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Synthesis of alkyl iodides/nitriles from carbonyl compounds using novel ruthenium tris(2,2,6,6-tetramethyl-3,5-heptanedionate) as catalyst

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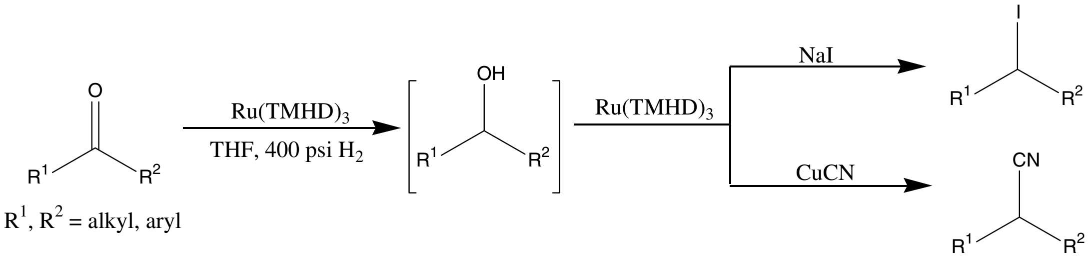
ABSTRACT

Aldehydes and ketones were hydrogenated to the corresponding alcohols, which were then transformed in situ into their respective iodides and nitriles in good yields. A structurally well-defined O-containing transition metal complex, Ru $(TMHD)_3$, was found to be the active catalyst for hydrogenation, iodination and cyanation reactions. It has high affinity for the transformation of benzylic alcohols to iodides and nitriles.

Alkyl halides are versatile intermediates in organic synthesis, and their transformation to useful compounds is well reported in the literature.[1] They also serve as important intermediates in the synthesis of fine chemicals and pharmaceuticals to treat diseases such as cancer,[2] HIV,[3] diabetes[4] and arthritis.[5] Amongst alkyl halides, alkyl iodides are of prime importance to synthetic chemists due to their application in substitution, elimination, coupling reactions, etc. Similarly, alkyl nitriles are useful intermediates for transformation into various functional groups such as acid, amide, amine and amidines, and also into N-containing heterocycles.[6] Introduction of the nitrile group into organic compounds can be achieved using different routes including the direct conversion of aldehydes, oxime ethers, thioamides, carboxylic acids and their esters, dehydration of aldoximes and amides, oxidation of amines, reduction of primary aliphatic nitro compounds, enzymatic methods and by application of organoborane/diazoacetonitrile.[7,8]

Various methods have been demonstrated for the iodination of alcohols such as BF_3–Et_2O/NaI,[9] BF_3–Et_2O/CsI,[10] BF_3–Et_2O/KI,[11] P_4/I_2,[12] Cl_2SO–DMF/KI,[13] MgI_2,[14] HI,[15] $ClSiMe_3$/NaI,[16] R_3PI_2–Et_2O or C_6H_6/HMPA,[17] $CeCl_3{\cdot}7H_2O$/NaI,[18] $ZrCl_4$/NaI,[19] PPh_3/DDQ/$R_4N^+X^-$,[20] PPh_3/DEAD/LiI,[21] I_2/petroleum ether[22] and NaI/Amberlyst-15.[23] Also, there are a few reports on one-pot conversions of alcohols



Scheme 1. Synthesis of alkyl iodides/nitriles from carbonyl compounds.

