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Transition metal-catalyzed redox isomerization of codeine and morphine in water†

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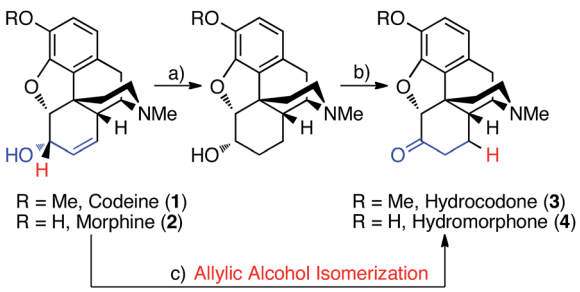
A water-soluble rhodium complex formed from commercially available $[Rh(COD)(CH_3CN)_2]BF_4$ and 1,3,5-triaza-7-phosphaadamantane (PTA) catalyzes the isomerization of both codeine and morphine into hydrocodone and hydromorphone with very high efficiency. The reaction is performed in water, allowing isolation of the final products by simple filtration, which results in very high isolated yields. The reactions can be easily scaled up to 100 g.

Opium and its derivatives have been used throughout history for medicinal and social purposes. Hydrocodone and hydromorphone are common semi-synthetic opiate drugs used in the treatment of different diseases as, for example, analgesics, antitussives, and sedatives.[1] Their use has increased in recent years,[2] as they have superior therapeutic and pharmacokinetic effects compared to codeine and morphine, and are less likely to cause physical dependence. The natural alkaloids codeine (**1**) and morphine (**2**) can be transformed into hydrocodone (**3**) and hydromorphone (**4**) in a two-step sequence: transition metal-catalyzed hydrogenation followed by Oppenauer oxidation using ^{t}BuOK and benzophenone (Scheme 1).[3,4] This synthesis route uses oxidants in stoichiometric amounts, and consequently requires tedious purifications, which diminishes the yields. A more efficient alternative to achieve these transformations is the transition metal-catalyzed redox isomerization of the allylic alcohol moieties (Scheme 1, path c).[5,6] This method yields the products in a single synthetic step through a formal 1,3-hydrogen shift.[5–7] Great advances have been made in this area of research in the past decade using simple substrates.[8–10] Applying the transition metal-catalyzed redox isomerization reaction to synthesize semi-synthetic opiate drugs requires overcoming important challenges.[5,6] For example, the presence of several functional groups in these molecules (*e.g.*, –OH, R^1–O–R^2, –NR_3) may hinder the activity of the metal complex, and in general, the isomerization of cyclic allylic alcohols is more difficult than that of acyclic ones. Some pioneering examples on the isomerization of codeine and morphine using transition metal complexes (Rh and Ru) in organic solvents have been reported.[5,6] Although these reported methods afford the corresponding hydrocodone or hydromorphone in moderate to good yields using catalytic amounts of transition metal complexes (0.3–4 mol%), they require the use of dried organic solvents such as toluene, MeOH or CH_2Cl_2.[6] In some instances, the activation of the catalysis using H_2 gas or MeONa was needed.[6b–d] However, there is no report of the use of this catalytic method (*i.e.* transition-metal-catalyzed isomerization of the allylic alcohol moiety) in water for the synthesis of hydrocodone and hydromorphone. This would greatly simplify the purification of the final products since organic solvents are not used, and the products can be separated by simple filtration. This would minimize their decomposition during tedious purifications and afford higher isolated yields.

Here we report the redox isomerization of codeine (**1**) and morphine (**2**) into hydrocodone (**3**) and hydromorphone (**4**), respectively, in water and in excellent yields using a commercially available rhodium complex. Compared with other systems described for the isomerization of codeine and morphine, this



Scheme 1 Synthesis of hydrocodone and hydromorphone. (a) Transition metal-catalyzed hydrogenation; (b) Oppenauer oxidation; (c) redox isomerization.[5,6]

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method displayed many advantages such as cost-effective reactions due to the low catalyst loading used and straightforward product isolation.

