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# Pd-catalyzed asymmetric aza-Wacker-type cyclization reaction of olefinic tosylamides

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ABSTRACT

The Pd-catalyzed asymmetric aza-Wacker-type cyclization reaction of the olefinic tosylamides with molecular oxygen as the green oxidant was developed. Under the optimized conditions, excellent catalytic activity and good enantioselectivity with up to 74% ee were obtained with quinolineoxazoline ligands. This reaction provides direct and easy access to chiral nitrogen-containing heterocycles which retain the olefin functionality.



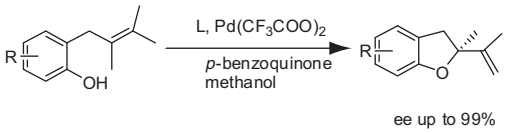
In recent years, considerable efforts have been prompted toward the synthesis of the nitrogen-containing heterocycles because many of them are core structures of potent drugs and bioactive natural products.[1] Pd-catalyzed aza-Wacker-type cyclization reactions are versatile and powerful tools to construct nitrogen-containing heterocycles under mild conditions, and the reactions become more and more attractive because their products retain the olefin functionality.[2]

A landmark in the field of aza-Wacker-type cyclization reaction was laid by Hegedus and co-workers, who initially used stoichiometric amounts of Pd(II) and later turned to the use of catalytic amounts.[3] Starting from 2-allylaniline derivatives, they obtained indoles using catalytic amounts of $PdCl_2(MeCN)_2$ or $PdCl_2$ and a stoichiometric amount of *p*-benzoquinone as reoxidant.[3b] The approach was afterward adopted by other authors for the preparation of dihydroindoles and dihydroquinolines.[4] Recently catalyst stability and product yields were improved by the use of compounds in which Pd(II) was coordinated to NHC ligands such as IMes, IPr, or the seven-membered heterocyclic carbene.[5] Asymmetric aza-Wacker-type cyclization reaction of the olefinic tosylamides was attempted by Stahl and co-workers, who used axially-chiral seven-membered *N*-heterocyclic carbene (NHC) ligands, however, the substrates underwent cyclization to afford essentially racemic products.[6]

We recently reported an efficient enantioselective Wacker-type cyclization of allylphenols catalyzed by axially chiral Pd complexes of biphenyl oxazoline ligands, which have shown the best catalytic activity and enantioselectivity so far (Scheme 1).[7] Encouraged by the results, we turned our interest toward the Pd-catalyzed asymmetric aza-Wacker-type cyclization reaction of olefinic tosylamides. Here we report our initial results about this reaction for the preparation of chiral nitrogen-containing heterocycle products with olefin functionality.

It was reported that substrate **1b** was easily prepared,[5] and compound **3** was the most efficient ligand for the asymmetric Wacker-type cyclization of allylphenols (Table 1, Fig. 1).[7c,7d] So substrate **1b** and ligand **3** were first used in the aza-Wacker-type cyclization reaction under similar conditions as Stahl's report.[5] However, only a trace product was obtained in toluene at 60 °C after 2 d (Table 1, entry 1). Since pyridine was a very efficient ligand in the preparation of *rac*-product, we anticipated that the chiral ligands containing the pyridine structure may be effective also in asymmetric aza-Wacker-type cyclization reaction. Therefore, a tridentate pyridine-bisoxazoline ligand **4** was employed. As expected, the reaction proceeded smoothly under the same conditions as above and afforded a very high yield of 91%, albeit with a lower enantioselectivity of 16% ee (entry 2). Another bidentate pyridine-oxazoline ligand **5** was also used here. As a result, the high yield was also obtained and the enantioselectivity was increased to 25% ee. It was interesting that the absolute configuration of the major enantiomeric product was reversed in comparison with that using ligand **4** (entry 3).

In order to further improve the enantioselectivities of the Pd-catalyzed aza-Wacker-type cyclization reaction, several quinolineoxazoline ligands **6** were prepared with our modified method as follows (Scheme 2): A mixture of methyl 2-quinolinecarboxylate




**Scheme 1.** Wacker-type cyclization of allylphenols.

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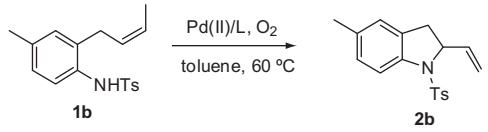
**Table 1**
Aza-Wacker-type cyclization reaction of **1b** with different ligands[a]




| Entry | Ligand | Time (d) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | **3** | 2 | Trace | — |
| 2 | **4** | 1 | 91 | 16 |
| 3 | **5** | 2 | 89 | −25 |
| 4 | **6a** | 1 | 94 | 27 |
| 5 | **6b** | 1 | 93 | 43 |
| 6 | **6c** | 1 | 91 | 42 |
| 7 | **6d** | 1 | 94 | 14 |

[a] All reactions were catalyzed by 10 mol % of Pd(II)–ligand complex generated in situ by mixing $Pd(OCOCH_3)_2$ with ligand (Pd/ligand 1:2) in the presence of oxygen in toluene at 60 °C.
[b] NMR yield (internal standard = ethyl acetate).
[c] Determined by the HPLC using chiral AD-H column.

