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$ZnCl_2$-catalysed transfer hydrogenation of carbonyls and chemoselective reduction of the C=C bond in α,β-unsaturated ketones†

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This manuscript describes chemoselective reduction of C=C in α,β-unsaturated ketones and the transfer hydrogenation of aldehydes and ketones catalysed by $ZnCl_2$-phosphinamino-triazolyl-pyridine (0.5 mol%) using KOH/^{i}PrOH as a H_2 source. A detailed mechanistic study using DFT calculations (B3LYP-D3/def2-TZVP) revealed the key role of metal–ligand cooperation (MLC) in the catalytic reaction demonstrating the non-innocent behaviour of the phosphine ligand.

The hydrogenation of organic compounds is one of the most fundamental transformations in synthetic chemistry.[1] These reactions are crucial in the industrial production of dyes, agrochemicals, pharmaceuticals, polymer building blocks, and several biologically active compounds.[2] The reduction of multiple bonds in different functional groups such as carbonyl, nitro, alkene and alkyne can be accomplished conventionally by using hydrogen gas and an appropriate catalyst. However, a tempting alternative is to use the easily available organic compounds, such as alcohols,[3] formic acid–triethylamine[4] and sodium formate[5] as hydrogen sources, a process typically referred to as transfer hydrogenation. The Meerwein–Ponndorf–Verley (MPV) reduction recognised as one of the most efficient and environmentally friendly methods in organic synthesis for the reduction of the carbonyl group,[6] employed $M(O^iPr)_3$ (M = Al, In and B) as a mediator in the MPV reduction and isopropanol as the hydride donor.[6,7] However, this method requires longer time, higher temperature and an excess of metal alkoxides.

Transfer hydrogenation is a convenient method because it does not require risky high-pressure hydrogen gas or a complicated experimental setup.[8] Catalytic transfer hydrogenation of carbonyl groups using transition metal-based catalysts with or without a hydrogen donor is more favourable, but restricted only to precious metals such as Ru,[9] Rh,[10] Ir[11] and Pd,[12] which are expensive, less abundant, and toxic as well.[13] As a consequence, attempts to develop organo-catalysts and/or catalysts based on main group or 3d-metals, which are typically more abundant and affordable substitutes for the noble metals, have risen substantially over the last few years.[13,14] However, the major drawback in the application of main group metal complexes in catalysis is their redox innocence, which diminishes their ability to participate in two important two-electron processes in catalysis; oxidative addition and reductive elimination.[14a,15] The metal is exclusively limited to a stable +2 oxidation state in homogenous zinc, calcium and magnesium-catalysed reactions, so the catalytic cycle requires a sigma-bond metathesis and/or insertion step to promote organic transformation.[13,14b]

Zinc has displayed exceptional activity for all of these transformations due to its low cost, relatively high abundance, and low toxicity.[13,16] Beller,[17] Milstein,[18] and Lacy[19] used zinc catalysts for the hydrogenation of carbonyl compounds by using H_2 pressure (7–80 bar) with 2.5–5 mol% catalyst loading (Scheme 1). However, the utility of zinc in hydrogenation remains understudied, with substrates limited to highly polarized moieties. Furthermore, the issue of selective hydrogenation with these types of catalysts is yet to be addressed.[20] In this context, we used a $ZnCl_2$-based catalytic system for the transfer hydrogenation of aldehyde and ketone derivatives. Our present study intended to achieve a chemoselective reduction of the C=C bond instead of the C=O bond in α,β-unsaturated ketones under mild conditions. DFT studies were also undertaken to examine the electronic structure, bonding, and reactivity in the catalytic process.