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Table 1
Optimization of the hydrogenation of benzaldehyde[a]

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
Influence of catalyst					
1	$RuCl_3$	THF	80	4	18
2	$Ru(acac)_3$	THF	80	4	70
3	$Ru(TMHD)_3$	THF	80	4	96
4	$Ru(TMOD)_3$	THF	80	4	85
5	$Pd(TMHD)_2$	THF	80	4	65
Influence of solvent					
6	$Ru(TMHD)_3$	CH_3CN	80	4	62
7	$Ru(TMHD)_3$	DMF	80	4	71
8	$Ru(TMHD)_3$	Toluene	80	4	82
9	$Ru(TMHD)_3$	CH_3OH	80	4	79
Influence of temperature					
10	$Ru(TMHD)_3$	THF	60	4	80
11	$Ru(TMHD)_3$	THF	90	4	97
Influence of time					
12	$Ru(TMHD)_3$	THF	80	2	72
13	$Ru(TMHD)_3$	THF	80	3	84
14	$Ru(TMHD)_3$	THF	80	5	98

[a] Benzaldehyde (5 mmol), catalyst (1 mol %), solvent (20 ml), 400 psi H_2, 500 rpm.

[b] GC yield.

to nitriles using $HCN/PPh_3/DEAD$,[24] acetone cyanohydrin,[25] $CCl_4/PPh_3/NaCN$,[26] $n\text{-}Bu_3P/CCl_4/KCN$/18-crown-6,[27] $PPh_3/n\text{-}Bu_4NCN/DDQ$,[28] $Me_3SiCl/NaI/NaCN$,[29] TsIm/NaCN,[30] NH_3/I_2,[31] NH_3/1,3-diiodo-5,5-dimethyl hydantoin,[32] etc. However, these methods suffer from major disadvantages such as the presence of hazardous and toxic I_2 and HCN vapours, risk of explosion in the case of DEAD, lower yields, harsh reaction conditions, non-commercially available materials and tedious work-up procedures, for example, in the separation of $Ph_3P{=}O$, unreacted Ph_3P and products.

Thus, developing novel and greener methods, which have higher efficiency, selectivity, less toxicity and easy to handle and commercially available materials, is still a challenging task. Previously, we reported metal-TMHD catalyzed transformations in organic synthesis.[33] The use of 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD) as a ligand resulted in excellent yields of products and such reactivity could be attributed to the fact that a good balance exists between the steric and electronic properties of the complex. Moreover, it is also a good substitute for various phosphine-based protocols.

In continuation of our work on hydrogenation reactions,[34] and exploring metal-TMHD as a catalyst for organic reactions,[33] we herein report a novel methodology for the synthesis of alkyl iodides/nitriles via hydrogenation using $Ru(TMHD)_3$ as the catalyst

Table 2
Hydrogenation of carbonyl compounds[a,35]

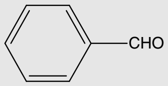
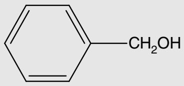
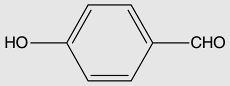
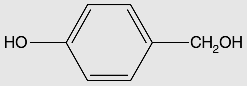
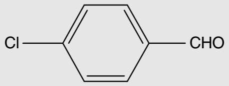
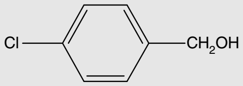
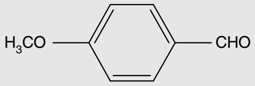
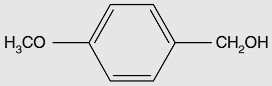
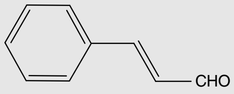
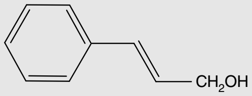
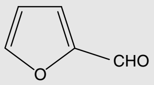
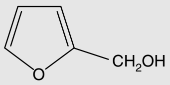
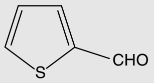
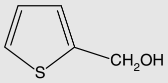
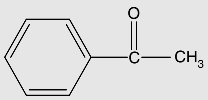
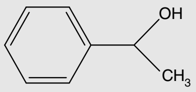
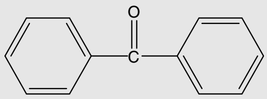
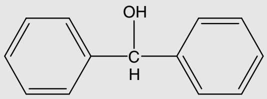
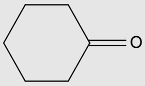
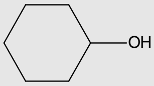
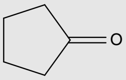
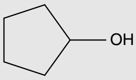
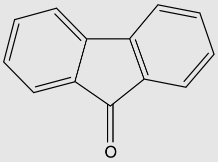
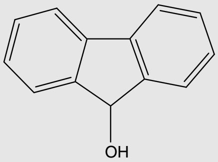
Entry	Carbonyl compound	Product	Time (h)	Yield[b] (%)
1			4	96
2			4	92
3			4	90
4			4	95
5			5	72
6			5	86
7			5	82
8			5	92
9			5	90