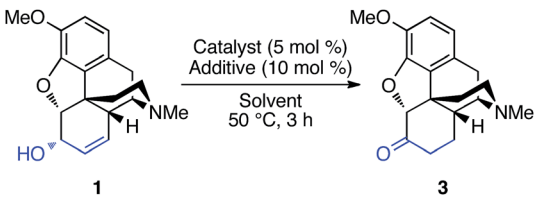
In order to get familiar with the reactivity and handling of these opiate compounds in our laboratory, we first investigated the redox isomerization of codeine (**1**) catalyzed by different readily available transition metal complexes based on ruthenium and rhodium (Table 1) in organic solvents. With Ru complexes (Table 1, entries 1–6), full conversion to the desired product **3** was only observed when $RuCl_2(PPh_3)_3$ was used in dry toluene in the presence of ^{t}BuOK (Table 1, entry 2).[11] $RuCpCl(PPh_3)_2$ gave a complex mixture of unidentified products (Table 1, entry 3) and $[Ru(p\text{-cymene})Cl_2]_2$ (Table 1, entry 4) afforded very low conversions. With the aim of being able to run the reaction in water, we turned our attention to the use of $[Ru(\eta^3:\eta^3\text{-}C_{10}H_{16})Cl_2]_2$, one of the most active Ru catalysts described for the redox isomerization of allylic alcohols in water.[10a] Unfortunately, the starting material was recovered with or without addition of Cs_2CO_3 (Table 1, entries 5 and 6). $RhCl_3\cdot 3H_2O$ did not catalyze the isomerization (Table 1, entry 7). However, $[Rh(COD)(CH_3CN)_2]BF_4$ (**5**) when combined with the water-soluble phosphine 1,3,5-triaza-7-phosphaadamantane (**L1**, PTA) in H_2O as the solvent[10b] gave >99% conversion of the starting codeine into hydrocodone (Table 1, entry 9 *vs.* entry 8).

Further optimization of the reaction catalyzed by $[Rh(COD)(CH_3CN)_2]BF_4$ (**5**) and PTA (**L1**) in H_2O was carried out (Table 2). An advantage of using water as the reaction medium is that the product precipitates, and it can therefore be easily purified by filtration. Since both starting material (**1**) and final product (**3**) are insoluble in H_2O, reactions were run to full conversion. All optimization reactions were performed on a one gram scale (3.34 mmol of **1**) to ensure reproducibility.

When the catalyst loading was decreased from 5 mol% to 1 mol% at 80 °C, the activity was not significantly affected (Table 2, entry 1 *vs.* 2). Lower catalyst loadings (0.1 mol%) did not give full conversion, despite prolonged reaction times (Table 2, entry 3). However, when the temperature was increased to 100 °C, full conversion was obtained with a catalyst loading as low as 0.1 mol% (Table 2, entry 4). With a further decrease in the Rh loading (0.05 mol%) a high yield of 93% was obtained at 100 °C (Table 2, entry 6), and this could be increased to 98% by running the reaction at 130 °C (Table 2, entry 7). However, 130 °C is less suitable for large-scale applications, and thus 100 °C was chosen as the optimal temperature. The ratio **5**/**L1** was also varied, and it was found that a ratio of 1 : 2 (metal/phosphine) was needed to obtain excellent yields (Table 2, entry 8 *vs.* entry 6). Optimization was also performed for the isomerization of morphine (**2**) (Table 2, entries 9–13). To obtain good results with this substrate (**2**), the lowest catalyst loading that could be used was 0.7 mol% (Table 2, entry 11 *vs.* 13). The lower reactivity of morphine (**2**) compared to codeine (**1**) could be due to the inhibition of the activity of the catalyst through interaction of the metal atom with the phenol moiety.

