CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Chem. Eur. J.* 10.1002/chem.201902240

Link to VoR: http://dx.doi.org/10.1002/chem.201902240

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Ligand Effect in Alkali Metal-Catalyzed Transfer Hydrogenation of Ketones

Iryna D. Alshakova, Hayden C. Foy, Travis Dudding, and Georgii I. Nikonov*[a]

Abstract: This paper unveils the reactivity patterns, as well as ligand and additive effect on alkali metal base catalyzed transfer hydrogenation of ketones. Crucially to this reactivity is the presence of a Lewis acid (alkali cation), as opposed to a simple base effect. With aryl ketones, the observed reactivity order is $Na^+ > Li^+ > K^+$, whereas for aliphatic substrates it follows the expected Lewis acidity, $Li^+ > Na^+ > K^+$. Importantly, the reactivity pattern can be drastically changed by adding ligands and additives. Kinetic, labelling, and competition experiments and DFT calculations suggested that the reaction proceeds via a concerted direct hydride transfer mechanism, originally suggested by Woodward. Lithium cation was found to be intrinsically more active than heavier congeners, but in the case of aryl ketones a decrease in reaction rate was observed at ~40% conversion with lithium cations. Non-covalent interaction analysis revealed that this deceleration effect originated from specific non-covalent interactions between the aryl moiety of 1-phenylethanol and the carbonyl group of acetophenone, which stabilize the product in the coordination sphere of lithium and thus poison the catalyst. The ligand/additive effect is a complicated phenomenon that includes a combination of several factors, such as the decrease of activation energy by ligation (confirmed by D/I calculations of a diamine, TMEDA) and the change in relative stabilization of reagents and substrates in the solution and the coordination sphere of the metal. Finally, we observed that lithium base catalyzed transfer hydrogenation can be further facilitated by the addition of an inexpensive and benign reagent, LiCl, which likely operates by re-initiating the reaction on a new lithium center.

Introduction

The discovery by Meerwein and Schmidt[1] and by Verley[2] of aluminum-catalyzed transfer hydrogenation of aldehydes by primary alcohols was a major milestone in the reduction chemistry of the 20th century. The further finding by Ponndorf[3] that secondary alcohols can be conveniently used for reduction of ketones and aldehydes laid grounds for the wide application of the MPV process in both industrial and academic settings up to the point when soluble main group hydrides were introduced as an alternative in mid 50-s. Labelling,[4] kinetic,[5] and computational[6] studies supported the notion that the reaction proceeds via a cyclic transition state **1**, with the rate determining step being the transfer of hydride from the carbon atom bearing the $OAl(OR)_2$ group (Chart 1). Further advances in the MPV process included the application of other Group 3 and 13 centers[7] and the use of tailored ligand platforms in the traditional aluminum catalysis to achieve enantioselective reduction[8] and/or increased activity.[9]

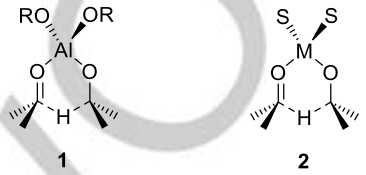

Chart 1. Suggested transition states in aluminum- (1) and alkali metal-catalyzed (2) MPV processes.

Although alkali metals are not generally considered as catalytic centers, but merely as innocent counter-cations, their role in catalysis is not negligible. In fact, the oldest alkali metal-mediated reaction, albeit usually not considered as such, is the classical Cannizzaro reaction,[10] i.e. disproportionation of aldehydes under the action of alkali metal bases, e.g. KOH. In 1945, Woodward et al. reported that alkali metal bases can catalyze the MPV reduction and Oppenauer oxidation,[11] which was successfully applied to the synthesis of quininone.[12] Mechanistic studies by von Doering and Aschner showed that radical intermediates were not formed in this reaction and that the hydride is transferred from the carbon atom of the carbinol group in essentially a symmetrical transition state **2**.[13] Despite this finding, the role of alkali metals in catalysis had been largely neglected[14] until Bäckvall et al. discovered the accelerating effect of bases in metal-mediated transfer hydrogenation (TH).[15] After that, the application of excess alkali metal bases (in the form of hydroxides, alkoxides, carbonates, or phosphates) as promoters in catalytic TH became very common.[16] Nevertheless, the idea that alkali metals themselves can be the catalytic centers had been dormant until 2004, when Crabtree et al. observed that carbonates M_2CO_3 (M = Rb, Cs) catalyzed transfer hydrogenation of 2-naphthaldehyde with 2-propanol.[17] Alkali metal catalysis was rediscovered again in 2007, when Adolfsson et al. reported reduction of an array of aryl and alkyl ketones in isopropanol mediated by lithium isopropoxide, albeit at elevated temperatures (180 °C).[18] Since these earlier reports a variety of alkali metals (Li-Cs), bases (hydroxides, alkoxides, carbonates, phosphates) and solvents (isopropanol, ethanol) have been studied in catalytic transfer hydrogenation[19] and in the closely related alkylation of alcohols and ketones.[20],[21] Ouali et al. provided convincing evidence that transition metal contaminants are not responsible for the catalysis and also made an interesting observation that the activity follows th e order Li < K < Na, which was explained by the balancing effect of alkali metal Lewis acidity on the carbonyl activation and product decomplexation steps.[19a] Two questions remain unanswered. First, can we improve the efficiency of this catalytic system by employing ligands in the same manner as