Table 2 (*continued*)

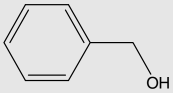
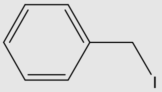
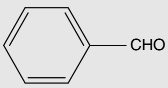
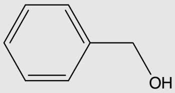
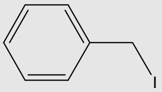
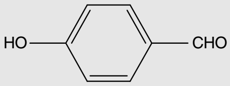
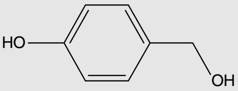
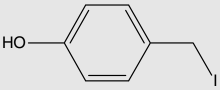
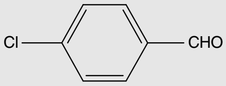
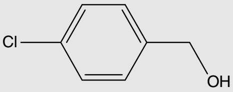
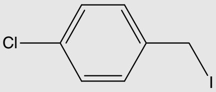
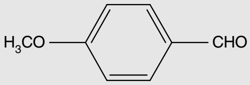
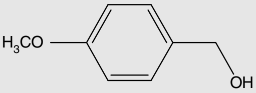
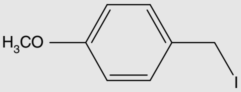
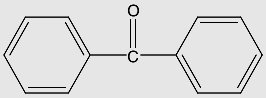
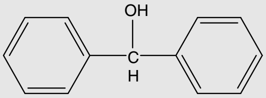
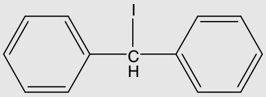
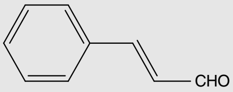
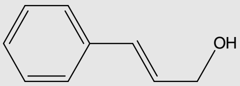
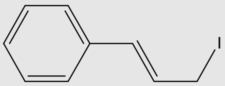
Entry	Carbonyl compound	Product	Time (h)	Yield[b] (%)
10			4	88
11			4	85
12			6	79

[a] Carbonyl compound (5 mmol), Ru(TMHD)$_3$ 1 mol %, THF 20 ml, 400 psi H_2, 500 rpm, 80 °C.

[b] GC yield.

(Scheme 1).[33e] Using this method, carbonyl compounds were hydrogenated to the corresponding alcohols, which were then transformed in situ into their respective iodides and nitriles in good yields. The Ru(TMHD)$_3$ catalyst was found to be highly active for both steps and hence the reactions could be carried out in a sequential manner. To begin with, the catalytic activity, choice of

Table 3
Synthesis of alkyl iodides[36]

Entry	Carbonyl compound	Time (h)	Alcohol	Time (h)	Alkyl iodide	Yield[a] (%)	Ref.
1	—	—		6		84	10
2		4		6		82	10
3		4		8		80	10
4		4		10		78	10
5		4		8		81	10
6		5		10		77	10
7		5		10		61	10

[a] Isolated yield.

solvent, reaction time and temperature were studied for the hydrogenation step. The results are summarized in Table 1.

