Transfer Hydrogenation

A Formally Zwitterionic Ruthenium Catalyst Precursor for the Transfer Hydrogenation of Ketones that Does Not Feature an Ancillary Ligand N–H Functionality**

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The ruthenium-mediated transfer hydrogenation (TH) of ketones under basic conditions employing iPrOH or other H2donor solvents has emerged as an atom-economical methodology for the synthesis of secondary alcohols.^[1] Although the catalytic abilities of Ru complexes supported by a range of structurally diverse ancillary ligands have been evaluated, precatalysts featuring a Ru-NH linkage commonly offer the highest levels of activity and selectivity in the TH of ketones. $^{[1,2]}$ In the case of the landmark $\{(\eta^6\text{-arene})Ru\}$ catalysts featuring chiral diamido ligands developed by Noyori and co-workers,^[3] this now well-established N-H effect has been rationalized in terms of an outer-sphere TH mechanism involving the concerted transfer of H₂ from a $\{(H)Ru-NH_2R\}$ intermediate to a ketone substrate.^[1c,3] More recently, Baratta and co-workers have reported an alternative class of precatalysts supported by 2-(aminomethyl)pyridine (ampy) coligands that give rise to the most active catalysts known for the TH of ketones.^[4] For both of these prominent Ru-based TH catalyst systems, the inferior performance exhibited by the analogous {Ru-NMe2R} species underscores the crucial role that the ancillary ligand NH2 terminus plays in enhancing catalyst activity and selectivity.^[3c,4] Notwithstanding the advancements in Ru-mediated TH that have been

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enabled through the development of ancillary ligands featuring N–H donors, such a structural prerequisite limits the future design of alternative classes of Ru-based TH catalysts for use in mediating new and increasingly challenging substrate transformations. In this context, the identification of novel ligation strategies that do not rely on the N–H effect and which give rise to highly active and selective Ru-based TH catalysts represents an important goal in modern catalysis research.^[1,2]

Encouraged by the catalytic abilities of Noyori's [(η^{6} -arene)Ru(diamido)] complexes,^[3] and in light of the observation that the pairing of P- and N-donor ligands is a common feature in several highly effective Ru-based TH catalysts,^[1c,2b,4] we became interested in developing new non-N–H [(η^{6} -arene)Ru(κ^{2} -*P*,*N*)(Cl)] precatalysts for use in the TH of ketones. In the context of our research comparing the reactivity properties of late-transition-metal cations and zwitterions derived from 1-H,^[5] we identified the cationic complexes $2^{+}X^{-}$ and the zwitterion **3** as being worthwhile candidates for catalytic studies (Scheme 1). Herein, we report



Scheme 1. Synthesis of 2^+X^- and 3. a) 0.5 [$\{\eta^6, p\text{-cymene}\}RuCl_2\}_2$] in CH_2Cl_2 (X = Cl), or 0.5 [$\{\eta^6, p\text{-cymene}\}RuCl_2\}_2$] with AgX (X = BF₄, SO₃CF₃) or Li(Et₂O)_{2.5}B(C₆F₅)₄ (X = B(C₆F₅)₄) in MeCN; b) 1) 0.5 [$\{\eta^6, p\text{-cymene}\}RuCl_2\}_2$] in CH_2Cl_2 , 2) K₂CO₃ in THF.

the synthesis and characterization of 2^+X^- and **3** as well as their application as precatalysts in the TH of ketones. Despite lacking an ancillary ligand N–H functionality, complex **3** is among the most active ketone TH precatalysts known, providing near-quantitative conversions and exhibiting consistently high turnover frequencies (TOFs; up to 220000 h⁻¹) for a diversity of alkyl and aryl ketone substrates at low catalyst loadings. Furthermore, while the anticipated zwitterionic hydrido complex **4** is formed quantitatively upon treatment of **3** with KOtBu in *i*PrOH, reactivity studies confirm that this hydrido species is not the active catalyst in TH reactions employing **3** as a precatalyst.



