). Substrate **1g** with a Boc- and *o*-nosyl protected amine did not react (Table 1, entry 12).

Table 1. Screening for Protecting Group and Catalyst System[a]



1 **2** **3**

entry	substrate	cat	conversion %	**2** : **3**[c]
1	R^1=Ph, R^2=PMP, R^3=H **1a**	A[b]	0	-
2	**1a**	B	0	-
3	R^1=Ph, R^2=Cbz, R^3=H **1b**	A[b]	100	60:40
4	**1b**	B	100	70:30
5	R^1=Ph, R^2=Ts, R^3=H **1c**	A[b]	100	45:55
6	**1c**	B	100	3:97
7	R^1=Ph, R^2=Boc, R^3=H **1d**	A[b]	10	35:65
8	**1d**	B	0	-
9	R^1=Me, R^2=Bz, R^3=H **1e**	A[b]	12	77:23
10	**1e**	B	100	80:20
11	R^1=Me, R^2=*o*-Ns, R^3=H **1f**	B	100	4:96
12	R^1=Me, R^2=*o*-Ns, R^3=Boc **1g**	C	0	-
13	R^1=Me  **1h**	A[d]	100	96:4
14	**1h**	B	100	>99:1
15	**1h**	C	80	94:6

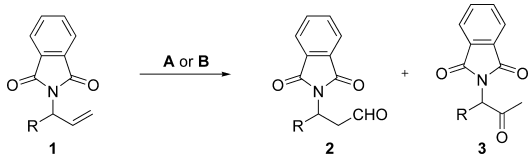
[a] A: $Pd(MeCN)_2Cl(NO_2)$ (1−5 mol %), $CuCl_2$ (5−20 mol %), *tert*-BuOH, O_2; 16 h. B: $PdCl_2$ (10 mol %), CuCl (1.0 equiv), DMF/H_2O (7:1). O_2; 3 d. C: $PdCl_2$ (10 mol %), $CuCl_2$ (50 mol %), DMF/H_2O (4:1), O_2; 3 d. [b] 5 mol % Pd-cat, 20 mol % $CuCl_2$. [c] Determined by ^{1}H NMR. [d] 1 mol % Pd-cat, 5 mol % $CuCl_2$.

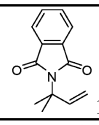
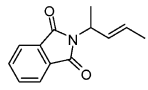
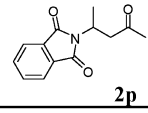
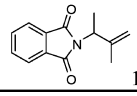
Phthalimide proved to be the optimal protecting group resulting in full conversion in the case of methods A and B (Table 1, entries 13−15). The highest aldehyde selectivities (>99:1) were achieved using catalyst B, but the reaction takes up to 3 days to completion. Catalyst A is more reactive, a lower catalyst loading can be used (1% mol of palladium, Table 1, entry 13), and it requires shorter reaction times (16 h), while aldehyde selectivities are only slightly lower (96:4). We observe lower conversion and slightly lower aldehyde selectivity when using catalyst C (Table 1, entry 15). We attribute the lower aldehyde selectivity in this case to the higher chloride concentration.[3,4a,c]

Next, we investigated the substrate scope in the oxidation of phthalimide protected allylic amines (Table 2). Starting materials were synthesized from the corresponding allylic alcohols using the Mitsunobu reaction. Substrate **1i** with a long alkyl chain was oxidized with excellent yield (91%) and selectivity (>99:1) (Table 2, entry 2).

10.1021/ja902591g CCC: $40.75

Table 2. Substrate Scope of Oxidation of Phthalimide Protected Allylic Amines[a]



entry	substrate	cat	**2** : **3**[a]	Isolated yield %
1	R = CH_3 **1g**	B	>99:1	94
2	R = C_5H_{11} **1h**	B	>99:1	91
3	 **1i**	A	>99:1	93
4	 **1k**	A	94:6	74[b]
5	R = Bn **1l**	B	>99:1	94
6	R = $BnOCH_2$ **1m**	B	>99:1	93
7	R = Ph **1n**	B	>99:1	95
8	 **1o**	B	>99:1	77
9	 **1p**	A	>1:99	89  **2p**
10	 **1q**	A B	- -	0 0

