Chiral Ruthenium PNNP Complexes of Non-Enolized 1,3-Dicarbonyl Compounds: Acidity and Involvement in Asymmetric Michael Addition

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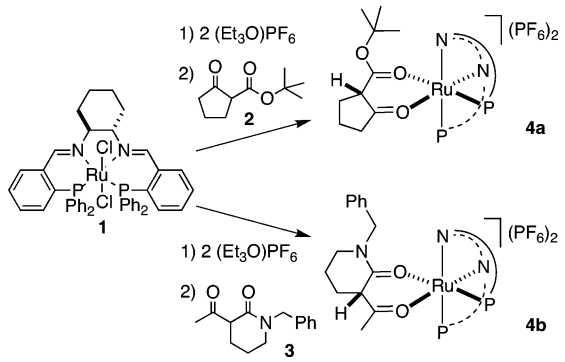
Received May 8, 2006

*Summary: The chiral complexes [Ru(**2**)(PNNP)]$^{2+}$ (**4a**) and [Ru(**3**)(PNNP)]$^{2+}$ (**4b**), containing the non-enolized 1,3-dicarbonyl compounds 2-((tert-butoxy)carbonyl)cyclopentanone (**2**) or α-acetyl-N-benzyl-δ-valerolactam (**3**), were deprotonated to the enolato complexes **5a**,**b**. Complex **4a** has a pseudo-aqueous pK_a value of 4.6 ± 0.5 (with pK_a(Ph$_3$PH$^+$) = 2.7 as reference) and catalyzes the 1,4-addition of **2** to methyl vinyl ketone with up to 79% ee.*

1,3-Dicarbonyl compounds are widely used nucleophiles for carbon−carbon and carbon−heteroatom bond-forming reactions,[1] in particular in enantioselective catalytic processes.[2,3] A recent development in this area is the discovery of Lewis acidic complexes based on ruthenium(II)[2a] (d^6) and palladium(II)[3a] (d^8) that catalyze Michael additions and related reactions. Following seminal work on the enantioselective α-functionalization of 1,3-dicarbonyl compounds catalyzed by Ti/TADDOLato complexes that includes fluorination,[4] chlorination,[5] hydroxylation,[6] and sulfenylation,[7] we applied Ru/PNNP complexes to the asymmetric hydroxylation[6] and fluorination[8] of β-keto esters and β-keto amides. We find now that the activation of [RuCl$_2$(PNNP)] (**1**; PNNP is (1*S*,2*S*)-*N*,*N*′-bis[*o*-(diphenylphosphino)benzylidene]cyclohexane-1,2-diamine) with (Et$_3$O)PF$_6$,[9] followed by reaction with the β-keto ester **2** (or with the β-keto lactam **3**) (1 equiv) in CD$_2$Cl$_2$ gives the dicationic adduct **4a** (or **4b**) as a single diastereoisomer (Scheme 1).[10] These species

Scheme 1



are rare examples of complexes containing 1,3-dicarbonyl compounds in their non-enolized form.[11]

Complex **4a** decomposes upon isolation and was, therefore, characterized in solution,[12] whereas **4b** was isolated in 91% yield by crystallization from CH$_2$Cl$_2$/hexane.[13] Thus, the ^{1}H NMR spectrum of **4a** features the signal of the methine proton H^d of **2** at δ 3.78 (δ 3.04 in the free β-keto ester **2**) (Figure 1). The one-bond ^{13}C−^{1}H HMQC spectrum proves that this is the signal of the hydrogen atom H^d bound to the 2-carbon atom (*C*−H^d), whose ^{13}C NMR signal appears at δ 55.5. The long-range ^{13}C−^{1}H HMQC shows correlations from H^d to both carbonyl carbons and to the adjacent methylene group in the cyclopentanone ring.[14]

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(9) (a) [RuCl$_2$(PNNP)] (30 mg, 36 μmol, prepared as described in ref 9b) and (Et$_3$O)PF$_6$ (18.3 mg, 74 μmol, 2.04 equiv) were dissolved in dry CD$_2$Cl$_2$ (0.8 mL) in an NMR tube fitted with a Young valve and stirred at room temperature for 14 h, after wich **2** or **3** (1.0 equiv) was added. (b) Gao, J. X.; Ikariya, T.; Noyori, R. *Organometallics* **1996**, *15*, 1087.