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10.1002/chem.201902240

used in transition metal catalysis? And, in particular, can an enantioselective reduction be accomplished? And second, what is the mechanism of alkali metal mediated transfer hydrogenation? The following report provides some answers to both these questions. Thus, we found evidence that lithium cation is intrinsically more active in promoting transfer hydrogenation and that its activity in the TH of acetophenone can be strongly affected by both ligands and additives. We further provide combined experimental and computational data explaining the unique role of lithium and a rationalization of the ligand effect.

Experimental Results

Effect of ligands on alkali metal-mediated transfer hydrogenation. We commenced our investigation with checking whether a strong, metal-free base can alone mediate catalytic reduction. To this end, acetophenone, the quintessential substrate for transfer hydrogenation, was employed using isopropanol with heating in the presence of 10 mol% phosphorus ylides, such as methylene(triphenyl)phosphorane and phenylmethylene(triphenyl)phosphorane, returned zero conversion.[22] However, addition of 10 mol% LiCl to a mixture of 10% $Ph_3P{=}CH_2$ and acetophenone in isopropanol results in 68% conversion after reflux for 8 hours. Carrying out the reaction in the presence of catalytic LiO^{i}Pr (10 mol%) under or without hydrogen atmosphere (1 atm) showed the same efficiency.

We then evaluated the relative activity of alkali metal cations (Li^+, Na^+, and K^+). Transfer hydrogenation of acetophenone with isopropanol catalyzed by 10 mol% MO^{i}Pr (M= Li, Na, K) was again chosen as the model system. The kinetic profiles, presented in Figure 1, show that the conversion increases in the order $Li^+<K^+<Na^+$, which largely agrees with the catalytic activity documented for other alkali metal bases.[19a] Since transfer hydrogenation is an equilibrium process, the maximum conversion of about 90% is achieved for NaO^{i}Pr after about 8 h, whereas for KO^{i}Pr the curve is much less steep but gives a high conversion of 54 % (80% after 20 h). In contrast, a very different behavior was observed for LiO^{i}Pr. The initial reaction is very fast, reaching 60% after 2 h vs 47% for NaO^{i}Pr, but then the reduction slows down and shows saturation behavior at about 68% conversion. These data clearly indicate that the lithium cation is intrinsically more active than its heavier congeners but is also passivated by the product of this reaction, $PhCH_2OH$.

To test this hypothesis, experiments we repeated with a substrate more resembling the HO^{i}Pr/acetone redox pair, that is cyclohexanone. To this effect, the kinetic profiles shown in Figure 2 conclusively prove that Li^+ was the most active, reaching 94% conversion after only 2 hours. The activity now decreases in the order $Li^+>Na^+>K^+$, consistent with the decreasing Lewis acidity of the alkali cation. The observation that cyclohexanone is more active than acetophenone is quite remarkable and counterintuitive, given the fact that dialkyl-substituted ketones have lower oxidation potential.[23] However, the abnormal oxidation behavior of cyclohexanone has been previously noted.[24]

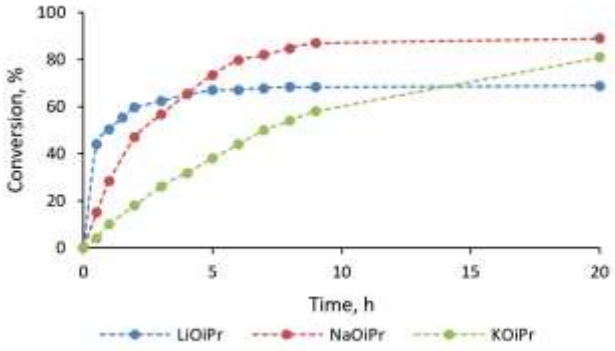

Figure 1. Kinetic profiles for the TH of acetophenone in isopropanol catalyzed by LiO^{i}Pr, NaO^{i}Pr, and KO^{i}Pr.

