Versatile Ruthenium Complex “RuPCY” for Directed Catalytic Hydrogen Management in Organic Synthesis

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Abstract: The ruthenium (Ru) precatalyst complex dichlorobis[2-[(dicyclohexylphosphino- κ P)methyl]pyridine- κ N]ruthenium(II) (RuPCY), first developed by us, was shown to be useful not only for the catalytic hydrogenation of inert carboxylic acid derivatives including amides and esters, but also for the catalytic dehydrogenation of primary (1°) and secondary (2°) alcohols and subsequent reactions. RuPCY is versatile, and different Ru catalysts derived therefrom are quite useful for realizing a variety of indiscrete/discrete catalytic hydrogen management (HyMA) reactions. The sequential use of different starting materials and different catalysts (all derived from RuPCY) permits otherwise challenging orthogonal HyMA processes. This accommodates, for example, a salt-free access and/or shortcut to synthetic intermediates of pharmaceutically important substances such as donepezil (Aricept[®]) and atorvastatin (Lipitor[®]).

1. Introduction

Hydrogenation and dehydrogenation are extremely useful for both industrial processes and laboratory experiments.¹ Hydrogenation of carbonyl compounds and dehydrogenation of alcohols (Figure 1a) are, in principle, a set of complementary reversible hydrogen transfer (HT) processes following an identical reaction coordinate.² HT involves the absorption/desorption of H_2 , 1 equivalent per reactant, in which two hydrogen atoms are sequentially incorporated into/removed from the carbon-oxygen framework. Among representative synthetic applications, asymmetric hydrogenation of ketones has been well established by Noyori and others.³ 2° alcohol-ketone interconversion is promoted by transition metal catalysts,^{2b-d,4} and chiral variants afford asymmetric versions of the dehydrogenation reactions.⁵ Dehydrogenation of 1° alcohols can also be followed by crossed aldol condensation of the resulting aldehydes with ketones,⁶ esters,⁷ and amides⁸ giving α,β -unsaturated carbonyl compounds, and subsequent (transfer) hydrogenation of the ene part gives α -alkylated carbonyl

compounds (Figure 1a $\rightarrow$ 1b).

In contrast, HTs involving effectively 2 equivalents of H_2 (four hydrogen atoms) are mechanistically more intricate (Figure 1a $\rightarrow$ 1c, 1c' $\rightarrow$ 1a', and 1a $\rightarrow$ 1b $\rightarrow$ 1d). These catalyst systems are exemplified by the hydrogenation of an ester,^{1a-c,9} carboxylic acid¹⁰ or amide^{1b-c,11} (Figure 1c' $\rightarrow$ 1a'). Two discrete hydrogenation steps (Figure 1c' and 1a') are involved during the three-step sequence consisting of: 1) hydrogen addition to the $X(C=O)R$ group (ester, carboxylic acid, or amide); 2) β -elimination of XH or H_2O ; and 3) hydrogen addition to the $H(C=O)R$ or $H(C=N)R$ group. The reverse processes, namely intermolecular dehydrogenative alcohol-alcohol,^{1a,b,2c,4d,9e,r,12} alcohol- H_2O ,¹³ and amine-alcohol^{1b,f,11e,g,12c,g,i,14} coupling reactions (giving esters, carboxylic acid, and amides, respectively; Figure 1a $\rightarrow$ 1c), have also been well investigated. On occasions where two or more alcohol molecules are involved in the coupling reaction, dehydrogenation of an alcohol is followed either by dehydrative dialkyl acetal formation,¹⁵ or by dehydrative carbon-carbon bond formation through aldol condensation with a carbonyl compound derived by dehydrogenation of

Figure 1. 1° (when $R^1=H$) and 2° (when R^1 =any carbon chains) alcohols in center of multifaceted hydrogen transfer (HT) processes in strategic hydrogen management (HyMA) for: (a) dehydrogenation of alcohol and (a') the reverse; (b) aldol condensation/ene hydrogenation of α,β -unsaturated carbonyl compound, giving α -alkylation; (c) dehydrogenative synthesis of carboxylic acid and its derivatives and (c') the reverse; (d) “post (b)” reaction: ketone hydrogenation; (e) “post (a)” reaction: dehydration/hydrogenative N-alkylation; (f) dehydrative N-alkylation.