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(12) Selected NMR data of **4a**: ^{31}P{^{1}H} NMR (CD$_2$Cl$_2$, 101 MHz) δ 61.2 (d, 1 P, $J_{P,P'}$ = 29.1 Hz), 51.3 (d, 1 P, $J_{P,P'}$ = 29.1 Hz); ^{1}H NMR (CD$_2$Cl$_2$, 250 MHz) δ 9.03 (d, 1 H, *J* = 9.0 Hz, *H*^{b}C═N), 8.83 (s, 1 H, *H*$^{b'}$C═N), 3.78 (dd, 1 H, *J* = 10.2, 10.2 Hz, C(O)C*H*^{d}COO), 3.40−3.32 (m, 1 H, *H*^{a}C−N), 2.42−2.35 (m, 1 H, *H*$^{a'}$C−N); ^{13}C{^{1}H} NMR (CD$_2$Cl$_2$, 126 MHz) δ 227.3 (*C*(O)CHCOO), 175.2 (C(O)CH*C*OO), 170.9 (d, *J* = 4.8 Hz, *C*═N), 168.6 (d, *J* = 4.9 Hz, *C*═N), 55.5 (C(O)*C*H^{d}COO).

(13) Selected NMR data of **4b**: ^{31}P{^{1}H} NMR (CD$_2$Cl$_2$, 101 MHz) δ 60.7 (d, 1 P, $J_{P,P'}$ = 28.9 Hz), 50.5 (d, 1 P, $J_{P,P'}$ = 28.9 Hz); ^{1}H NMR (CD$_2$Cl$_2$, 250 MHz) δ 8.90 (d, 1 H, *J* = 9.5 Hz, *H*^{b}C═N), 8.36 (s, 1 H, *H*$^{b'}$C═N), 3.63 (dd, 1 H, *J* = 11.0, 5.5 Hz, C(O)C*H*^{f}C(O)N), 2.73−2.65 (m, 1 H, *H*^{a}C−N), 1.97−1.88 (m, 1 H, *H*$^{a'}$C−N); ^{13}C{^{1}H} NMR (CD$_2$Cl$_2$, 176 MHz) δ 218.8 (*C*(O)CHC(O)N), 169.2 (d, *J* = 5.0 Hz, *C*═N), 167.4 (d, *J* = 5.0 Hz, *C*═N), 167.2 (C(O)CH*C*(O)N), 50.5 (C(O)*C*^{f}HC(O)N).

(14) See the Supporting Information.

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Publication on Web 05/26/2006

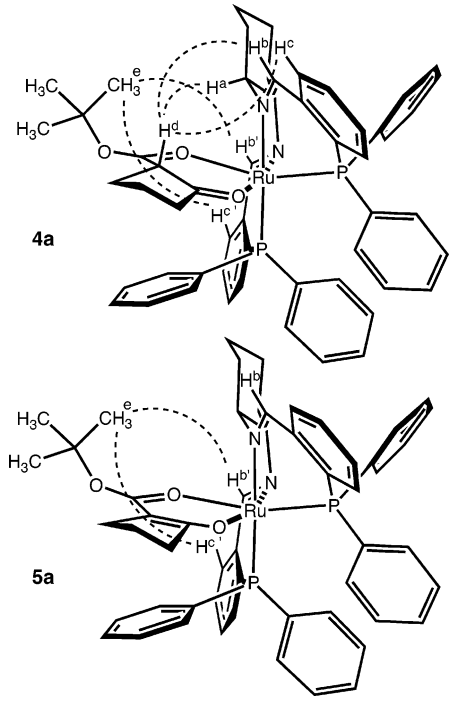


Figure 1. Selected NOE contacts in **4a** and **5a**.