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Figure 1. ORTEP diagrams for $2^{+}BF_{4}^{-}$, $3 \cdot (OC_{4}H_{8})_{2}$, and 4; thermal ellipsoids set at 50% probability, selected hydrogen atoms and the THF solvates have been omitted for clarity. Selected bond lengths [Å] for $2^{+}BF_{4}^{-}$ and $3 \cdot (OC_{4}H_{8})_{2}$ (the latter given in parentheses): Ru-P 2.3503(8) (2.374(1)), Ru-N 2.228(2) (2.218(4)), Ru-Cl 2.3909(8) (2.390(1)), P-C3 1.810(3) (1.755(5)), N-C2 1.450(4) (1.473(6)), Cl-C2 1.501(4) (1.383(7)), C2-C3 1.341(4) (1.413(7)). Selected bond lengths [Å] for 4: Ru-P 2.297(1), Ru-N 2.206(3), P-C3 1.757(4), N-C2 1.475(5), Cl-C2 1.379(5), C2-C3 1.408(5).

Addition of 1-H^[6a] to 0.5 equivalents of $[{(\eta^6-p-cymene)RuCl_2}_2]$ afforded 2^+Cl^- , isolated in 93% yield, while the corresponding 2^+X^- (X = BF₄, SO₃CF₃, or B- $(C_6F_5)_4$) complexes were prepared and isolated in 88-91% yield by treatment of [(η^6 -*p*-cymene)- $(CH_3CN)_2RuCl]^+X^-$ (formed in situ) with 1-H.^[6b] As well, 2⁺Cl⁻ was transformed cleanly into the zwitterion 3 upon exposure to K₂CO₃, thereby allowing for the isolation of 3 in 81% yield following workup. The κ^2 -P,N connectivity in both 2^+X^- and 3, which was determined initially on the basis of solution NMR spectroscopy data, was confirmed by use of X-ray diffraction techniques;[6c] the crystal structures of $2^+\mathrm{BF_4^-}$ and $3\cdot$ $(OC_4H_8)_2$ (Figure 1) can be compared with those of other $[(\eta^6$ arene)Ru(κ^2 -P,N)(Cl)] complexes.^[2d,7] Whereas the Ru coordination environments in $2^+BF_4^-$ and 3are similar, the interatomic distances within the backbone of the P,N ligands differ significantly; pronounced bond-length alternation is observed within the indene fragment of $2^+BF_4^-$, while the indenide unit in 3 exhibits a more delocalized structure, in keeping with a 10π electron indenide framework.[5]

The reduction of acetophenone in refluxing *i*PrOH in the presence of KO*t*Bu was selected to assess the catalytic utility of 2^+X^- and 3 (0.05 mol%, denoted [Ru]) for the TH of ketones [Eq. (1)].^[6d] The cations 2^+X^- (X = Cl, BF₄, SO₃CF₃, or B(C₆F₅)₄) exhibited modest activity, with conversions of

$$R^{O} + H^{O} + \frac{R^{U}}{KOtBu \ 1 \ mol\%} R^{V} + R^{V} + \frac{R^{U}}{KOtBu \ 1 \ mol\%} R^{O} + R^{V} + \frac{R^{U}}{R}$$
(1)

acetophenone to 1-phenylethanol ranging between 4 and 23 % after 15 min.^[6b] In contrast, the zwitterion **3** proved to be an extremely active precatalyst for this reaction, providing 99 % conversion into 1-phenylethanol after only 5 min (Table 1, entry 1), and with a TOF value (180000 h⁻¹) that is among the highest reported for the TH of ketones.^[2c-e,4] Excellent catalytic performance was also observed when employing 0.025 mol % **3** in refluxing *i*PrOH (93 %, 15 min, TOF = 170000 h⁻¹) or by use of 0.2 mol % **3** at 45 °C (97 %, 15 h).

Table 1: Transfer hydrogenation of ketones (0.1 M) with 3 (0.05 mol%) and KOtBu (1 mol%) in *i*PrOH.^[a]

Entry	Ketone	<i>t</i> [min]	Conversion [%] ^[b]	TOF [h ⁻¹] ^[c]
1	€ C	5	99	180000
2		5	98 ^[d]	220 000
3		15	94	180 000
4	F ₃ C CF ₃	5	97	180 000
5		15	95	125 000
6	CI	15	99	57000
7	MeO	5	97	120 000
8	° L	5	99	54 000
9		5	99	91 000
10	° I	15	99	150000

[a] 0.8 mmol scale (ketones (0.1 M), **3** (0.05 mol%), KOtBu (1 mol%)) in refluxing *i*PrOH. [b] Conversion to the secondary alcohol determined on the basis of GC-FID data at time *t* stated in column 3. [c] Turnover frequency (mole of ketone converted into alcohol per mole of catalyst per hour) measured at 20 seconds (50% conversion for entry 1). [d] When the reaction was conducted on a 2.0 mmol scale, $Ph_2CH(OH)$ was isolated with 96% yield.