Figure 2. Our studies on multifaceted hydrogen management (HyMA) in virtually “salt-free” organic synthesis. Reactions in lines are promoted by RuPCY. (a) alcohol in α -alkylation of ketone; (b) alcohol formation by hydrogenation of amide and ester; (c) β -amino alcohol in α -alkylation of ketone and imine formation for pyrrole synthesis; (d) alcohol generated by ester hydrogenation for α -alkylation of ketone that leads to donepezil.

the other alcohol and subsequent (transfer) hydrogenation of the ene and carbonyl groups, giving carbon-elongated saturated alcohols (Guerbet-type reaction) (Figure 1a $\rightarrow$ 1b $\rightarrow$ 1d).¹⁶

In the presence of an amine, dehydrogenation of the alcohol followed by dehydrative reaction with the amine produces an imine, after which the reaction ceases,¹⁷ or further (transfer) hydrogenation of the C=N bond affords N-alkylation, giving an amine^{2h,14d,18} (Figure 1a $\rightarrow$ 1e). Our group previously reported exceptional N-alkylation with 1°, 2°, and tertiary (3°) alcohols, where only dehydration, in the absence of dehydrogenation, was involved (Figure 1f).¹⁹ This dehydration took place merely as a consequence of (mainly S_N2) substitution of the alcoholic carbon by the amine nitrogen. In contrast, allylic alcohols are converted into π -allyl metal complexes and frequently used as N-allylating agents.^{19c-i}

In each reaction, specific Z-H (Z=H, C, N or O) bonds are cleaved, accompanied by subsequent C-Z (Z=H, C, N or O) bond formation without producing salt wastes (Figure 1a-1f). Alcohol is in center of hydrogen management (HyMA), working not only as a reactant, but also as a hydrogen shuttle/hydrogen storage. Thus catalytic HyMA can control great diversity in bond cleavage and formation involving various HT reactions (many involving alcohols) by altering the behavior and movement of hydrogen atoms (e.g., H^+ , H^- , $H^\cdot$, $H^+ + e^-$), abstracted from H-H, C-H, N-H, and O-H bonds. Overall scenario depicted in Figure 1 clearly indicates that the hydrogens generated in HyMA are incorporated into desirable product(s) including H_2 (2H) and/or H_2O (as a byproduct), and are not transferred to an inorganic/organic base for neutralization, forming salt waste/byproducts. Each HT step involves a distinct mechanism, and thus, each HT may require a specialty transition metal catalyst developed separately. Thus, directed assembly of an HT catalyst pool using the same

precatalyst to achieve an intricate array of HyMA strategies to allow complementary Z-H bond cleavage and C-Z bond formation in one-pot, is a significant challenge and a desirable goal. The ruthenium precatalyst complex “RuPCY” (PCY=PhosphinatodiCYclohexyl), can discretely catalyze a variety of HT reactions including hydrogenation of amides²⁰ and esters,²¹ as well as dehydrogenation of 1° and 2° alcohols²² and subsequent carbon-carbon bond-forming reactions (Figure 2). In addition, RuPCY is versatile in maintaining the consecutive nature of a multistep HyMA catalysis such that different reactants (e.g., ester, H_2 , alcohol, ketone, olefin) can, in turn, undergo multifaceted HTs in one pot. One example of the overall sequence can be represented by: i) hydrogenation of ester giving alcohol; ii) transfer dehydrogenation of the alcohol giving the aldehyde or ketone; iii) crossed aldol condensation of the resulting carbonyl compound with a second ketone giving an α,β -unsaturated ketone; and iv) transfer hydrogenation of the olefin of the α,β -unsaturated ketone giving the saturated ketone. These four steps can be applied for an atom- and step-economical one-pot synthesis of donepezil (HCl salt: Aricept®).²¹ The core pyrrole structure of Lipitor® is similarly accessible, as it is synthesized via a set of different HT reactions.²²

2. Hydrogenation of Unactivated Amides

Amides are ubiquitous and abundant in nature and our society. For example, they could be found in the repeating units of polypeptide macromolecules and artificial polymeric materials (e.g., poly(acrylamide), nylons, Kevlar), and their respective monomers (e.g., α,β -unsaturated carboxamides, caprolactams), which can be produced on an enormous scale via existing industrial processes. They also exist as potent pharmacophores,^{9i,23} which are useful building blocks accessible via many

synthetic methods.²⁴ Were it possible to develop catalytic transformations of amide resources without the salt-containing wastes formed in stoichiometric amounts with respect to the amide, such chemical processes would provide a shortcut or alternative route to presently known and/or unknown materials or chemicals. However, amides are very stable and reluctant to salt-free, catalytic chemical transformations, which are significantly challenging, as there is a lack of basic knowledge concerning the catalytic activation. As a part of our continuous research on the catalytic transformation and functionalization of amides (AD),²⁵ we recently found a more general method than precedents,^{1b-e,11} for the hydrogenation of unactivated amides, affording selective C–N or C=O bond cleavage using a new Ru complex RuPCY.²⁰