As all attempts at isolating **4a** and crystallizing **4b** have been unsuccessful so far, structural information was gathered by comparing their NMR spectra with those of the enolato analogues **5a**,**b**,[15,16] which were prepared and structurally characterized (see below). Thus, the ^{1}H and ^{1}H−^{1}H NOESY NMR spectral patterns indicate that **4a** and **5a** are structurally similar. Both complexes feature NOE contacts of the *tert*-butyl group of β-keto ester **2** to one imine hydrogen and to one PNNP benzylidene, suggesting that these complexes have similar structures and the same relative configuration (Figure 1). Additionally, the NOESY spectrum of **4a** shows contacts between the methine hydrogen of the β-keto ester (H^d) and three protons of the PNNP ligand, namely the cyclohexyl ipso hydrogen H^a, the imine hydrogen H^b, and the benzylidene hydrogen H^c, indicating that H^d points up toward the cyclohexane backbone of the PNNP ligand.

In an analogous manner, the relative configuration of **4b** was determined by comparison with **5b**. In both complexes, the endo benzylic hydrogen and the N-benzyl ortho H of the β-keto lactam **3** display NOE contacts to the same imine hydrogen and benzylidene ortho H atoms of the PNNP ligand.[14] Again, the enolizable hydrogen of the coordinated β-keto lactam points up toward the cyclohexane backbone, as indicated by its NOE contacts involving the PNNP cyclohexane ipso H^a, the imine hydrogen H^b, and H^c of one PNNP benzylidene.

Deprotonation of **4a**,**b** with Et_3N (1 equiv) gives the monocationic enolato complexes **5a**,**b** as a single diastereoisomer (Scheme 2).[15,16] The reaction is reversed by addition of HBF_4·OEt_2 (1 equiv, $pK_a^{aq} = -3.6$). The pK_a of **4a** on the pseudo-aqueous scale has been measured in CD_2Cl_2 relative to Ph_3PH^+ from the equilibrium in Scheme 3 by integration of the ^{31}P{inverse-gated ^{1}H} NMR spectra.[14] Assuming a pK_a value of 2.7 for Ph_3PH^+, a pK_a^{aq} value of 4.6 ± 0.5 is obtained for **4a**.[17] Deprotonation of **4a** with PPh_3 and protonation of **5a** with Ph_3PH^+ gave the same equilibrium position.

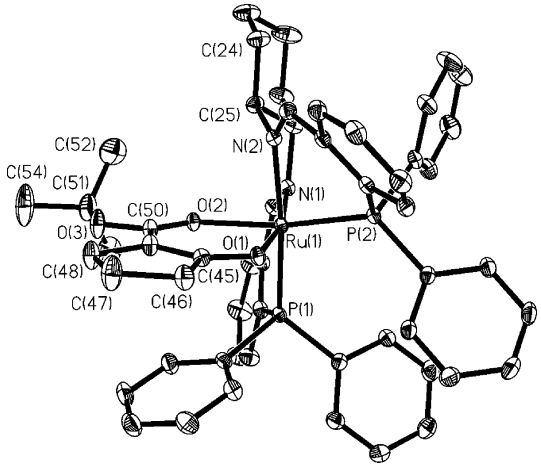
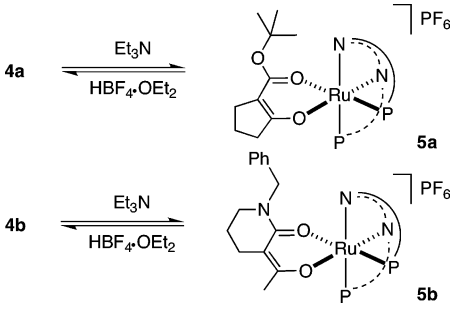
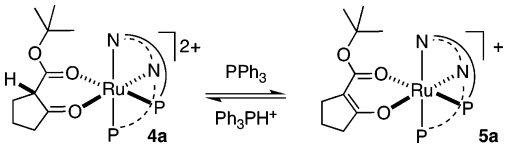


Figure 2. ORTEP drawing of the enolato complex **5a**.

