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Dicationic [(BINAP)Pd(solvent)$_2$]$^{2+}$[TfO$^-$]$_2$: enantioselective hydroamination catalyst for alkenoyl-*N*-oxazolidinones

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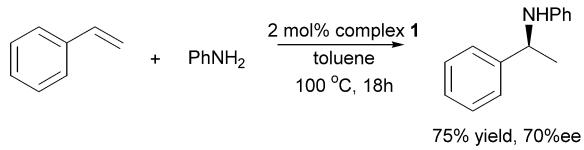
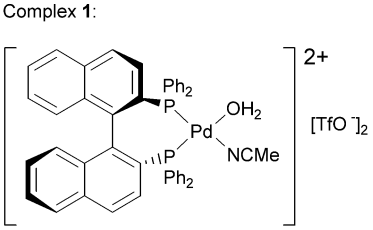
Dicationic (BINAP)palladium(II) complex induced high enantioselectiviies in the addition of primary (and secondary) aromatic amines to α, β-unsaturated oxazolidinones (up to 93% ee).

The hydroamination (HA) reaction involves the addition of an N–H bond across a double or triple bond, furnishing valuable nitrogen-containing molecules from readily available and non-hazardous precursors with 100% atom economy, making it one of the most desirable processes, economically and environmentally. Alkenes containing electron-withdrawing substituents (*e.g.* CO_2R, CN) are more susceptible to nucleophilic attack by alkyl amines, and these so-called *aza*-Michael addition reactions may occur in the absence of catalysts. Nonetheless, in many cases (*e.g.* disubstituted alkenes, non-nucleophilic aromatic amines), the reaction has an unfavourable ΔG^0 and gave poor yields, even at extremely high reaction temperatures and pressures.[1]

Much of the development of catalysts for the HA reaction were largely concerned with overcoming this energetic barrier.[2] With prochiral alkenes, the reaction poses further synthetic challenges in regio- and stereoselectivity. Catalytic enantioselective HA reactions have been achieved by late transition metal complexes of nickel,[3,4] palladium[5] and iridium[6] in recent years. However, these catalysts are somewhat specific to the type of substrates, and the reactions still require excessively long reaction times/high catalytic loadings.

Our contribution to the catalytic HA chemistry includes a class of palladium(II) thiocyanate complexes that catalyse the addition of aromatic and aliphatic amines to cyclic dihydrofuran and pyran rings under pH neutral conditions.[7] Subsequently, we reported cationic (diphosphine)palladium(II) complexes that are capable of facilitating the addition of a range of amines to acyclic alkenes (styrene, crotonates, cinnamates and acrylates) at low catalytic loadings (0.25 mol%, 400 turnovers).[8] We also described the preparation and characterisation of dicationic (BINAP)palladium(II) complex **1**, which catalysed the regiospecific addition of aniline to styrene, in 75% yield and 70% ee, with just 2 mol% catalytic loading (Scheme 1).





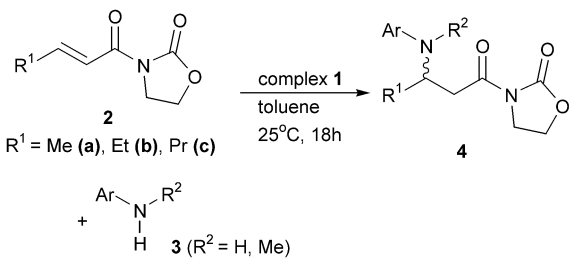
Scheme 1 Enantioselective addition of aniline to styrene catalysed by complex **1**.

Herein, we report results from the study of the activity and selectivity of catalyst **1** in the addition of aromatic amines, including the first examples of enantioselective addition of *primary aromatic amines*, to α,β-unsaturated oxazolidinones **2** (Scheme 2).

Table 1 displays the results of the addition of a number of aromatic amines to alkenoyl oxazolidinones **2a–c**, catalysed by complex **1**.

The addition of primary aromatic amines to crotonyl oxazolinidnone **2a** occurred readily at rt. In all cases, very good conversions (85–96%) were obtained in a relatively short period of time (18 h), compared to other enantioselective HA catalytic reactions. Among the different primary amines, the addition of aniline proceeded with the highest ee (93%, entry 1).[9] Interestingly, the presence of an electron-withdrawing Cl substituent did not appear to alter the yield or selectivity significantly (entry 2), whereas the addition of increasingly electron-rich amines such as *p*-tolylamine and *p*-anisidine reduced the ee to 73 and 37% respectively (entries 3 and 4).

In light of these results, the addition of the sterically and electronically demanding *N*-methyl aniline confounded our expectations. Under the same reaction conditions, it afforded the product in unexpectedly high yield and ee (Table 1, entry 5). The result is comparable to that achieved previously by Ni(II)



Scheme 2 Addition of aromatic amines to α,β-unsaturated oxazolidinones **2**.

Table 1 Addition of aromatic amines to α,β-unsaturated oxazolidinones

Entry	R^1	Amine	*T*/°C	Yield (%)[a]	ee[b]
1	Me	$PhNH_2$	25	93	93
2	Me	4-Cl–$C_6H_4NH_2$	25	96	90
3	Me	4-Me–$C_6H_4NH_2$	25	85	73
4	Me	4-MeO–$C_6H_4NH_2$	25	89	37
5	Me	PhNHMe	25	75	87[c]
6	Et	$PhNH_2$	60	66	41
7	Et	4-Cl–$C_6H_4NH_2$	60	95	55
8	Et	4-Me–$C_6H_4NH_2$	60	94	32
9	Et	4-MeO–$C_6H_4NH_2$	25	52	3
10	Pr	$PhNH_2$	60	72	27
11	Pr	4-Cl–$C_6H_4NH_2$	60	77	33
12	Pr	4-Me–$C_6H_4NH_2$	60	68	nd[d]

[a] Reactions were conducted in toluene with 10 mol% catalyst **1** for 18 h. Calculated by ^{1}H NMR spectroscopy. [b] Determined by chiral HPLC (Daicel Chiralpak AD). [c] Determined by chiral HPLC (Daicel Chiracel OD-H). [d] Not determined, enantiomers cannot be resolved.