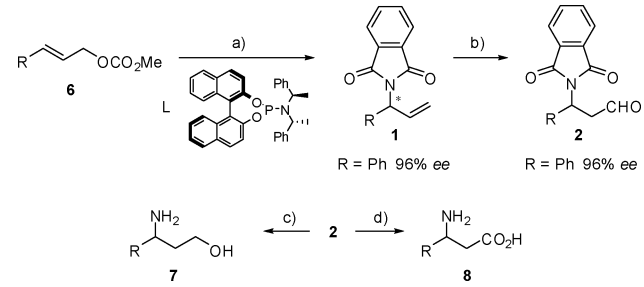
[a] A: $Pd(MeCN)_2Cl(NO_2)$ (5 mol %), $CuCl_2$ (20 mol %), *tert*-BuOH, O_2; 16 h; B: $PdCl_2$ (10 mol %), CuCl (1.0 equiv), DMF/H_2O (7:1), O_2; 3 d. [b] By ^1H NMR. [c] $Pd(MeCN)_2Cl(NO_2)$ (15 mol %), $CuCl_2$ (60 mol %). [d] 96% *ee*.

Catalyst A was used to oxidize branched amine **1k** in high yield and selectivity (Table 2, entry 3). Quartenary amine **1l** required a higher catalyst loading of A, and the aldehyde was isolated in good yield and a selectivity of 94:6 (Table 2, entry 4). With a benzyl group in the side chain excellent yield and selectivity were achieved using catalyst B (Table 2, entry 5). The benzyl protected amino alcohol **1n** was oxidized in 93% yield (Table 2, entry 6). The aromatic substrate **1o** as well as the heteroaromatic thienyl amine **1p** gave excellent yields and selectivities (Table 2, entries 7−8). The internal olefin **1q** could be converted selectively to the β-ketone by using catalyst A (Table 2, entry 9). However, 2-methyl-substituted olefin **1r** could not be oxidized with any of the catalysts (Table 2, entry 10).

The high selectivity for the anti-Markovnikov oxidation[7] to the aldehyde with these catalysts might result from coordination of the protecting group with the palladium catalyst.[8] Additionally, an electronic effect of the nitrogen protecting group can play a role, although the *N*-tosyl and *N*-nosyl substituted substrates give full conversion to the ketones (Table 1, entries 6 and 11).

We envisioned that the new aldehyde selective oxidation allows the asymmetric synthesis of β^3-amino acids from allylic compounds using three consecutive catalytic transformations (Scheme 1). In an asymmetric allylic amination, allylic carbonate **6** reacted with phthalimide to **1o** with 96% *ee* catalyzed by an iridium/phosphoramidite complex (Scheme 1).[9,10] The subsequent oxidation did not affect the stereochemistry, and aldehyde **2o** was obtained with 96% *ee* (Table 2, entry 7).[11] This catalytic (asymmetric) synthesis of amino aldehydes provides an alternative to current methods to prepare this class of compounds, e.g., using amino acids, amino alcohols, or Mannich

Scheme 1. Three Consecutive Catalytic Steps for the Asymmetric Synthesis of β-Amino Acids[a]



[a] (a) 1% $[Ir(COD)Cl]_2$, 2% (*R*,*R*,*R*)-L, TBD, THF; (b) cat. B; R = Ph 95%; (c) (i) $NaBH_4$, MeOH; R = Me 95%; (ii) H_2NNH_2, EtOH, Δ; R = Me 90%; (d) (i) 0.5% Mn-tmtacn, Cl_3CCO_2H, H_2O_2, H_2O, MeCN; R = Me 87%; (ii) H_2NNH_2, EtOH, Δ; R = Me 100%.

condensations.[1] Catalytic oxidation of **2** with Mn-tmtacn[12] and subsequent deprotection with hydrazine[13] gave the β-amino acid **8** in 87% yield in two steps. Reduction with 1.0 equiv of $NaBH_4$ and deprotection with hydrazine gave the β-amino alcohol **7** (86%).[14]

In summary, we have demonstrated that a catalytic Wacker-type oxidation produces selectively aldehydes from allylic phthalimides. This methodology is used as a key step in a new procedure for the asymmetric synthesis of a β^3-amino acid involving three consecutive catalytic steps.

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Supporting Information Available: Spectroscopic data for all compounds and detailed reaction procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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