Treatment of a toluene solution of AD-**a** and RuPCY (2 mol %) with sterically bulky base BS-**a** (20 mol %) under hydrogen pressure (P_{H_2}) of 8 MPa at reaction temperature (T) of 160 °C for reaction time (t) of 24 h gave the corresponding alcohol (AL) and amine (AM), AL-**a** and AM-**a**, in 92% yield (eq. 1). The steric bulkiness of the base was more important than its basicity under similar conditions ($[\text{Ru}]_0 = 6.7 \text{ mM}$; $P_{\text{H}_2} = 6 \text{ MPa}$, 160 °C, 48 h): use of phenoxide BS-**b** in place of BS-**a** gave AL-**a** with similar effectiveness (AL-**a**: 94%, AM-**a**: 86%). Smaller bases including NaOtBu, KOtBu, NaOMe and NaOH gave lower productivity (AL-**a**: 2–43%). According to control experiments using smaller RuPCY derivatives, the combined use of RuPCY and a base additive such as BS-**a** or BS-**b**, both being sterically demanding, is crucial for selective hydrogenation.

This hydrogenation method was selective (i.e., negligible dearomatization) and showed wider substrate scope with respect to unactivated amides. Selective C–N bond cleavage of linear amides was uniformly observed (eqs 2–8).¹¹ⁱ 1° and 3° amides AD-**b** and AD-**c**, and simple aliphatic 2° amides AD-**d** and AD-**e**, were also applicable substrates. The active species maintained its catalytic integrity even after a lengthy reaction time in the hydrogenation of 1° amide AD-**b** (eq. 2), but marginal hydrogenation took place with more bulky AD-**f** (eq. 6). The hydrogenation of ϵ -caprolactam (AD-**g**), a cyclic amide, showed a similar pattern of bond cleavage (eq. 7). Hydrogenation was rather sluggish with AD-**h** derived by N-methylation of AD-**g** (eq. 7). Product AA-**g** and AA-**h** could be a synthetic precursor of *N,N*-dimethyl-6-amino-1-hexanol, a polymerization initiator.²⁶

Hydrogenation of urea^{11o-q} AD-**i** is important with respect to the methanol economy,²⁷ since ureas are excellent chemical reservoirs and carriers of CO_2 (eq. 8). However, a larger amount of base (20 mol %) only ensured a reasonable reaction rate for the more inert aliphatic amides.

In contrast, C=O bond cleavage predominated with five-

and six-membered lactams AD-**j** and AD-**k** (eq. 9). This apparent C=O bond scission can be explained by a multistep HyMA sequence consisted of hydrogenative C–N bond cleavage of the amides giving $\text{NH}_2(\text{CH}_2)_n\text{OH}$, followed by oxidation of the HOCH_2- group giving $\text{NH}_2(\text{CH}_2)_{n-1}\text{CHO}$, then intramolecular imine formation, and finally, imine hydrogenation (Figure 3). In fact, when AA-**k** was used as the starting material in the absence of H_2 or with $P_{\text{H}_2} = 8 \text{ MPa}$ under otherwise identical conditions ($T = 160 \text{ °C}$, $t = 24 \text{ h}$), amide AD-**k** and piperidine (AM-**k**) were obtained in 53% and 25%, and 28% and 48% yields, respectively.

Hydrogenation was generally sluggish ($t > 24 \text{ h}$) and

Figure 3. Control experiments using AA-**k** in the presence or absence of H_2 .

required harsh reaction conditions. A high temperature and a high P_{H_2} may be required either to produce a catalytic species from RuPCY, or for the hydrogenation of amide. To probe this speculation, BS-a (4 mol %) was exposed to a toluene solution of RuPCY (2 mol %) in the absence of amide (e.g., AD-a) for preactivation of the catalyst (P_{H_2} =8 MPa, T =160 °C, t =5 h), and the resulting matured catalyst was used for the hydrogenation of AD-a under milder conditions with a shortened t (P_{H_2} =4 MPa, T =140 °C, t =12 h). Indeed, AL-a and AM-a were produced in 89% and 89% yields, respectively. When even milder conditions were used for the hydrogenation of AD-a (P_{H_2} =2 MPa, T =120 °C) using the preactivated catalyst, a high yield of AL-a (93%) and AM-a (92%) was still obtained by prolonging the reaction time to 60 h.