Scheme 2



Scheme 3



5a,**b** were isolated as air-stable solids in 64% and 55% yields, respectively. The crystal structures of racemic **5a**,**b** show a distorted-octahedral coordination with the PNNP ligand in a cis-β configuration, which is Λ in the enantiomers containing (*S*,*S*)-PNNP (Figures 2 and 3). A phenyl group of PNNP shields the *Si* face of the enolato ligand, leaving the *Re* face accessible to electrophilic attack, with the implications for catalysis discussed below.

Complex **4a**, formed in situ by treating **1** with $(Et_3O)PF_6$ (2 equiv) and **2** (20 equiv), catalyzes the Michael addition of β-keto ester **2** to the methyl vinyl ketone **6** (Scheme 4). Product **7** was obtained in 94% yield and with 79% ee. The *R* absolute configuration[14] of **7** is consistent with the *Re* face attack of the β-keto ester, which is the accessible enantioface in **4a** and **5a**. Addition of PPh_3 (1 equiv vs **4a**) shuts down the catalytic reaction, **7** being formed in less than 1% yield after 24 h.

(15) Selected NMR data of **5a**: ^{31}P{^{1}H} NMR (CD_2Cl_2, 101 MHz) δ 63.4 (d, 1 P, $J_{P,P'} = 31.2$ Hz), 52.5 (d, 1 P, $J_{P,P'} = 31.2$ Hz); ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 8.89 (s, 1 H, H^bC═N), 8.69 (d, 1 H, $J_{P,H} = 9.5$ Hz, H^bC═N), 3.80−3.71 (m, 1 H, H^aC−N), 2.30−2.21 (m, 1 H, $H^{a'}$C−N); ^{13}C{^{1}H} NMR (CD_2Cl_2, 126 MHz) δ 192.0 (C═*C*−O), 168.3 (*C*OO), 166.7 (d, $J = 3.1$ Hz, *C*═N), 163.5 (d, $J = 5.2$ Hz, *C*═N), 93.1 (*C*═C−O).

(16) Selected NMR data of **5b**: ^{31}P{^{1}H} NMR (CD_2Cl_2, 121 MHz) δ 61.5 (d, 1 P, $J_{P,P'} = 30.4$ Hz), 51.9 (d, 1 P, $J_{P,P'} = 30.4$ Hz); ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 8.56 (s, 1 H, $H^{b'}$C═N), 8.54 (d, 1 H, $J_{P,H} = 11.7$ Hz, H^bC═N), 3.20−3.05 (m, 1 H, H^aC−N), 2.00−1.88 (m, 1 H, $H^{a'}$C−N); ^{13}C{^{1}H} NMR (CD_2Cl_2, 176 MHz) δ 178.3 (C═*C*−O), 164.9 (*C*═N), 163.1 (*C*(O)N), 161.6 (*d*, $J = 5.3$ Hz, *C*═N), 89.0 (*C*═C−O).

(17) (a) Alternatively, a pK_a value of about 1.9 results if a recent revision of the commonly used pK_a^{aq} value of Ph_3PH^+ from 2.7 to about 0 (in water) is accepted.[17b] (b) Pestovsky, O.; Shuff, A.; Bakac, A. *Organometallics* **2006**, *25*, 2894.

