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Hydrogenolysis-hydrogenation of aryl ethers: selectivity pattern[†]

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The selectivity pattern of nickel-catalyzed hydrogenolysishydrogenation of aryl ethers has been studied in the micellar media. The micellar conditions selectively formed arenes and alcohols with enhanced yields.

Breaking aromatic C–O bonds is one of the most demanding processes in synthetic organic chemistry especially because of the stability of C–O linkages.¹ However, cleavage of C–O bonds is very important in the fields of deoxygenated fuels and fine chemicals.²

Aliphatic C–O bonds are relatively easy to cleave using either hydrolysis or dehydration reactions. However, aromatic C–O bonds are resistant to these simple processes.³ In the case of aryl ethers even harsh reaction conditions often fail to selectively cleave C–O bonds. The breaking of aryl C–O bonds and hydrogenation of arene rings generally lead to the mixture of phenols, cycloalkanols, saturated cyclic hydrocarbons (cycloalkanes), and arenes.⁴ Due to the low yields, lack of chemoselectivity (towards an aryl C–O bond and towards a particular product), and waste of hydrogen gas; hydrogenation cleavage reactions have not been extensively utilized on an industrial scale. The few methods currently available to achieve selective aryl C–O bond cleavage generally require expensive electrocatalytic processes⁵ or the use of a stoichiometric quantity of alkali metal catalysts.⁶ Hence, the cost limits their use at an industrial scale.²

In the last few decades, the nickel (Ni) metal complexes have been developed for C–O bond cleavage reactions because of their ability to activate aromatic C–O bonds in the presence of aliphatic C–O bonds.⁷ Efforts were made to improve reaction conditions and catalytic efficiency.⁴ However, inhomogeneity of the system due to reduction of catalysts and modest reactivity of hydrogen restricts the use of these processes for hydrogenolysis of aromatic C–O bonds. It is currently very difficult to achieve selective cleavage of an aromatic C–O bond in the presence of an aliphatic C–O bond. Recently, a very important study was carried out on Ni catalyzed hydrogenolysis in an effort to achieve selectivity towards phenol and arene functionality.⁸ However, the need of the specific ligand, heavy catalyst loading (Ni, 20 mol%), hydrogen gas, substrate specificity (substrates with specific directing groups), and long reaction times limit the use of this process at an industrial scale on the basis of scope, safety and cost.² Hence, the need for a selective, commercially viable C–O scission process remains, especially in the fine chemical industry and in the energy industries focused on generating brown coal from lignocellulosic biomass with a C–O bonds network.⁹ In the pharmaceutical industry for example, the fragmentation study of drugs such as nitroscanate (1-(4-isothiocyanatophenoxy)-4-nitrobenzene, an anthelmintic drug) (Section S3 and Fig. S1, ESI†) is very important.

Here, we report the use of reverse micelles as a reaction medium to improve the hydrogenolysis–hydrogenation (H–H) of aromatic C–O bonds. We previously reported the use of surfactants and various polymeric media in transition metal catalyzed reactions,¹⁰ syntheses of bioactive compounds,¹¹ and radiolabeling studies.¹²

We initiated the H–H study by using diphenyl ether (DPE), a tricyclohexylphosphine ligand (L), nickel(II) acetylacetonate (Ni(acac)₂), and sodium *tert*-butoxide (NaO^tBu) as a base. Lithium tri-*tert*-butoxyaluminum hydride (LiAl(O^tBu)₃H) was used as the hydrogen source.† Under these reaction conditions the yield of products (from hydrogenolysis and/or hydrogenation) was negligible and DPE remained unreacted (Table 1, No. 1). We then increased the reaction times along with the catalyst concentration however; the selectivity of reaction was lost. The reaction produced cyclohexane and cyclohexene as the main products (Table 1, No. 2). The formation of these products presumably was a result of destruction of the carbon–phosphine bond in the L which ultimately destroyed the catalyst.