The experiments were performed using isopropanol as the solvent at 80 °C and acetophenone as the model substrate to find the optimal conditions for the transfer hydrogenation reaction (Table S1, ESI†) by varying the ligands, and solvents. As a preliminary investigation, several ligands (**L1–L4**, Table 1)

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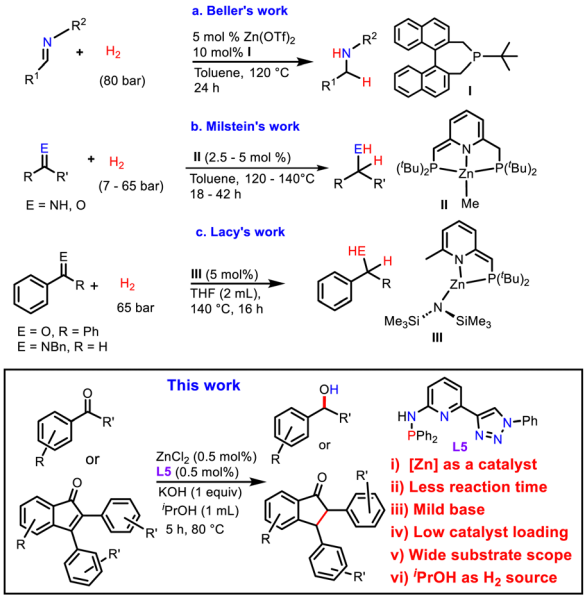
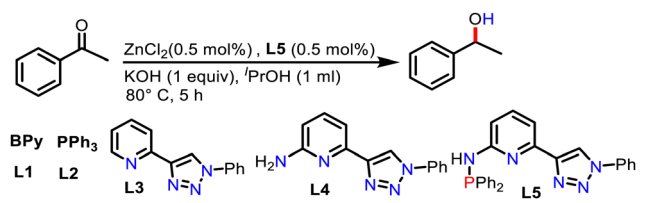


Scheme 1 Carbonyl group reduction methodologies.

were examined along with $ZnCl_2$ and the hydrogenated products were isolated in < 58% yield in 3 h. Addition of $ZnCl_2$ to $[2,6\text{-}Ph_2PN(H)(C_5H_3N)(C_2HN_3C_6H_5)]$ (**L5**) resulted in 85% conversion in just 3 h and complete conversion of acetophenone into the secondary alcohol was observed in 5 h. The catalytic reaction using only $ZnCl_2$ or using only **L5** without $ZnCl_2$, and without base (entry 5) did not show any conversion. Replacing ^{i}PrOH with MeOH and EtOH had no success (entry 4), probably due to their unfavourable redox potential.[21]

The scope of the catalytic system [$ZnCl_2$ + **L5**] towards transfer hydrogenation was studied for various acetophenone derivatives under the optimized conditions and the results are summarised in Table 2. Both the electron-withdrawing and electron-donating groups on the phenyl rings of the carbonyl compounds were tolerated, resulting in the corresponding secondary alcohols in excellent yields (**Aa–Aw**). It was observed

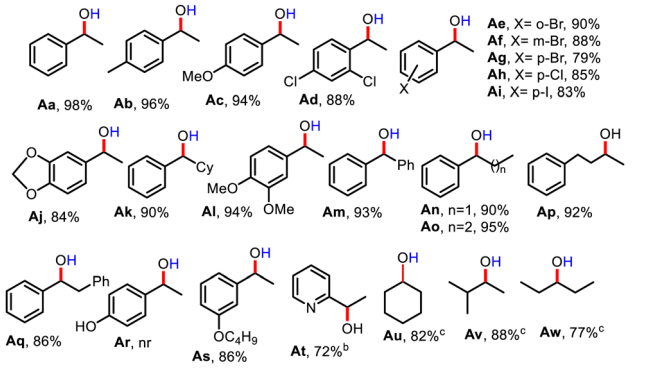
Table 1 Optimized reaction conditions for transfer hydrogenation of acetophenone



Entry	Variations from the optimised conditions	Yield[a]
1	None	100
2	**L1–L4** (3 h)	<58
3	**L5** (3 h)	85
4	EtOH, MeOH	0
5	No catalyst, no ligand, no base	0

[a] Yields are based on NMR spectra with 1,3,5-trimethoxybenzene as an internal standard.