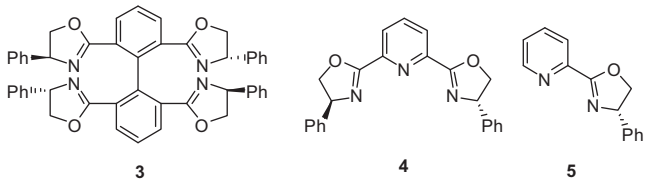
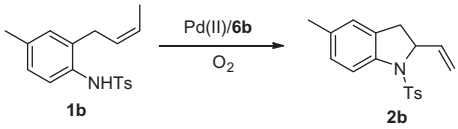



**Figure 1.** The ligands used for the aza-Wacker-type cyclization reaction.

**Table 2**
Condition optimization of the aza-Wacker-type cyclization reaction of **1b** with ligand **6b**[a]




| Entry | Solvent | Time (d) | Temp (°C) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | Toluene | 1 | 100 | 89 | 28 |
| 2 | Toluene | 1 | 80 | 95 | 39 |
| 3 | Toluene | 1 | 60 | 93 | 43 |
| 4 | Toluene | 1 | 40 | 94 | 51 |
| 5 | Toluene | 1 | 20 | 94 | 58 |
| 6 | Toluene | 5 | 0 | 94 | 69 |
| 7 | Toluene | 5 | −10 | 46 | 70 |
| 8 | Toluene | 5 | −20 | Trace | — |
| 9 | THF | 5 | 0 | 36 | 57 |
| 10 | Methanol | 5 | 0 | 55 | 56 |
| 11 | Dichloromethane | 5 | 0 | 66 | 54 |
| 12 | Acetone | 5 | 0 | 56 | 46 |
| 13 | Benzotrifluoride | 5 | 0 | 93 | 69 |
| 14[d] | Toluene | 5 | 0 | 93 | 66 |
| 15[e] | Toluene | 5 | 0 | 6 | 14 |
| 16[f] | Toluene | 5 | 0 | 45 | 20 |
| 17[g] | Toluene | 5 | 0 | 73 | 74 |

[a] All reactions were catalyzed by 10 mol % of Pd(II)–ligand complex generated in situ by mixing $Pd(OCOCH_3)_2$ with ligand **6b** (Pd/ligand 1:2) in the presence of oxygen.
[b] NMR yield (internal standard = ethyl acetate).
[c] Determined by the HPLC using chiral AD-H column.
[d] 3 Å molecular sieves was added (200 mg/mmol substrates).
[e] 20 mol % $HNTf_2$ and 3 Å molecular sieves were added (200 mg/mmol substrates).
[f] 1 equiv. of $K_2CO_3$ was added.
[g] 2 equiv. of KOAc was added.

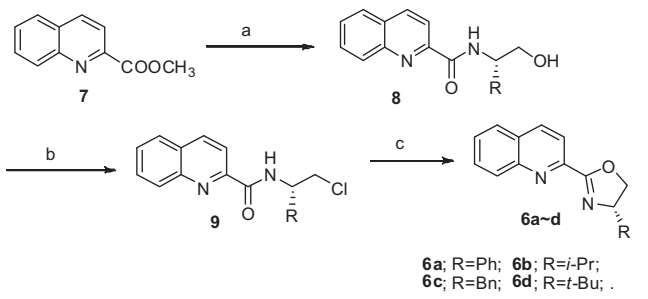
**7** and aminoalcohol was heated to give the crude hydroxylethylamide **8**. Direct treatment of **8** with $SOCl_2$ gave the crude chloroethylamide **9**, which was subjected to the oxazoline ring formation by treatment with sodium hydroxide to give the ligands **6a–d** with the overall yields from 32% to 42%.[8]

Next ligands **6a–d** were applied to the Pd-catalyzed aza-Wacker-type cyclization reaction of **1b** and the results were shown in Table 1. All of the four ligands showed excellent catalytic activities with 91–94% yields and moderate enantioselectivities (Table 1, entries 4–7). It was found that the substituent R on the oxazoline ring had some effect on enantioselectivity, and ligand **6b** with an isopropyl group on the oxazoline ring afforded the best enantioselectivity (entry 5).