We then carried out the reaction in the presence of cetyltrimethylammonium bromide (CTAB) (0.60 mmol in toluene) and a reduced quantity of Ni(acac)₂ and of the L. Remarkable enhancements in % conversion of DPE were observed. Surprisingly, in the homogeneous catalysts system cyclohexane and cyclohexanol were formed as the products in just 5 h reaction time (Table 1, No. 3). On the other hand, when the same reaction was performed in sodium dodecyl sulphate (SDS) (0.60 mmol in toluene), conversion was very low (Table 1, No. 4). Thus, the presence of cationic reverse micelles in the reaction increases the conversion of diphenyl ether to cyclohexane and cyclohexanol rather than a mixture of phenols, cycloalkanols and saturated cyclic hydrocarbons.^{1–4}

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Table 1 Optimization of hydrogenolysis-hydrogenation of DPE

	$\underbrace{\begin{array}{c} & \text{Ni}(acac)_2, L, NaO'Bu, \\ & \text{LiAI}(O'Bu)_3H \end{array}}_{\textbf{la}} + \underbrace{\begin{array}{c} & \text{OH} \\ & \text{OH} \\ & \text{Im} $			
	Reaction conditions	Total % conversion ^a	$\operatorname{Yield}^{d}(\%)$	
1	Ni (10 mol%), L (20 mol%), LiAl(O ^t Bu) ₃ H (2.5 eq.), toluene (1.5 mL), 24 h 70 °C s r ^c 1 67 Hz	<5 ^b	_	
2	Ni (20 mol%), L (40 mol%), LiAl(O ^t Bu) ₃ H (12 eq.), toluene (1.5 mL), 48 h, 120 °C, s. r. 1.67 Hz	10^{b}	—	
3	Ni (5 mol%), L (10 mol%), LiAl(O ^t Bu) ₃ H (2.5 eq.), toluene (1.5 mL), CTAB (0.60 mmol), 5 h, 70 °C, s. r. 1.67 Hz	60, 1a (50), 1b (50)	1a (99), 1b (99)	
4	Ni (5 mol%), L (10 mol%), LiAl(O ^t Bu) ₃ H (2.5 eq.), toluene (1.5 mL), SDS (0.60 mmol), 5 h, 70 °C, s. r. 1.67 Hz	4, 1a (50), 1b (50)	_	

^{*a*} Determined by gas chromatography, (% selectivity). ^{*b*} Mixture of benzene, phenol, cyclohexane and cyclohexene. ^{*c*} Stirring rate. ^{*d*} Isolated yield, substrate recovered. Each experiment was repeated three times.

The yield and selectivity of H–H reaction were found to be dependent on the head-group charges of the surfactant used in the reaction (Section S5, ESI†). These results were unexpected and distinct from the previous study done for palladium (Pd) catalysed reactions, where there is no relationship between the head-group charges and the yield of the reaction.¹⁰

 $LiAl(O^tBu)_3H$ was used as the hydrogen source instead of hydrogen gas to test its utility as a solid hydrogen source and also because of the safety issue. In preliminary runs, NaO^tBu and LiAl(O^tBu)₃H were not particularly soluble in toluene even though fine powdered reagents were used. This problem was overcome by the use of CTAB in toluene due to the formation of reverse micelles in the reaction medium.

Since the intermediate and/or final product may contain benzene, which is a low boiling liquid (80 °C boiling point, b.p.), we used 70 °C reaction temperature. At high reaction temperatures (120 °C), percent conversions are detrimentally affected (Table S2, No. 4 (ESI \dagger)). To study the effect of moisture on the product yield this reaction was carried out in the reverse micellar media under atmospheric conditions and no significant differences in the product yields were observed (Table S2, No. 3 (ESI \dagger)).

Due to the presence of a surfactant in the reaction medium, there is always a problem with respect to the formation of foam. In most reactions the formation of the foam negatively affects the yield of the reaction. We know from our previous studies^{10,11,13} that foam formation is directly related to the stirring rate, and the position of the magnetic bar in the reaction media. We performed extensive study on the effect of stirring on the yield of the H-H by using a magnetic stirrer to control stirring (Section S4, ESI[†]). Both slow stirring rate (s. r.) and high s. r. in the reaction caused decreases in the yield of the product without affecting selectivity (Table S1, ESI[†]). This might be due to the lack of good contact between the reactants in the case of slow s. r. and due to the formation of foam in the case of high s. r. Also with slow or no stirring, dispersion of the solid reagents became a problem. Hence, we decided to maintain 1.67 Hz s. r. for the reaction.

The complete optimization study was done with the intention to provide a process of value in large scale reactions of interest to industry (Tables S1, S2, and Section S3, ESI[†]). All the above reactions suggest that in the presence of reverse micellar medium (0.60 mmol CTAB) the yield of H–H of DPE was not influenced due to the presence of moisture. It also gave good yield with reduced quantities of the Ni catalyst and L (5 mol% Ni and 10 mol% L). The s. r. affected the yield of the reaction in micellar medium. This optimization study proves the use of micellar media for selective H–H of DPE to form cyclohexanol and cyclohexane.