What would be the structural change of RuPCY that occurs during the induction period of catalyst under a high temperature and a high P_{H_2} ? To clarify this, the $^{31}\text{P}\{^1\text{H}\}$ NMR (toluene- d_8) spectrum of the reaction mixture obtained after a period of the optimal preactivation (vide infra) showed a major singlet at δ -15.2 ppm corresponding to saturated amino phosphine AP-a. In order to further confirm the identity of the catalytic species involving AP-a, the reaction mixture was quenched with excess $\text{BH}_3\cdot\text{THF}$ and was analyzed via electrospray ionization mass spectroscopy. The base peak obtained matched fully saturated AP-a complexed with BH_3 . The mercury test²⁸ was also employed, in which Hg(0) was added during the hydrogenation step to probe the possibility of catalysis by a Ru nanoparticle. The catalytic activity was not perturbed during the course of the reaction (AL-a: 94%; AM-a: 92%). All these control experiments suggest that either RuPCY- h_{16} or RuPCY- h_8 would be a resting state of the catalyst (Figure 4). In any event, hydrogenative HyMA was involved in reduction of the interior structural part of precatalyst RuPCY during induction period of catalyst.

Figure 4. Proposed mechanism "multi-hydrogenation" of RuPCY involved behind catalyst preactivation.

3. Hydrogenation of Esters

Since catalytic RuPCY and alkoxide base BS-a was proven to be effective for the hydrogenation of unactivated amides (P_{H_2} =2–8 MPa, T =120–160 °C, toluene), these optimized amide hydrogenation conditions were also used for the hydrogenation of esters (ES). The hydrogenation of methyl benzoate (ES-a) took place, however, sluggishly. Use of catalytic NaBH_4 and THF in place of BS-a and toluene was more promising. Hydrogenation of ES-a gave AL-a quantitatively (P_{H_2} =6 MPa, T =160 °C, t =24 h; $[\text{Ru}]_0$ =3.3 mM; RuPCY (1 mol %) in THF, NaBH_4 (10 mol %)). The Hg(0) test²⁸ was again employed, in which the catalytic activity was not perturbed (AL-a: 94%), excluding the possibility of catalysis by a Ru nanoparticle. In addition to the methyl ester, ethyl- (Et-), isopropyl- (iPr-), benzyl- (Bn-) and phenyl (Ph) benzoates underwent effective hydrogenation under otherwise identical reaction conditions, consistently giving AL-a in near quantitative yields (94–99%). In contrast, hydrogenation of *tert*-butyl (*t*Bu) benzoate was very ineffective (AL-a: 4%). The hydrogenation of ES-a was mildly affected by P_{H_2} (Figure 5a), and proceeded even under P_{H_2} =1 MPa, albeit with a decline in reaction rate of nearly one half from that observed under P_{H_2} =3 MPa. In contrast, the hydrogenation rate was significantly affected by T (Figure 5b).

Figure 5. Effects of: (a) P_{H_2} (MPa) at 160 °C; and (b) T (°C) at P_{H_2} =6 MPa on yields (%) of AL-a (filled circle) and ES-aa (cross) in hydrogenation of ES-a. Reaction time (t)=12 h; $[\text{Ru}]_0$ =3.3 mM (RuPCY (1 mol %) in THF); NaBH_4 (10 mol %).

A temperature of at least 140 °C was critical in order to maintain fair to excellent catalytic activity, and the rate dropped significantly at 130 °C and below. Hydrogenation of ES-a was faster with $[\text{Ru}]_0$ =10 mM than with $[\text{Ru}]_0$ =3.3 mM. Under the most expedient conditions (P_{H_2} =6 MPa; T =160 °C; $[\text{Ru}]_0$ =10 mM), the induction period of catalyst (preactivation period) was ca. 2 h, with a total reaction time of 4–5 h for full conversion of ES-a. During preactivation, alcohols CH_3OH

and AL-a (BnOH) were gradually generated as the hydrogenation proceeded, and concomitantly, the reaction rate sped up. It was therefore envisaged that added alcohol would have some effect on accelerating the catalyst preactivation. Indeed, when the hydrogenation of ES-a was initiated in the presence of catalytic AL-a (2 mol %), the original preactivation period of ca. 2 h was significantly shortened to <20 min (Figures 6 and 7). Thus, to best affect the preactivation, an appropriate amount of AL-a should be added before starting the hydrogenation of ES. This addition of an alcohol to shorten the induction period of catalyst is a new strategy in the development of catalysts promoting ester hydrogenation.

Figure 6. Effects of catalytic BnOH on hydrogenation of ES-a.

Figure 7. Effects of catalytic alcohol on *t*-dependent yield (%) of AL-a with: AL-a (2 mol %) (filled circle); and without BnOH (cross) in hydrogenation of ES-a. P_{H_2} =6 MPa, T =160 °C; $[Ru]_0$ =10 mM (RuPCY (1 mol %) in THF); $NaBH_4$ (10 mol %).