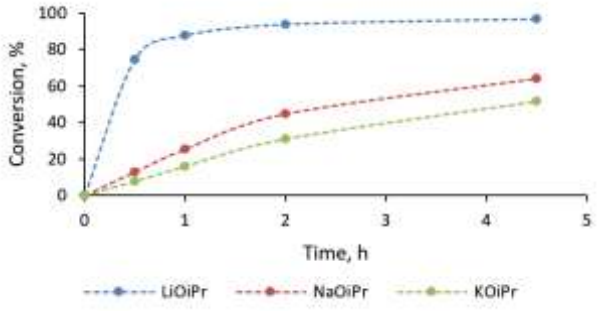

Figure 2. Kinetic profiles for the TH of cyclohexanone in isopropanol catalyzed by LiO^{i}Pr, NaO^{i}Pr, and KO^{i}Pr.

The important conclusion from these two sets of experiments is that the catalytic activity may depend not only on the substrate and reductant but also on compounds being added to the mixture or formed during the reaction. This idea prompted us to investigate systematically the ligand effect on alkali metal catalyzed transfer hydrogenation. Reduction of acetophenone in isopropanol was again chosen as the model system, while the efficiency of additives was gauged by the time required to reach equilibrium. Gratifyingly, addition of simple chelating diamines, such as ethylenediamine and TMEDA, significantly improves the conversion after 12 hours (Table 1, entries 2 and 3 vs entry 1). Both a chelating diether, such as DME, and even a monoligating ether, 1,4-dimethoxybenzene, were more effective, as equilibrium was reached in a much shorter time, 8 h (entries 4 and 5). Unexpectedly, soft donors, such as the chelating diphosphine dppe (entry 6) and monoligating phosphines (entries 7 and 8) turned out to be even stronger promoters, whereas the *N*-heterocyclic carbene IMes (entry 9) was just a bit weaker. The highest activity was achieved using the chelating DalPhos ligand **3** featuring both hard amino and soft phosphine sites (entry 10). Interestingly, using an equimolar amount (10 mol%) of 12-crown-4 still had a beneficial effect on catalysis (entry 11) and, in fact, this cyclic polyether was more effective that diamines (entries 2

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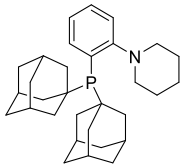
and 3) as equilibrium was reached in a shorter time. Though, using two equivalents of this crown ether per lithium resulted in sequestering of the cation, likely in the form of a sandwich, and partial inhibition of catalysis (entry 12).



3 DalPhos

Table 1. TH of acetophenone with 10 mol% LiO^{i}Pr in the presence of various ligands (10 mol%).[a]

Entry	Ligand	Time	Conversion[b]
1	-	12h	68%
2	ethylenediamine	12h	83%
3	TMEDA	12h	82%
4	DME	8h	83%
5	1,4-dimethoxybenzene	8h	84%
6	dppe	7h	86%
7	PPh_3	7h	84%
8	PEt_3	7h	85%
9	IMes	10h	84%
10	DalPhos	4h	86%
11	12-Crown-4 (10%)	10h	84%
12	12-Crown-4 (20%)	12h	51%

[a] Reaction conditions: acetophenone (50 μL), LiO^{i}Pr (2.8 mg), ligand (0.043 mmol), and 2-propanol (1.5 mL), 100°C; [b] conversions were determined by NMR analysis.

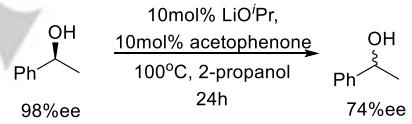
Encouraged by the discovery of the ligand effect, we moved on to address the question whether enantioselective reduction can be accomplished. Several chiral ligands were tried, and the results are shown in Table 2. Unfortunately, in neither case was any asymmetric induction obtained as evinced by the Feringa's chiral test.[25] For example, (-)-sparteine, a naturally occurring alkaloid that is a common chiral inducer for asymmetric lithiation reactions,[26] failed to bring about any asymmetric induction in this transfer hydrogenation (Table 2, entry 1). In terms of efficiency, chelating nitrogen-based ligands**,** (-)-sparteine and 2,6-bis[(4*R*)-(+)-isopropyl-2-oxazolin-2-yl]pyridine (PyBox), performed the best, reaching equilibrium in 7 and 4 hours, respectively (entries 1 and 2). Conversely, no reaction took place in the case of a chelating diphenol ligand, such as BINOL (entry 5), likely because of the increased stability of its dianionic form and hence decreased concentration of the reactive isopropoxide in solution.