The exact mechanism for Ni catalyzed H–H in reverse micellar media is still the unsolved obscurity (Section S6, ESI†). Nevertheless, in micellar medium the formation of a L–Ni(II) complex seems to take place in hydrophobic bulk. Other reagents like NaO^tBu and LiAl(O^tBu)₃H may be present near the anisotropic palisade layer. The separation of catalyst–L from other reagents might protect the catalyst from decomposition.

The positive effect of strong base NaO^tBu may be due to the formation of an anionic Ni complex which is the main reactive species for hydrogenolysis. The formation of an anionic Ni complex is supported by the very low yield in the presence of anionic surfactant SDS. On the other hand, increased yields and shorter reaction times in the presence of CTAB (cationic surfactant) can be explained by considering the attraction between the anionic Ni complex (from bulk) and concentrated positive charge (from reverse cationic micelles). This may facilitate the contact between anionic Ni complex and the ArOAr (near palisade layer). The spatial orientation of phenol (intermediate product) in the palisade layer of micelles may be responsible for restricting the further hydrogenolysis of the C-O bond in phenol and conferring the selectivity towards arene hydrogenation. In the past, we verified the spatial orientation of aromatic compounds in palisade layers in the nuclear magnetic resonance study.¹³ The formation of colloidal Ni species was also considered as one of the reasons for selective arene hydrogenation in the homogeneous catalysts system (Section S7, ESI⁺). The inactivity of the Ni catalyst system in the presence of mercury (Hg) proves the formation of colloidal Ni species in the reaction medium.

To comprehend the scope of the H–H in the micellar media, we studied various aryl ethers (Table 2). This process maintained selectivity of H–H in the presence of other functional groups (Table 2, No. 1: NO₂ and NCS, No. 2 and 3: OMe). We found that less reactive derivatives of DPEs produced good yields and selectivity (Table 2, No. 2 and 3). In unsymmetrical DPEs,

 Table 2
 Hydrogenolysis-hydrogenation of representative compounds

	Substrate (total % conversio	n) ^a	Products (% yield ^{b})
1	O2N NCS	(61)	4-NCS–cyclohexanol (95), NO ₂ –cyclohexane (97)
2	Meo OMe	(60)	3-MeO–cyclohexanol (88), cyclohexanol (3), MeO– cyclohexane (86), MeOH (nq ^c), cyclohexane (2)
3	MeO	(58)	3-MeO-cyclohexanol (92), cyclohexanol (2), MeOH (nq), cyclohexane (89)
4		(58)	Cyclohexanol (87), cyclohexane (89)
5	OMe	$(60)^d$	Decahydronaphthalene (87), MeOH (nq)
6	OEt	(57)	Decahydronaphthalene (85), EtOH (nq)
7	OMe	(57)	Me-cyclohexane (85), MeOH (nq)
8	COMe COMe	(58)	Me-cyclohexane (82), MeOH (nq)

^{*a*} Determined by gas chromatography. ^{*b*} Isolated yield, substrate recovered. ^{*c*} Not quantified. Each experiment was repeated three times. ^{*d*} AlMe₃ (1 equiv.).

cleavage of the C–O bond took place next to the aryl ring containing electron withdrawing functionality. For 3,3'-oxybis-(methoxybenzene), selectivity in hydrogenolysis was maintained towards the aromatic C–O bond (Table 2, No. 2). The formation of decahydronaphthalene from 2-alkoxy-naphthalenes (Table 2, No. 5 and 6) reveals selectivity in H–H of the aromatic C–O bond. The interesting formation of methyl-cyclohexane from benzyl ethers (Table 2, No. 7 and 8) indicates the preference for cleavage towards more electron dense species. This series clearly indicate the selectivity pattern including (i) selectivity towards arene hydrogenation, (ii) selectivity towards aromatic C–O bond cleavage, (iii) selectivity towards cleavage of Ar–O–Ar in the presence of Ar–OMe (Table 2, No. 2 and 3). In the absence of Ar–O–Ar bonds, cleavage was done at Me/EtO–Ar bonds (Table 2, No. 5–8).

An imperative pronouncement of this study is the obtained selectivity pattern for H–H of aryl ethers because of the anisotropic palisade layer of CTAB reverse micelles. The stability of catalysts and the spatial orientation of the aromatic alcohol (phenol) appear to show a positive effect on the yield and selectivity of the particular products, respectively.

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