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Complex **3** also proved to be an effective precatalyst for the TH of other diaryl (Table 1, entries 2 to 4), aryl alkyl (Table 1, entries 5 to 7), and dialkyl (Table 1, entries 8 to 10) ketones. Notably, the ability of **3** to mediate the rapid (5– 15 min) reduction of such structurally diverse ketones with high conversions (94–99%) and with remarkably high TOF values (54000–220000 h⁻¹) is unprecedented for a precatalyst not featuring a Ru–NH linkage. To our knowledge, the activity afforded by **3** in ketone TH is surpassed only by a selection of N–H-containing {Ru(ampy)} complexes reported recently by Baratta and co-workers.^[4] The practical utility of **3** (0.01 mol%) was demonstrated through the 0.91 g scale reduction of benzophenone to afford benzhydrol (91% conversion by GC-FID (gas chromatography–flame ionization detector); isolated in 82% yield).

To gain insight into the divergent catalytic performance of 2^+X^- and 3 in the TH of acetophenone, we sought to determine the fate of 2^+Cl^- and 3 upon heating at reflux for 10 min in an *i*PrOH solution containing 20 equivalents of KO*t*Bu; in both cases, quantitative conversion into a single, phosphorus-containing, product 4 was detected spectroscopically [Eq. (2)]. Complex 4 was prepared rationally from 3



(employing 1 equiv of KOtBu in iPrOH) and isolated in 71% yield; both NMR spectroscopy and X-ray diffraction data support the identity of 4 as the hydrido analogue of 3(Figure 1). We have confirmed independently that 2^+Cl^- is transformed cleanly into 3 upon net extrusion of HCl with 1 equivalent of KOtBu in THF, and the conversion of 3 to 4 in basic iPrOH can be viewed as arising from the reaction of KO*i*Pr with **3** to give $[(\eta^6 - p - \text{cymene})\text{Ru}(\kappa^2 - P, N - 1)(OiPr)]$ with subsequent β -H elimination and loss of acetone. The formation of Ru-H complexes from {Ru-Cl} precursors under such conditions is well-established,^[8] and the preponderance of empirical and theoretical evidence points to hydrido species as the active catalysts formed in situ from Ru-Cl precatalysts during the course of ketone TH reactions conducted in basic *i*PrOH.^[1,9] In this regard, our observation that 4 (0.05 or 0.2 mol %) is completely inactive for ketone TH, both in the presence and absence of added KOtBu, is surprising. Evidently, the formation of 4 represents a catalyst deactivation pathway in ketone TH reactions employing $2^+X^$ or 3 as precatalysts. However, such an observation does not rule out the involvement of alternative hydrido species as catalysts in reactions employing precatalysts 2^+X^- or 3, including species that might arise from intramolecular C-H activation involving a ligand NMe fragment.^[5a]

In summary, donor-substituted indenides, such as 1 in the zwitterion 3, are established as a promising new class of non-N-H ancillary ligands for use in constructing highly active

Ru species for the TH of ketones in basic iPrOH. In fact, 3 is the most active in a limited series of precatalysts for ketone TH that do not exploit Ru-NH interactions, providing nearquantitative conversions in minutes for a range of ketone substrates at low catalyst loading and with TOF values as high as 220000 h⁻¹. Interestingly, all previously reported cationic ketone TH precatalysts of the type $[(\eta^6-\text{arene})Ru(\kappa^2-$ P,N(Cl)]⁺X⁻ feature neutral P,N ligands, and are commonly 10^2 to 10^3 times less active than **3**.^[10] Such observations, when considered in the context of the diminished catalytic abilities of 2^+X^- relative to 3, suggest that the anionic nature of the P,N ligand 1 may play an important role in engendering desirable reactivity properties to ketone TH catalysts formed in situ from 3. Experimentation directed toward elucidating the source of the observed reactivity differences between 2^+X^- and 3, as well as identifying the catalytically active intermediates that are generated in ketone TH reactions featuring these precatalysts, is ongoing.

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