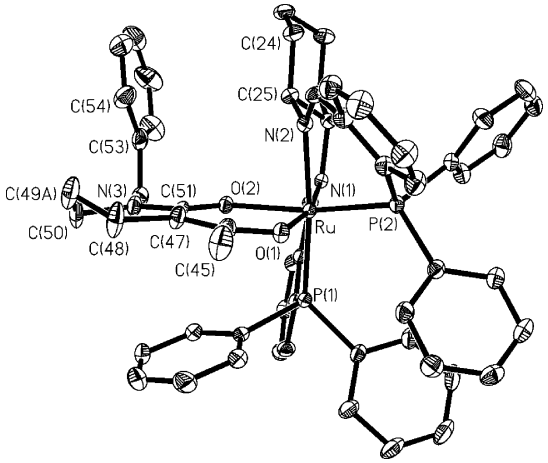
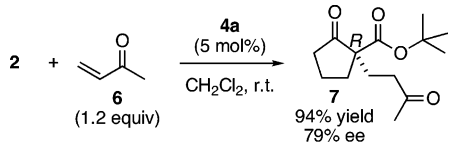


Figure 3. ORTEP drawing of the enolato complex **5b**.

Scheme 4



Stoichiometric reactions gave additional mechanistic insight. Complex **4a** reacts with **6** (1.2 equiv) to give **7** in 93% yield and with 90% ee after 4 h. This enantioselectivity is comparable to that of the catalytic reaction, suggesting that **4a** might be an intermediate in catalysis. Interestingly, the enolato complex **5a** does not react with **6** (1 equiv) (0% yield after 48 h). No reaction occurs upon addition of $(HNEt_3)BPh_4$ (1 equiv) as a weak acid over 48 h.

These results are relevant to the palladium-catalyzed 1,4-addition of 1,3-dicarbonyl compounds to enones.[3a] In this context, Sodeoka recently reported that the stoichiometric 1,4-addition of a palladium-coordinated enolate to **6** is induced by a strong acid (CF_3SO_3H), which was proposed to activate the enone by protonation. However, the effect of the acid on the enolato complex was not discussed. Our results with ruthenium show that a strong acid protonates the enolato complex **5a** to **4a**, which, in turn, is not acidic enough to protonate methyl vinyl ketone (**6**) to a significant extent (the pK_a^{aq} value of protonated **6** can be estimated to be ~ -4). Therefore, it would be interesting to examine the effect of the strong acid in the case of the palladium enolato complex as well.

In summary, we have reported rare examples of late-transition-metal complexes containing non-enolized 1,3-dicarbonyl compounds as ligands. Upon coordination to ruthenium, the acidity of the β-keto ester **2** is enhanced by 6 orders of magnitude at least. Additionally, we have shown that **4a** smoothly reacts with **6** to give the 1,4-addition product both stoichiometrically and catalytically, whereas the enolato complex **5a** does not react with methyl vinyl ketone **6**, not even in the presence of Et_3NH^+. In fact, Et_3NH^+ is too weak an acid ($pK_a^{aq} \approx 11$) to react with the enolato ligand of **5a** to give a significant amount of **4a** but would protonate the enolate intermediate formed by the first step of the 1,4-addition reaction between **6** and **5a**, the corresponding ketone having a $pK_a^{aq} \approx 20$. Conversely, a stronger acid would protonate **5a** rather than **6**. The nature (including acidity) and the role of complexes of type **4** containing non-enolized 1,3-dicarbonyl compounds in metal-assisted 1,4-addition reactions will be the object of future studies. Finally, it should be noted that the present approach involves a Lewis acidic metal complex and, therefore, is opposite to the use of basic metal complexes that promote the formation of enolato derivatives, such as Ikariya's amido ruthenium(II) catalyst.[2a]

Acknowledgment. We thank Dr. Sebastian Gischig for measuring the X-ray crystal structures of complexes **5** and Prof. Antonio Togni for fruitful discussions.

Supporting Information Available: Text, tables, and figures giving experimental details of synthesis and catalysis and CIF files giving crystallographic data for **5a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM060389K