Catalyst screening showed that $Ru(TMHD)_3$ was the best catalyst for hydrogenation of carbonyl compounds at 80 °C. $RuCl_3$ was poorly active, whereas $Ru(acac)_3$ was found to give a 70% yield of benzyl alcohol (entry 2). $Ru(TMHD)_3$ was also compared with the Ru complex of 2,7,7-trimethyl-3,5-octanedione (TMOD), which gave an 85% yield (entry 4). This result could be attributed to the fact that the TMHD ligand increases the bulk of the complex and results in high stability thereby increasing the catalytic efficiency of the catalyst. $Pd(TMHD)_2$ was also screened and gave a 65% yield of benzyl alcohol (entry 5). $Ru(TMHD)_3$ catalyst was found to give good yields in the iodination and cyanation reactions compared to that of other hydrogenation catalysts used in the present study, which gave 40–60% yields of iodides/nitriles. The influence of solvent has a great impact as it should be compatible for all the steps. THF was found to be an excellent solvent for hydrogenation, iodination and cyanation and was used for further study. When methanol was used as the solvent, acetal formation was observed, whereas with acetonitrile, DMF and toluene, unreacted benzaldehyde was observed (entries 6–9). Hydrogenation at a lower temperature 60 °C, gave a satisfactory yield, whereas increasing the temperature to 90 °C did not improve the result (entries 3, 10 and 11). The influence of time shows that hydrogenation was complete in 4 h.

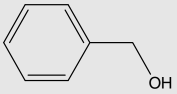
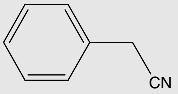
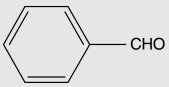
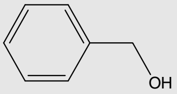
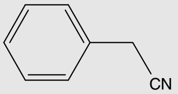
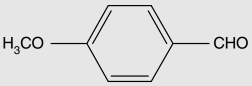
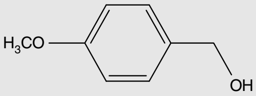
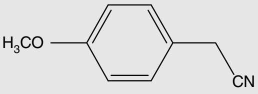
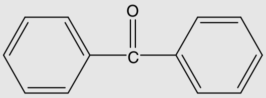
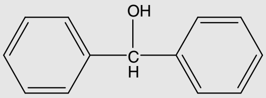
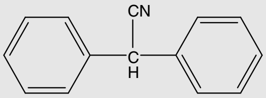
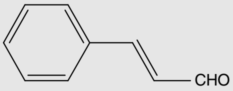
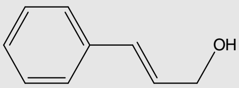
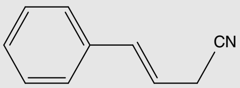
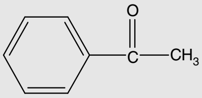
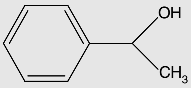
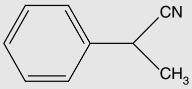
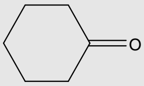
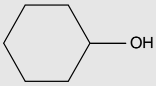
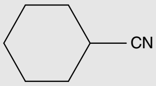
Carbonyl compounds such as aldehydes and ketones were hydrogenated to the corresponding alcohols in short reaction times (Table 2). Benzaldehydes having substituents such as 4-hydroxy, 4-chloro and 4-methoxy were hydrogenated to the corresponding benzyl alcohols in 90–95% yields (entries 2–4). Selective hydrogenation of cinnamaldehyde is a challenging task.[34c] Cinnamaldehyde was selectively hydrogenated to cinnamyl alcohol in 72% yield (entry 5). Heterocyclic aldehydes such as furyl and thienyl were also hydrogenated to alcohols in 86% and 82% yields, respectively (entries 6 and 7). Ketones including acetophenone and benzophenone were hydrogenated to the corresponding alcohols in 92% and 90% yields (entries 8 and 9). Cyclohexanone, cyclopentanone and 9-fluorenone were also hydrogenated to the corresponding alcohols in 79–88% yields (entries 10–12).

Thus, after completion of the hydrogenation reaction, the resulting mixture was treated with NaI or CuCN to afford alkyl iodides or nitriles in good yields (Tables 3 and 4).