The ester was switched from aromatic ES-a to aliphatic ES-b, and several parameters that affect the hydrogenation rate were investigated (Figure 8). The effect of alcohol identity on preactivation was explored, and other alcohols including EtOH (and *i*PrOH) had a similar but less efficient effect (eq. 10). All reactions shown here were thus carried out with a catalytic amount of AL-a. Hydrogenation took place reason-

Figure 8. Effect of P_{H_2} and amounts of RuPCY and catalytic AL-a on hydrogenation rate.

ably even under low P_{H_2} (entries 1–3 vs. 4). Catalyst loading was successfully reduced to the range of 0.1–0.4 mol % (entries 5–7) and the maximum turnover number (TON) so far observed was ca. 720 (entry 7).

In an effort to elucidate how the alcohol affects catalyst preactivation, control experiments were carried out (Figure 9). When RuPCY was heated in toluene under N_2 with $NaBH_4$ in the absence or presence of EtOH (toluene/EtOH (v/v)=1/1), RuPCY-H(BH_4) was formed (66%) only in the latter case. Therefore, the alcohol may activate $NaBH_4$, promoting abstraction of chloro groups from a Ru center and liberating NaCl, facilitating smooth generation of a Ru-H species, even without H_2 .^{9r,29}

Figure 9. Effect of alcohol on formation of Ru-hydride species (no H_2).

The substrate generality of the ester hydrogenation system was tested using catalytic RuPCY, AL-a and $NaBH_4$. The results are listed in eqs 11–16. Methyl esters and 1° alkoxy carbonyl compounds including bigger and smaller aliphatic esters (ES-c and -g), aliphatic and aromatic diesters (ES-h and -i), and triesters (lipids (triglycerides) ES-j, -k, and -l) are all compatible with the present reaction conditions, giving AL-c and AL-g-l. The market demand of diol AL-i (eq. 14) is increasing very rapidly as a monomer of poly(urethane)s.³⁰ Internal olefins were unfortunately hydrogenated (eq. 15). Three different lipids also underwent almost full conversion of all the interior ester moieties, albeit with the requirement of a higher T and a prolonged t (eq. 15). To the best of our knowledge, this is the first example of effective lipid hydrogenation using a homogeneous mononuclear Ru complex as a catalyst precursor.²¹ It is clear that in the hydrogenation of both amides and esters, RuPCY can essentially maintain a molecular structure of the form $Ru(P,N)_n$ ($n=1$ or 2) even for a lengthy t at high T . Thus, the catalyst generated during ester hydrogenation could be used subsequently for a different reaction.

N-benzyl-4-ethoxycarbonylpiperidine (ES-m), which has been proposed by Eisai Co., LTD. to be a cheaper alternative ingredient for production of donepezil,³¹ was also fully hydrogenated (eq. 16). This reaction encouraged us to seek out a set of different HT processes, in which dehydrogenation of (1-benzylpiperidin-4-yl)methanol (AL-m) giving the aldehyde *N*-benzyl-4-formylpiperidine (AH-m), followed by aldol condensation (dehydration) of the aldehyde with ketone KE-a and subsequent chemoselective (transfer) hydrogenation of the olefin over the carbonyl group of the α,β -unsaturated ketone KE-am, gives donepezil (Figure 10).

Figure 10. Proposed scenario for intricate HyMA: multifaceted HT involving hydrogen movement from 2H_2 to produce donepezil.

4. Dehydrogenation of Alcohols for Carbon–Carbon Bond Formation

4.1 α -Alkylation of Ketones Initiated by Dehydrogenation of 1° and 2° Alcohols and Subsequent (transfer) Hydrogenation: Donepezil Synthesis

To complete the consecutive orthogonal HyMA processes for synthesis of donepezil, the capability of a single Ru complex (RuPCY), catalyzing different HT ((transfer) dehydroge-

nation/hydrogenation) reactions, was also surveyed in the alkylation of the α -carbon of a ketone (KE) with an alcohol. Here, an α,β -unsaturated ketone having two functional groups (an olefin and a carbonyl), both potentially susceptible to undergoing (transfer) hydrogenation, is the reaction intermediate. It is not a trivial task to control/limit the selectivity of hydrogen addition to an olefin vs. a carbonyl group using catalytic base and a transition metal catalyst in cross-coupling reactions involving HT. 5,6-dimethoxy-1-indanone (KE-a) was chosen as a model substrate, since KE-a serves as a pivotal carbon fragment of donepezil. KE-a was reacted with various alcohols including CH_3OH , 1° and 2° alcohols (Figure 11) in the presence of RuPCY (1 mol %).

Figure 11. α -Alkylation of KE-a. $\text{R}=\text{CH}_3$ (400 mol %), Et (170 mol %), PhCH_2 , $\text{CH}_3(\text{CH}_2)_{17}$, $i\text{Pr}$ (400 mol %), and Cy. Values in parentheses are isolated yields.