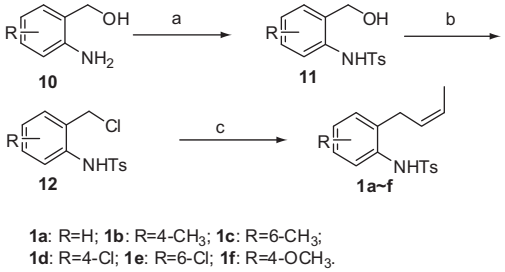
The effect of reaction conditions on the aza-Wacker-type cyclization reaction was taken into account. It was shown that when the temperature was decreased from 100 to 0 °C, the yield did not change obviously, however, the enantioselectivity increased dramatically from 28% to 69% ee (Table 2, entries 1–6). Further decreasing the temperature did not show any improvement of enantioselectivity, but reduced the yield greatly (entry 7). When the temperature was decreased to −20 °C, only trace product was afforded (entry 8). It was also found that solvents had some effect on this reaction (entries 6 and 9–13) and toluene was tested to be the most efficient one based on the catalytic activity and enantioselectivity (entry 6).

It was reported that 3 Å MS was used in the related Pd-catalyzed enantioselective oxidative cyclizations.[2d] However, 3 Å MS had no obvious effect in our reaction (Table 2, entry 14). It was also reported that acid and base had some effect on the aza-Wacker-type cyclization reaction catalyzed by NHC-coordinated Pd complexes.[5] Therefore, some acids and bases were selected to examine our reaction. It was shown that the enantioselectivity as well as catalytic activity of the reaction was dramatically reduced when using $HNTf_2$ or $K_2CO_3$ (entries 15 and 16). When using KOAc, the enantioselectivity was increased, but the catalytic activity was reduced (entry 17).

In order to explore the scope of the Pd(II)-catalyzed aza-Wacker-type cyclization reaction, substrates **1** with different substituted group were prepared with Stahl's method (Scheme 3).[5,9] Then we used these olefinic tosylamides in the Pd(II)-catalyzed

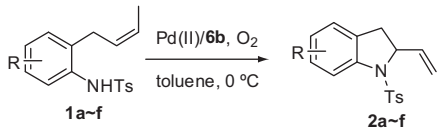



**Scheme 2.** Reagents and conditions: (a) aminoalcohol, 120 °C; (b) $SOCl_2$, $CH_2Cl_2$, reflux; (c) NaOH, EtOH, reflux (32–42%, overall yield).




**Scheme 3.** Reagents and conditions: (a) TsCl, pyridine, $CH_2Cl_2$, reflux (75–91%); (b) $SOCl_2$, $CH_2Cl_2$, reflux; (c) 1-propenyl Grignard reagent, THF, rt (45–72%, one-pot yield from **11**).

**Table 3**
Aza-Wacker-type cyclization reaction of different substrates with ligand **6b**[a]




**1a~f** **2a~f**

| Entry | Substrate | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | **1a** (R = H) | 90 | 69[d] |
| 2 | **1b** (R = 4-$CH_3$) | 94 | 69 |
| 3 | **1c** (R = 6-$CH_3$) | 37 | −8 |
| 4 | **1d** (R = 4-Cl) | 90 | 68 |
| 5 | **1e** (R = 6-Cl) | 4 | −35 |
| 6 | **1f** (R = 4-$OCH_3$) | 75 | 74 |

[a] All reactions were catalyzed by 10 mol % of Pd(II)–ligand complex generated in situ by mixing $Pd(OCOCH_3)_2$ with ligand **6b** (Pd/ligand 1:2) in the presence of oxygen in toluene at 0 °C for 5 d.
[b] NMR yield (internal standard = ethyl acetate).
[c] Determined by the HPLC using chiral AD-H column. The relative configuration of the **2b–f** was assigned by similarity to **2a** in the order of retention time in the HPLC analysis.
[d] The specific rotation of the product: $[\alpha]_D^{26.6}$ = +120.2.

aza-Wacker-type cyclization reaction, and the corresponding nitrogen-containing heterocycles **2** were afforded as expected (Table 3).[10] Excellent catalytic activity and good enantioselectivity were achieved for *p*-substituted substrates, regardless of electron-rich or electron-poor group on the substrates (entries 1, 2, 4 and 6), and **1f** with a methoxy group at *p*-position afforded the best enantioselectivity with 74% ee (entry 6). However, the catalytic activity and enantioselectivity were dramatically reduced for *o*-substituted substrates, and the absolute configuration of the major enantiomeric products was inversed (entries 3 and 5).