Benzaldehyde was converted effectively to benzyl iodide in 82% yield within 6 h after hydrogenation to benzyl alcohol (Table 3, entry 2). It was observed that a comparable yield of benzyl iodide was obtained to that when commercially available benzyl alcohol was treated with sodium iodide in the presence of $Ru(TMHD)_3$ (entry 1). Similarly, substituted benzaldehydes such as 4-hydroxy, 4-chloro and 4-methoxy were transformed into the corresponding iodides after hydrogenation in good yield (entries 3–5). Benzophenone was hydrogenated to benzhydrol, which was then converted to its iodide in 77% yield (entry 6). Cinnamaldehyde was transformed into cinnamyl iodide in 61% yield after selective hydrogenation to cinnamyl alcohol (entry 7). These results indicate that iodination of benzylic alcohols occurs smoothly in the presence of $Ru(TMHD)_3$ giving high yields of aliphatic iodides.

Benzaldehyde was converted to phenylacetonitrile in 84% yield within 10 h after hydrogenation to benzyl alcohol (Table 4, entry 2). A comparable yield of phenylacetonitrile obtained when commercially available benzyl alcohol was treated with cuprous cyanide in the presence of $Ru(TMHD)_3$ as catalyst (entry 1). Similarly, 4-methoxybenzaldehyde was transformed into the cor-

Table 4
Synthesis of alkyl nitriles[37]

Entry	Carbonyl compound	Time (h)	Alcohol	Time (h)	Alkyl nitrile	Yield[a] (%)	Ref.
1	–	–		10		87	27
2		4		10		84	27
3		4		11		82	28
4		5		12		75	28
5		5		12		58	27
6		5		10		78	28
7		4		13		70	28

[a] Isolated yield.

responding nitrile after hydrogenation in good yield (entry 3). Benzophenone, cinnamaldehyde, acetophenone and cyclohexanone were converted to their respective nitriles, yields of 58% to 78% (Table 4, entries 4–7). Similar to iodides, cyanation of benzylic alcohols proceeded smoothly giving high yields of benzylic nitriles compared to those of the aliphatic nitriles of cinnamaldehyde and cyclohexanone.

In conclusion, a structurally well-defined O-containing transition metal complex Ru(TMHD)$_3$ was found to show good catalytic activity in hydrogenation, iodination and cyanation reactions under mild conditions in a sequential one-pot fashion. Alkyl iodides and nitriles were obtained in good to high yields from carbonyl compounds without isolation of the intermediate alcohols. The catalyst has high affinity for benzylic alcohols and tolerates a range of substituents.

References and notes

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35. *Typical procedure for the hydrogenation of carbonyl compounds*: To a 100 ml high pressure reactor, carbonyl compound (5 mmol), Ru(TMHD)$_3$ catalyst (33 mg, 1 mol %) and THF (20 ml) were added. Hydrogen (400 psi) was then charged into the reactor, which was heated to 80 °C for the desired time (Table 2). The reactor was cooled and the remaining hydrogen was carefully vented off. The reaction mixture was analyzed by GC, and the products were characterized by GC–MS and by comparison with authentic samples.
36. *Typical procedure for the synthesis of alkyl iodides*: The reaction mixture after hydrogenation was transferred into a two-necked flask and sodium iodide (1.5 g, 10 mmol) was added. The resulting mixture was stirred at 80 °C for the desired time (Table 3). The reaction mixture was cooled and treated with aq sodium dithionite solution and the product was extracted with ethyl acetate. The extracted product was analyzed and characterized by GC–MS. The product could be isolated easily after removal of the solvent in vacuo.
37. *Typical procedure for the synthesis of alkyl nitriles*: The reaction mixture after hydrogenation was transferred into a two-necked flask and cuprous cyanide (896 mg, 10 mmol) was added. The resulting mixture was stirred at 80 °C for the desired time (Table 4). The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The extracted product was analyzed and characterized by GC–MS. The organic layer was dried and evaporated under vacuo to afford the product in good yield.