Without purging H_2 , the α -alkylation proceeded under N_2 most selectively with high productivity using NaOtBu (10 mol %) as the base additive, where the ketone functionality consistently remained unreacted. Using NaOtBu or KOtBu alone, no reaction took place. Less volatile 1° alcohols such as AL-a were generally among the most efficient substrates for such selective α -alkylation (KE-a:ROH (mol:mol)=1:1), while the more volatile MeOH and EtOH, and 2° alcohols including $i\text{PrOH}$ and CyOH, were used in excess amounts, affording α -alkylation in low to good yields. The HT-based α -alkylation of a ketone with a 2° alcohol, which corresponds to a direct crossed aldol condensation of two different ketones giving β,β -disubstituted- α,β -unsaturated ketones, followed by selective (transfer) hydrogenation of the resulting interior olefin, appears only very scarcely in the literature.^{6,16j,k}

A similar catalyst system was applied to the α -alkylation of KE-a with AL-m for the synthesis of donepezil. Screening of additives and solvents using precatalyst RuPCY was carried out in the absence of H_2 gas. Donepezil was not obtained at all without RuPCY. Under the reaction conditions, toluene was the solvent of choice, rather than THF or dioxane. A combination of NaBH₄ (10 mol %) and RuPCY (1 mol %) in THF (the conditions which were the most effective for ester hydrogenation) was less satisfactory for the α -alkylation of KE-a (donepezil: 37% with $T=160^\circ\text{C}$, $t=24\text{ h}$). Different additives had a significant influence on the reaction rate, and donepezil (99%) was obtained most effectively again with catalytic NaOtBu (eq. 17). A shortened reaction ($t=1\text{ h}$) even afforded 72% of donepezil under otherwise identical conditions.

Although AH-m has been thought to be a key intermedi-

ate,³¹ this result is in contrast to the prior synthesis and isolation of AH-m (Figure 12), in which formation of salt waste could not be avoided.³²

Figure 12. Conventional synthesis of donepezil in three-to-four batch reactions, compared with present method.

4.2 α -Alkylation of Ketones Initiated by Hydrogenation of Esters Followed by Dehydrogenation of 1° Alcohols: Donepezil Synthesis

Although it was considerably challenging, synthesis of donepezil from ES-m using multistep HyMA catalysis was carried out in a one-pot operation using the same RuPCY precatalyst (Figure 13). The optimal additives and solvents were different for hydrogenation of ES-m and α -alkylation of KE-a with AL-m. The hydrogenation of ES-m in THF was followed by addition of KE-a, NaOtBu and excess toluene. The reaction mixture (THF/toluene (v/v)=1/1) was subjected to the reaction conditions for the subsequent α -alkylation step (Figure 13a). By carrying out the α -alkylation of the crude mixture of KE-a at 160 °C without removal of any volatile components produced in the first (hydrogenation) step, donepezil was obtained in 49% yield; however, 2-ethyl-5,6-dimethoxy-1-indanone (KE-c, Figure 11) was also obtained in 36% yield. The EtOH generated during the hydrogenation of ES-m in the first step reacted smoothly with KE-a giving KE-

In order to remove the EtOH generated in the ester hydro-

Figure 13. Synthesis of donepezil in one pot through multifaceted HyMA.

genation step before proceeding to the α -alkylation step, the solvent was evaporated *in vacuo* after the hydrogenation of ES-m, and toluene was added to the residual mixture for the second step. As a representative procedure (Figure 13b), a THF solution of ES-m was hydrogenated (P_{H_2} =6 MPa) using RuPCY (2 mol %) and NaBH₄ (20 mol %) at 160 °C for 24 h. After the autoclave cooled, H₂ gas was carefully vented from the leak valve and the solvent was removed *in vacuo* at 100 °C for 1 h. Finally, KE-a, NaOtBu (20 mol %) and toluene were added to the crude mixture in a Teflon tube inserted into the autoclave, and the reaction was resumed under N₂ (T =160 °C, t =5 h). Donepezil was obtained in ~90% yield (by NMR). In the reported synthesis (Figure 12),^{31,33} donepezil was available from ES-m in four steps^{33b} using four reaction vessels and giving non-negligible amounts of different salt wastes. On the other hand, we succeeded in synthesizing donepezil from ES-m via multistep HT processes in a one-pot operation. Furthermore, the amount and variety of salt wastes generated during the reactions were significantly reduced in comparison with any prior donepezil synthetic approaches.³³ Thus, it has been demonstrated here that a HyMA strategy can serve as an overwhelmingly powerful concept for achieving high atom- and step economy when combining various processes in a single reaction vessel.