Table 2 Substrate scope of ketones[a]



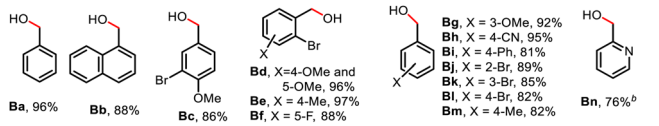
[a] Conditions: ketone derivatives (1 mmol), given are isolated yields only. [b] 12 h instead of 5 h. [c] GC-MS yields.

that the substrates with electron-withdrawing groups underwent faster reduction compared to those with electron-donating groups. This is due to the ease of hydride transfer from the *in situ* generated Zn–H intermediate to the carbonyl substrate, and an increase in the electrophilicity of the carbonyl group. In the case of substrate **Ar** due to the presence of a strongly coordinating hydroxy group, no conversion was observed. In contrast, on OH protection with an *n*-butyl group, 86% conversion was observed. Furthermore, 2-acetylpyridine (**At**) showed less conversion in 5 h, but the yield was improved considerably after 12 h.[22]

Aliphatic ketones were very efficiently reduced to the corresponding secondary alcohols (**Au–Aw**). However, the reaction time has to be increased from 5 h to 15 h to achieve higher conversions. The catalytic system [$ZnCl_2$ + **L5**] was also found to be suitable for transfer hydrogenation of aldehydes. A series of substituted aldehydes examined under optimized conditions also yielded the corresponding alcohols in good to excellent yields (Table 3).

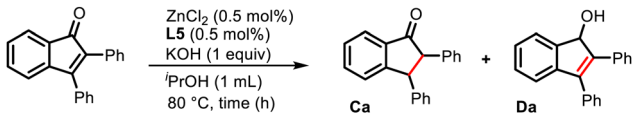
The catalytic potential of [$ZnCl_2$ + **L5**] in the transfer hydrogenation of α,β-unsaturated carbonyls was also examined (Table 4). The catalytic system promoted the chemo-selective hydrogenation of C=C bonds in 6 h, producing saturated ketones. However, indenol was the predominant product after 1 h primarily due to the reduction of C=O bonds (Table 4, entries 1–6). In the beginning, the time was optimised for chemo-selective hydrogenation of the C=C bond using 2,3-diphenyl-1*H*-inden-1-one as a model substrate. From here, the reaction was monitored with respect to time and the results are summarised in Table 4. The catalytic system [$ZnCl_2$ + **L5**]

Table 3 Substrate scope of aldehydes[a]



[a] Conditions: aldehyde derivatives (1 mmol). [b] 12 h, all isolated yields.

Table 4 Optimization of the reaction conditions for transfer hydrogenation of α,β-unsaturated ketones[a]



Entry	Time (h)	Ca[b]	Da[b]
1	**6**	**97 (94)**	**3**
2	5	75	21
3	4	58	29
4	3	42	36
5	2	28	45
6	1	15 (13)	55 (51)

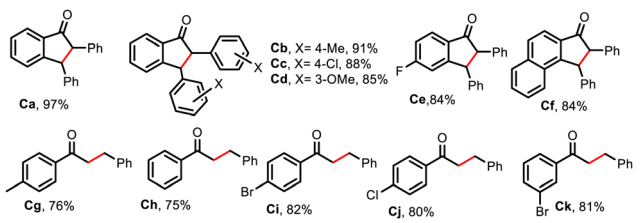
[a] Reaction conditions: 2,3-diphenyl-1*H*-inden-1-one (0.5 mmol), time = 6 h; isopropanol (1 mL). [b] Yields based on NMR data with 1,3,5-trimethoxybenzene as the internal standard; isolated yields are given in parentheses.

showed 100% conversion of 2,3-diphenyl-1*H*-inden-1-one in 6 h at 80 °C, wherein chemo-selective C=C hydrogenated product **Ca** was obtained in 97% yield, and completely hydrogenated **Da** in 3% yield (entry 1). Notably, within 1 h, indenol was obtained in 55% yield (entry 6). Table 4 clearly shows that the **Da** yield increases as the reaction time decreases, demonstrating that **Da** is initially produced before being converted into the corresponding indanones.