Sulfonate phosphine sodium salts have been extensively used as water-soluble ligands in transition metal catalysis.[12] When water-soluble phosphines **L2–L4** [13] (Fig. 1) were used in

Table 1 Screening of ruthenium and rhodium catalysts[a]

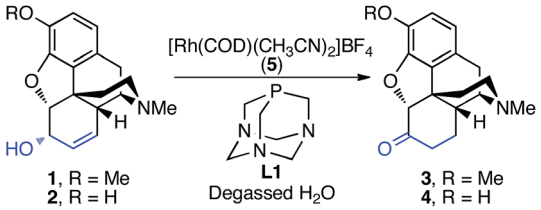


1 **3**

Entry	Catalyst	Additive	Solvent	Yield[b] (%)
1	$RuCl_3\cdot xH_2O$	^{t}BuOK	Toluene	<1
2	$RuCl_2(PPh_3)_3$	^{t}BuOK	Toluene	>99
3	$RuCpCl(PPh_3)_2$	^{t}BuOK	Toluene	n.d.[c]
4	$[Ru(p\text{-cymene})Cl_2]_2$	^{t}BuOK	Toluene	<1
5	$[Ru(\eta^3:\eta^3\text{-}C_{10}H_{16})Cl_2]_2$	—	H_2O	<1
6	$[Ru(\eta^3:\eta^3\text{-}C_{10}H_{16})Cl_2]_2$	Cs_2CO_3	H_2O	<1
7	$RhCl_3\cdot 3H_2O$	^{t}BuOK	Toluene	<1
8	$[Rh(COD)(CH_3CN)_2]BF_4$ (**5**)	—	H_2O	<1
9	**5**	PTA	H_2O	>99

[a] **1** (0.1 mmol), metal complex (5 mol%), and additive (10 mol%) in degassed solvent (2 mL) at 50 °C, for 3 h under an atmosphere of N_2 in a sealed tube. [b] Determined by ^{1}H NMR spectroscopy. [c] A complex mixture of by-products was formed. Cp = cyclopentadienyl; $C_{10}H_{16}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl; COD = 1,5-cyclooctadiene; PTA = 1,3,5-triaza-7-phosphaadamantane.

Table 2 Optimization of the reaction conditions using **5** and **L1**[a]



1, R = Me
2, R = H

3, R = Me
4, R = H

Entry	Substrate	**5** (mol%)	**L1** (mol%)	*t* (h)	*T* (°C)	Yield[b] (%)
1	**1**	5	10	2	80	93
2	**1**	1	2	3	80	94
3	**1**	0.1	0.2	12	80	87
4	**1**	0.1	0.2	24	100	>99
5	**1**	0.05	0.1	21	70	30
6	**1**	0.05	0.1	21	100	93
7	**1**	0.05	0.1	24	130[c]	98
8	**1**	0.05	0.05	20	100	19
9	**2**	5	10	2	100	>99
10	**2**	1	2	20	100	>99
11	**2**	0.7	1.4	20	100	>99
12	**2**	0.5	1	21	100	86
13	**2**	0.1	0.2	21	100	<1

[a] Unless otherwise noted: **1** or **2** (1 g, 3.34 mmol or 3.50 mmol) in degassed H_2O (7 mL), under a N_2 atmosphere in a sealed tube. [b] Determined by ^{1}H NMR spectroscopy after isolation by filtration. [c] At this temperature, **1** and **3** did not precipitate from the reaction medium.

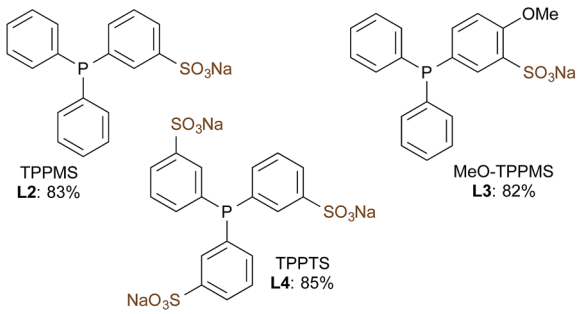
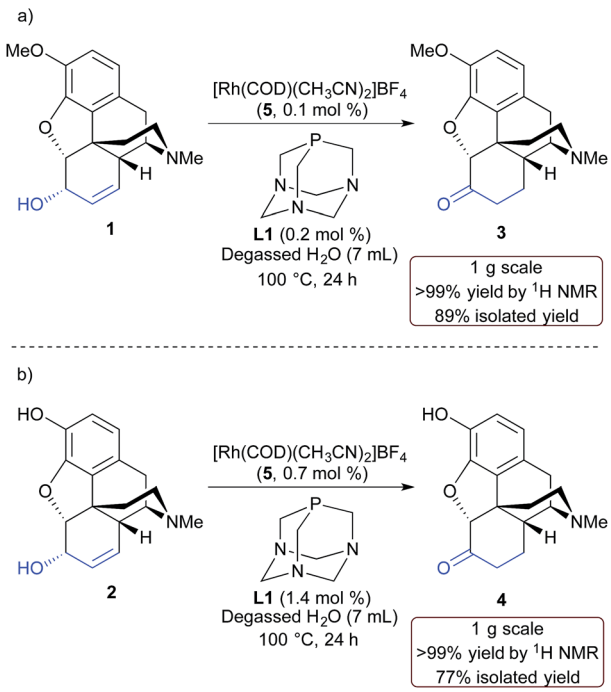