4.3 α -Alkylation of Ketones for Pyrrole Synthesis Initiated by Dehydrogenation of β -Amino 1° Alcohols: Rapid Access to the Core Pyrrole Structure of Lipitor®

As demonstrated in the donepezil synthesis (eq. 17 and Figure 13), a HyMA process starting from (transfer) dehydrogenation of an alcohol followed by a crossed aldol reaction can be a useful tool in organic synthesis. In order to expand the potential of RuPCY as catalyst in the α -alkylation of ketone(s), simple alcohols used (Figure 11) were switched to more functionalized alcohols such as β -amino alcohols.

Related fundamental processes, frequently referred to as “hydrogen autotransfer,”^{1k,l} “borrowing hydrogen,”¹ⁱ or “acceptorless dehydrogenation,”^{1f} have usually been carried out using a transition-metal catalyst based on Ru,³⁴ Ir,^{16f,34} Ni,³⁵ Pd,^{16j,36} Ag,³⁷ Cu,^{16h,1,38} Fe³⁹ or Au⁴⁰ in the presence of a *stoichiometric* (or in rare cases, *catalytic*^{16l}) amount of an alkali metal base. Non-transition metal-based systems,^{6a} e.g., stoichiometric KOtBu,⁴² and catalytic KOH (or NaOH)/air⁴¹ or NaOH/H₂-promoted versions,^{43a} can also be effective. However, detailed studies are lacking as to *which species, the transition metal or the base, is more responsible for the catalysis*. Our original studies demonstrated that even “only base” could promote the α -alkylation of ketones^{16l} or β -alkylation of alcohols with alcohols,^{43a} but RuPCY could cooperate significantly with the base in promoting the catalysis. Thus, a virtually salt-free and highly versatile synthesis of *N*-unsubstituted pyrroles (PY) using a catalytic amount of RuPCY and an alkali metal base, in which readily available and easily varied ketones (KE) react with α -amino aldehydes generated *in situ* from fully unmasked β -amino alcohols, was attempted (Figure 14).

From a synthetic point of view, successful control of the reactivity of otherwise unstable “fully unmasked” α -amino aldehydes in cross-coupling reaction is rare. Fully unmasked α -amino aldehydes are notoriously unstable synthetic intermediates, difficult to isolate, and rarely used in organic synthesis.⁴⁴ For example, rapid degradation of valinal is accompanied by self-dimerization giving the symmetric pyrazine.⁴⁵ Recently,

Figure 14. Overview of dehydrogenative and dehydrative HyMA involved in the synthesis of pyrrole rings.

Ishii,⁴⁶ Kempf,⁴⁷ Milstein⁴⁸ and Beller^{22b,49} reported a similar pyrrole synthesis starting from β -amino alcohols (or its equivalent), a combination of 1° amines and ethylene glycol derivatives. That system was further extended to the syntheses of pyridine and quinoline derivatives using γ -amino alcohols in place of β -amino alcohols.⁵⁰ Nevertheless, it had proved possible for us to couple two different unmasked β -amino alcohols giving substituted pyrroles using rhodium catalysts with catalytic alkali metal base^{43b} and to couple ketones and β -amino alcohols using only a catalytic amount of NaOH or KOtBu *without any transition metals*.^{43a}

To begin, a 1:2 molar ratio of valinol (AA-a) to propiophenone (KE-h) was subjected to catalytic amounts of RuPCY and KOtBu in toluene to synthesize 2,3,5-trisubstituted pyrrole PY-ah (eq. 18).

We knew from our previous studies⁴³ that the concentration of alkali metal alkoxide significantly affects catalytic activity, depending on the solvent used, presumably due to the structure diversity of different clusters of alkoxides and enolates (dimers, tetramers, hexamers, etc.) which also show intricate structural dynamics.⁵¹ Therefore, the effect of several factors, namely [RuPCY]₀ (0–15 mM; 0–2 mol % relative to AA-a), [KOtBu]₀ (25–74 mM; 10 mol %), and [KOtBu]₀/[RuPCY]₀ (1/0 to 100/1), on the yield of PY-ah were investigated. The noteworthy results obtained during the investigation of the synthesis of 2,3,5-trisubstituted pyrroles are: (1) without RuPCY, the yield of pyrrole PY-ah averaged around 30% using catalytic KOtBu. In order to obtain PY-ah in higher yields in the presence of RuPCY (than in its absence), [KOtBu]₀ should be higher than 37 mM; (2) In contrast, when [KOtBu]₀ was lower (e.g., 25 mM), the best yield of PY-ah (~40%) was obtained without RuPCY (0.25–2 mol %). In this case, the addition of RuPCY was detrimental to the effective production of PY-ah; (3) at a higher concentration of [KOtBu]₀ (74 mM), a [KOtBu]₀/[RuPCY]₀ of 40 ([RuPCY]₀=1.9 mM) gave the highest yield of PY-ah (52%) with AA-a/KE-h=~1.2; (4) The [KOtBu]₀/[RuPCY]₀ ratio was more critical than the [AA-a]₀ or [KE-h]₀ to the reaction rate in the dehydrogenation of AA-a (which corresponds to the yield of AL-ah), and to an increase in the apparent overall reaction rate leading to PY-ah. All these preliminary experiments suggest that RuPCY would help the role of (KOtBu)_n clusters or vice versa, although it is difficult to ascertain which chemical entity is the major player for inducing catalysis.