Inspired by this result, different 2,3-diphenyl-1*H*-inden-1-one derivatives were loaded under the optimised conditions (Table 5), and functional groups such as Me, OMe, F, and Cl were well tolerated. The relative configuration of **Cf** was determined by single crystal X-ray analysis (CCDC 2330701†); both the phenyl groups are in anti-dispositions with respect to each other. The unit cell of **3f** consists of both the enantiomers, which clearly shows that the racemic mixture was obtained in the hydrogenation of indanone derivatives (Fig. 1).

The transfer hydrogenation of simple chalcones was also performed for different α,β-unsaturated ketones with different substitutions on the benzoyl rings. Thus, chalcones containing electron-donating alkyl and electron withdrawing halides substituted at the *para* position of benzoyl reacted smoothly to deliver moderate to good yields of saturated ketones. To gain more insight into the chemo-selective transformation of indanone, several control experiments (Scheme 2a–c) were conducted. Under standard conditions, the reaction of 2,3-diphenyl-1*H*-inden-1-one was halted after 1 h.

Table 5 Substrate scope of α,β-unsaturated ketones[a]



[a] Conditions: α,β-unsaturated ketone (0.25 mmol), all isolated yield.

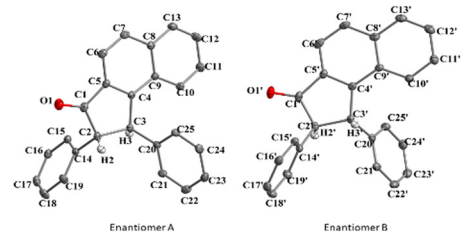
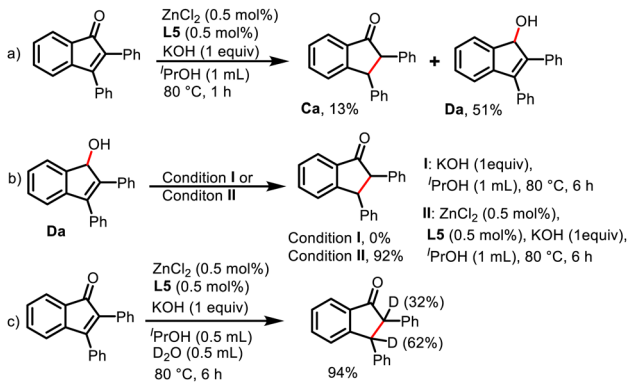


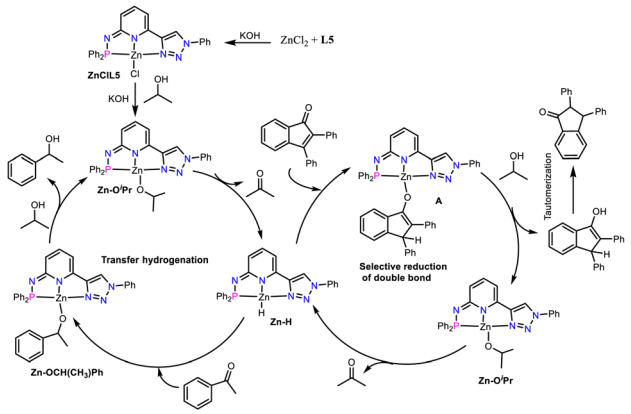
Fig. 1 Molecular structure of **Cf**.