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complex of a chiral *bis*(oxazolidine) ligand DBFOX-Ph (5 mol% catalytic loading, rt, 40 h, 62% yield, 90% ee).[3] We are not able to explain this result at this particular juncture, suffice to say that the selectivity of the reaction is obviously dictated by a number of delicately balanced steric and electronic parameters.

Changing the substituent of the alkenoyl functionality has a dramatic effect on the rate of the reactions. The addition of primary aromatic amines to pentenoyl oxazolidinone **2b** was considerably slower at rt. Performing these reactions at an elevated temperature (60 °C), moderate ee's of 41% and 55% were obtained for aniline and 4-chloroaniline respectively (entries 6 and 7), compared with the more electron rich 4-tolylamine (32% ee, entries 8). The addition of the more nucleophilic *para*-anisidine may be effected at rt, but there was virtually no enantioselectivity (entry 9).

Extending the homology, the addition of the primary aromatic amines to hexenoyl oxazolidinone **2c** proceeded in even lower selectivities (entries 10–12).

Amination mechanisms involving alkene and/or amine activation have been proposed, particularly in the HA of less activated alkenes such as styrenes and norbornene.[6,10] However, since complex **1** failed to induce any reaction between aniline and methyl crotonate (even at 60 °C), we believe that the cationic palladium catalyst is probably acting as a chiral Lewis acid in these systems. The unsaturated double bond is activated towards attack by the weak nitrogen nucleophile by the chelation of the oxazolidinone functionality to the metal centre (Fig. 1), which also bestows stereodifferentiation to the process. A very similar reaction intermediate has been previously proposed by Jørgensen.[3]

In this communication, we have demonstrated that [(BINAP)Pd]$^{2+}$ complex **1** is able to catalyse HA reactions between primary and secondary aromatic amines and alkenoyl oxazolidinones enantioselectively, under pH neutral conditions. Even though the catalytic loading used was quite high (10 mol%), the reactions proceeded in high yields under a relatively short period of time. This has given us sufficient impetus to explore other cationic transition metal catalysts, as well as matching substrates, in stereoselective HA reactions. The results of these studies will be reported in due course.

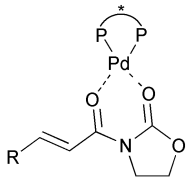

Fig. 1 Proposed catalytic intermediate.

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Notes and references

1 Recent reviews in this area: (*a*) M. Beller, C. Breindl, M. Eichberger, C. G. Hartung, J. Seayad, O. R. Thiel, A. Tillack and H. Trauthwein, *Synlett*, 2002, 1579; (*b*) M. Nobis and B. Driessen-Holscher, *Angew. Chem., Int. Ed. Engl.*, 2001, **40**, 3983; (*c*) T. E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675.
2 D. M. Roundhill, *Catal. Today*, 1997, **37**, 155.
3 W. Zhuang, R. G. Hazell and K. A. Jørgensen, *Chem. Commun.*, 2001, 1240.
4 L. Fadini and A. Togni, *Chem. Commun.*, 2003, 30.
5 M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 9546.
6 R. Dorta, P. Egli, F. Zurcher and A. Togni, *J. Am. Chem. Soc.*, 1997, **119**, 10857.
7 X. Cheng and K. K. Hii, *Tetrahedron*, 2001, **57**, 5445.
8 K. Li, P. N. Horton, M. B. Hursthouse and K. K. Hii, *J. Organometallic Chem.*, 2003, **665**, 250.
9 **Typical reaction procedure:** 22 mg (0.020 mmol) of complex **1** and 3-(*E*)-2-butenoyl-1,3-oxazolidin-2-one (46 mg, 0.30 mmol) were placed into a thick-walled Young's tube. 1.0 mL of toluene and aniline (20 μL, 0.20 mmol) were added *via* syringe. The tube was sealed *via* a PTFE tap and the reaction mixture was stirred at rt for 18 h. Conversion was monitored by ^{1}H NMR spectroscopy (93%). The ee (93%) was determined by HPLC using a Chiralpak AS column (hexane:^{i}PrOH = 80:20; t_r(major) = 14.6 min, t_r = 19.3 min). The homogeneous red solution was subjected to column chromatography (SiO_2, EtOAc:hexane, 1:2) to furnish the product, which was recrystallised from EtOAc:hexane to give a white solid. $[\alpha]_D^{20}$ = + 8.2° (*c* = 0.018, $CHCl_3$, 86% ee). ^{1}H NMR ($CDCl_3$): δ 7.15 (t, 2H, *J* = 8.6 Hz), 6.69 (t, 1H, *J* = 7.3 Hz), 6.62 (d, 2H, *J* = 8.6 Hz), 4.25–4.37 (m, 2H), 4.06–4.17 (m, 1H), 3.84–3.96 (m, 2H), 3.79 (br s, 1H), 3.35 (dd, 1H, *J* = 15.0, 7.3 Hz), 3.01 (dd, 1H, *J* = 15.0, 5.5 Hz), 1.30 (d, 3H, *J* = 6.4 Hz). ^{13}C {^{1}H} NMR ($CDCl_3$): δ 172.1, 154.0, 147.2, 129.6, 117.9, 113.9, 62.3, 46.7, 42.9, 41.8, 21.6.
10 U. Nettekoven and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 1166.