In summary, we have demonstrated the first Pd-catalyzed asymmetric aza-Wacker-type cyclization reaction of olefinic tosylamides. The reaction result is dependent on the solvent, reaction temperature, especially ligand and substituent group. Under the optimized conditions, excellent catalytic activity and good enantioselectivity were obtained and the substrate with a methoxy group at *p*-position afforded the best enantioselectivity up to 74% ee. This method provides direct access to chiral nitrogen-containing heterocycles with olefin functionality. Further study toward more efficient ligand for this reaction is in progress in our laboratory.

## Acknowledgments

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8. Characterization data of the ligand **6a, 6b** and **6d** agree with reference: (a) Chelucci, G.; Medici, S.; Saba, A. *Tetrahedron: Asymmetry* **1999**, *10*, 543–550; Characterization data of the ligand **6c** agree with reference: (b) Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 3076–3077.
9. Characterization data of substrates **1a–d** agree with Ref. 5. Characterization data of substrate **1e**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (d, $J$ = 8 Hz, 2H), 7.24–7.19 (m, 3H), 7.16–7.08 (m, 2H), 6.22 (s, 1H), 5.68–5.59 (m, 1H), 5.54–5.45 (m, 1H), 3.72 (d, $J$ = 8.0 Hz, 2H), 2.42 (s, 3H), 1.75–1.71 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 144.2, 143.7, 136.9, 133.0, 131.3, 129.7, 129.2, 128.8, 128.3, 127.8, 127.4, 126.2, 30.2, 21.9, 13.2. HRMS calcd for $C_{17}H_{18}ClNNaO_2S$ ($M+Na^+$), 358.0644; found, 358.0630. Characterization data of substrate **1f**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.54 (d, $J$ = 8 Hz, 2H), 7.24–7.17 (m, 3H), 6.71–6.66 (m, 1H), 6.65–6.62 (m, 1H), 6.38 (s, 1H), 5.65–5.55 (m, 1H), 5.26–5.18 (m, 1H), 3.76 (s, 3H), 2.96 (d, $J$ = 8.0 Hz, 2H), 2.39 (s, 3H), 1.65–1.61 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 144.3, 139.5, 138.3, 135.9, 135.8, 129.8, 129.7, 127.9, 127.8, 127.7, 123.6, 116.3, 65.5, 35.7, 21.9. HRMS calcd for $C_{18}H_{21}NO_3S$, 331.1242; found, 331.1240.
10. Characterization data of products **2a–d** agree with Ref. 5. Characterization data of product **2e**: $^1$H NMR (400 MHz $CDCl_3$) $\delta$ 7.60 (d, $J$ = 8.0 Hz 2H), 7.28–7.20 (m, 3H), 7.09–6.97 (m, 2H), 5.73–5.64 (m, 1H), 5.35–5.29 (m, 1H), 5.08–5.03 (m, 1H), 4.99–4.94 (m, 1H), 2.77–2.69 (m, 1H), 2.44–2.36 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 144.3, 139.5, 138.3, 135.9, 135.8, 129.8, 129.7, 127.8, 127.7, 127.6, 123.6, 116.3, 65.5, 35.7, 21.9. HRMS calcd for $C_{17}H_{16}ClNO_2S$, 333.0590; found, 333.0595. Characterization data of product **2f**: $^1$H NMR (400 MHz $CDCl_3$) $\delta$ 7.58 (d, $J$ = 8.0 Hz 1H), 7.52 (d, $J$ = 8.0 Hz 2H), 7.17 (d, $J$ = 8.0 Hz 2H), 6.78–7.73 (m, 1H), 6.59–6.56 (m, 1H), 5.93–5.83 (m, 1H), 5.42–5.36 (m, 1H), 5.17–5.12 (m, 1H), 4.73–4.67 (m, 1H), 3.74 (s, 3H), 2.81–2.74 (m, 1H), 2.56–2.50 (m, 1H), 2.36 (s, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 157.6, 144.0, 137.6, 135.2, 134.9, 133.6, 129.8, 127.4, 118.7, 115.9, 113.0, 111.1, 64.2, 55.8, 35.3, 21.8. HRMS calcd for $C_{18}H_{19}NO_3S$, 329.1086; found, 329.1084.