It was found that in addition to a significant quantity of unreacted starting compound, the targeted molecule **Ca** and indenol **Da** were also isolated in 13% and 51% yield, respectively (Scheme 2a). Pure indenol **Da** under standard reaction conditions produced **Ca** in 92% yield (Scheme 2b). These results clearly indicate that the indenol **Da** is a kinetic controlled product in the reaction. A control experiment further confirmed that no target product **Ca** was detected from **Da** in the absence of $ZnCl_2$ (Scheme 2b), thus suggesting that catalytic system [$ZnCl_2$ + **L5**] is essential for the hydrogen transfer process. The reaction of **Ca** with 0.5 mL of D_2O under standard conditions afforded the desired **Ca** in 94% yield, with 32% and 62% deuterium being incorporated into the α- and β-positions of the ketone moiety, respectively (Scheme 2c).

The mechanism, adapted from experimental findings and DFT calculation, is depicted in Scheme 3 and Scheme S1 (ESI†). Initially, the zinc complex **(ZnCl)L5** was formed by the reaction of **L5** and $ZnCl_2$ in the presence of KOH. The optimised geometry of the **(ZnCl)L5** catalyst, along with other intermediates, is shown in Fig. S97 (ESI†). The HRMS spectrum of **(ZnCl)L5** showed a molecular ion peak at *m/z* = 520.0460 (calcd 520.0431) corresponding to $[M + H]^+$ (Fig. S93, ESI†). Complex **(ZnCl)L5** reacts with ^{i}PrOH to form **Zn–O^{i}Pr** (confirmed by HRMS, Fig. S94, ESI†), which undergoes *β*-H elimination to form a **Zn–H** species, thereby releasing acetone. The formation of **Zn–H** from Zn complexes is documented, and similar *in situ* formed **Zn–H** species are known to act as active catalysts for the transfer hydrogenation of carbonyl compounds.[20,23] Coordination of the carbonyl group to the metal centre and insertion of the **Zn**−**H** bond to the carbonyl group results in



Scheme 2 Mechanistic investigation and control experiments (a–c).



Scheme 3 Plausible reaction mechanism.

Zn–OCH(CH$_3$)Ph, which on further reaction with ^{i}PrOH gives the desired product and regenerates complex **Zn–O^{i}Pr**. For selective reduction of the double bond, since 1,4-addition is more favourable than 1,2-addition, initially nucleophilic addition of **Zn**−**H** to indenone affords alkoxyzinc intermediate **A**, which on further reaction with ^{i}PrOH furnishes 1,2-diphenyl-1*H*-inden-3-ol and regenerates **Zn–O^{i}Pr** species. The desired indanone **Ca** was formed after tautomerization of 1,2-diphenyl-1*H*-inden-3-ol.

$ZnCl_2$-catalyzed hydrogenation of ketones and aldehydes is achieved under mild conditions (5 h, 80 °C) with ^{i}PrOH as a hydrogen source. The same system also catalysed chemo-selective hydrogenation of α,β-unsaturated carbonyls. DFT calculations and spectroscopic studies demonstrated the presence of metal–ligand cooperation, with the phosphine moiety significantly reducing the kinetic barrier due to the stronger Zn–P bond and efficient Zn–ligand interactions (Fig. S102, S103 and Tables S2–S20, ESI†). This has been validated by second-order perturbation analysis and energy span approximation, which reveals higher stabilization energy with stronger donor–acceptor interaction, and high catalytic efficiency, demonstrating the faster reactivity of the complex with ligand **L5** compared to **L3**. A careful analysis of the frontier orbitals reveals that the electron donation from the phosphorus moiety to the $d_{x^2-y^2}$ orbital of Zn^{II} facilitates the transfer of hydride from Zn to the carbonyl group of ketone (Fig. S105 and S106, ESI†). Different rate-limiting steps are observed with each ligand, highlighting the role of ligand structure. TDTS-TDI analysis provided insight into the overall energetics of the catalytic cycle, enhancing understanding of this catalytic process (see ESI†).[24]

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Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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