Fig. 1 Yields determined by ^{1}H NMR spectroscopy obtained in the isomerization of **1** catalyzed by **5** and ligands **L2–L4** (**5**, 1 mol%; **L**, 2 mol%, 100 °C, 3.5 h in H_2O). TPPMS = sodium (3-sulfonatephenyl)-diphenylphosphine; MeO-TPPMS = sodium (4-methoxy-3-sulfonatephenyl)-diphenylphosphine; TPPTS = trisodium tris(3-sulfophenyl) phosphine.

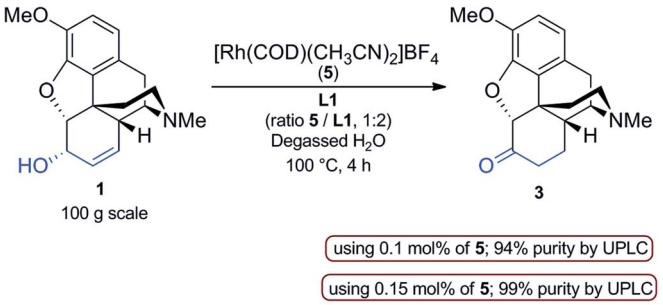
the isomerization of **1** catalyzed by **5**, yields ranging from 82 to 85% were obtained after 3.5 h at 100 °C in degassed H_2O (Fig. 1). However, yields as high as those obtained with PTA (**L1**) were not achieved. Also, PTA can be easily synthesized in a multigram scale from readily available reagents.[14]

Next, we carried out the redox isomerization of codeine (**1**) and morphine (**2**) on a gram scale under the optimal reaction conditions found (Table 2, entries 4 and 11) and determined the isolated yields. The products, **3** and **4** respectively, were isolated by filtration in 89 and 77% yield (Schemes 2a and b, see ESI† for details).

To show further the potential of catalytic system **5**/**L1**, the isomerization of codeine **1** was also performed on a 100 g scale and using 0.1 mol% of **5** (Scheme 3). This procedure gave



Scheme 2 Synthesis of **3** and **4**.



Scheme 3 Synthesis of **3** on a 100 g-scale.

hydrocodone **3** in 90% isolated yield in only 4 h. The purity of the product was determined by UPLC analysis (see ESI† for details), and it was of 94%. The isolated solid contained 3% of the starting codeine **1**. To increase the conversion of the redox isomerization, at this large scale, the same reaction described above was carried out using 0.15 mol% of the Rh complex **5**, and the purity of the final isolated product **3** was successfully increased up to 99% (Scheme 3).

Conclusions

In conclusion, we have reported an easy, scalable, practical, and high-yielding procedure for the synthesis and isolation of hydrocodone and hydromorphone from codeine and morphine in water. The method is based on the redox isomerization of the corresponding allylic alcohols catalyzed by low loadings of a water soluble complex formed from commercially available $[Rh(COD)(CH_3CN)_2]BF_4$ (**5**) and 1,3,5-triaza-7-phosphaadamantane (PTA, **L1**). The reactions were carried out in H_2O, and isolation of the products could be performed by simple filtration, avoiding tedious purifications, and thus minimizing decomposition of the products, resulting in very high isolated yields. Having demonstrated the efficiency of this water-soluble catalytic system for the synthesis of these semi-synthetic opiate drugs in up to 100 g-scale, we believe that the results reported here will be of significant interest for the commercial preparation of these compounds at a much larger scale, which may even allow to further reduce the catalyst loading.

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