Among the higher concentrations of [KOtBu]₀ tested, non-solvent (neat) conditions ([KOtBu]₀=ca. 260 mM; [RuPCY]₀=6–7 mM) afforded the highest yield of PY-ah (77%). When other ruthenium complexes, such as CpRuCl(PPh₃)₂ (0.25 mol %) and [(p-cymene)RuCl]₂ (0.125 mol %), were reacted for 6 h in place of RuPCY under otherwise identical neat conditions, PY-ah was obtained in lower yields (49% and 32%, respectively). Not more than one out of two equiv of KE-h relative to AA-a should be required to work as the H₂ acceptor for the synthesis of 2,3,5-trisubstituted pyrroles. Examples of catalytic synthesis of 2,3,5-trisubstituted pyrroles PY-ah-ak, PY-bh, PY-bk, PY-ch, and PY-dh using RuPCY (0.25 mol %) under neat conditions using β -amino alcohols AA-a-d and ketones KE-h-k are summarized (Figure 15). KE-h-k also worked as hydrogen acceptors and ALs are always generated as sacrificial byproducts.

Figure 15. Unless otherwise specified, the solvent-free reaction was carried out at 165 °C for 24 h under N₂ with [KOtBu]₀=ca. 260 mM; [KOtBu]₀/[Ru]₀=40; RuPCY:KOtBu:AA:KE=1:40:400:800. Yields % are based on AA, determined by ¹H NMR. The values in parentheses are of isolated, purified PY. ^at=6 h.

In contrast, the reaction of AA-a with methyl ketones such as acetophenone (KE-l) that gives 2,5-disubstituted pyrrole (e.g., PY-al) was unselective under such solvent-free, "neat" conditions. Rather, a more dilute toluene solution, with [KOtBu]₀=ca. 90 mM and [RuPCY]₀=2–3 mM (1 mol %), was promising for the prevention of the self-dimerization of KE-l. The reactions were faster and nearly complete within 3 h. Evolution of H₂ was detected in all cases by micro-GC analysis, demonstrating the acceptorless dehydrogenation^{1f} followed by a bimolecular aldol reaction. Synthesis of 2,5-disubstituted pyrroles PY-al-an, PY-cl and PY-ao using amino alcohols and different ketones KE-l-o are listed (Figure 16).

The versatile nature of this approach was further demonstrated by the shortest access to the core pyrrole (PY-ap) of Lipitor® (atorvastatin calcium)⁵² upon reaction of the natural resource AA-a with KE-p (eq. 19). 2,3,4,5-Tetraphenyl-1H-pyrrole⁵³ (PY-ek) was formed by reaction of AA-e with KE-k in a simplest way (eq. 20). In these cases, PY-ap and PY-ek

Figure 16. Unless otherwise specified, the reaction was carried out in toluene for 3 h under N₂ with [KOtBu]₀ = ca. 90 mM; [KOtBu]₀/[Ru]₀ = 40; RuPCY:KOtBu:AA:KE = 1:40:150:100. Yields are based on KE, determined by ¹H NMR. The values in parentheses are of isolated, purified PY. ^at = 24 h. ^bAA-a:KE-I = 1:1. ^cReaction conditions, those described in the footnote in Figure 15.

were not formed without using RuPCY, as ascertained by ¹H NMR. PY-ap was synthesized previously in a more tedious multistep reaction⁵⁴ or via three component coupling^{22b,49} prior to being converted to Lipitor® through a few synthetic steps.⁵⁴

5. Conclusion

A HyMA strategy based on the use of RuPCY has been shown to be effective for controlling diverse HTs, thereby rendering multiple, separate processes consecutive for the rapid synthesis of valuable products, e.g., donepezil and Lipitor®. The results constitute a paradigm shift from a synthesis generating salt (metallic) waste to a HyMA-based atom- and step-economical synthesis. The multistep synthesis starting from inert organic substances in high oxidation states is consisted of a new portfolio of selective reduction (functional group transformation) and subsequent skeletal carbon-carbon bond-forming reactions using alcohol.

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