Table 2. The effect of chiral ligands (10 mol%) on the TH of acetophenone catalyzed by 10 mol% LiO^{i}Pr.[a]

Entry	Ligand	Time	Conversion[b]
1	(-)-sparteine	7h	86%[c]
2	PyBox	4h	85%[c]
3	(S)-DTBM-SEGPHOS	8h	85%[c]
4	(S)-BINAP	10h	85%[c]
5	(S)-BINOL	12h	NR

[a] Reaction conditions: acetophenone (50 μL), LiO^{i}Pr (2.8 mg), ligand (0.043 mmol), and 2-propanol (1.5 mL), 100°C; [b] conversions were determined by NMR analysis; [c] no asymmetric induction.

To elucidate, whether the lack of enantioselectivity was due to fast racemization of the chiral product, racemization of (*R*)-1-phenylethanol with 10 mol% LiO^{i}Pr as catalyst and 10 mol% of acetophenone as hydrogen acceptor was studied (Scheme 1). Emerging from this study was a very slow decrease from 98% ee to 77% ee after 24 hours, thus further substantiating the point that the TH at lithium center is impeded by 1-phenylethanol.



Scheme 1. Racemization of (*R*)-1-phenylethanol in the presence of LiO^{i}Pr in 2-propanol.

Examples of synthetic application. To demonstrate the synthetic utility of this catalytic system, we screened reduction of several substrates (Scheme 2). Acetophenone, benzophenone, *p*-chloroacetophenone, and *p*-cyanoacetophenone were reduced much faster in the presence of 10% dppe, whereas the ligand addition had no effect on the reduction of aliphatic ketones, cyclohexanone and methyl tert-butyl ketone. Surprisingly, the TH of p-methoxyacetophenone was also insensitive to the addition of dppe.

The possibility of phosphorus coordination to lithium was probed by ^{31}P NMR and ^{6}Li NMR spectroscopy. Addition of LiO^{i}Pr to a solution of dppe in isopropanol did not result in any change of the chemical shift of phosphine. Likewise, no coupling to ^{31}P was observed in the lithium spectrum, suggesting that in the case of dppe coordination to lithium cation is minimal and the activating effect should have a different origin (vide infra).

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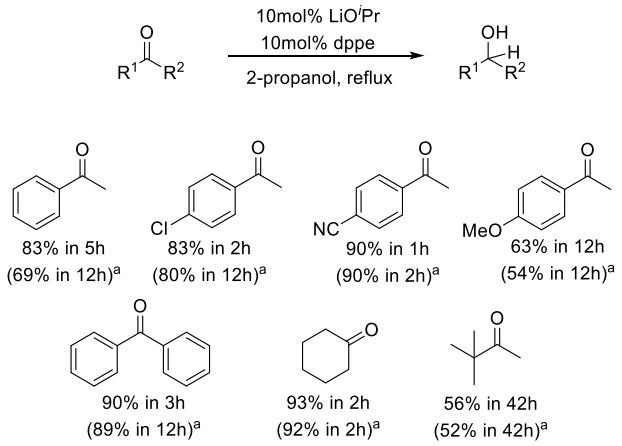

Scheme 2. Ligand-assisted transfer hydrogenation of ketones. [a] No ligand was added.

Additive effect on alkali metal-mediated transfer hydrogenation. We were intrigued that quite a vast diversity of ligands containing potential oxygen, amine, phosphine, and aromatic binding sites can significantly enhance the catalytic activity of LiO^{i}Pr. The activating effect of phosphine in the absence of apparent Li-P interactions in NMR (*vide supra*) was equally puzzling. To understand whether the mere presence of a simple functional group, such as arene ring or oxygen atom, can have a beneficial effect on catalysis, we decided to investigate the effect of aromatic and ethereal additives on the lithium-catalyzed TH.

To our surprise, addition of benzene and methyl substituted benzenes also resulted in the enhancement of catalytic activity of LiO^{i}Pr. Thus, the presence of 0.5 equivalents (relatively to the substrate) of benzene, toluene, mesitylene, or hexamethylbenzene allowed the reaction to reach 81-83% conversion in 10 h (Table 3, entries 1-4), as compared to the maximum 68% conversion observed in the absence of these additives. A similar enhancement effect was found upon addition of THF (Table 3, entry 5). The dependence of the catalytic activity on toluene loading was studied next (entries, 2, 6-10), which revealed increasing the amount of toluene up to 0.5 equivalent led to a steady advancement of the reaction to 82% conversion in 10 hours (Table 3, entry 2). However, addition of a larger amount of toluene (1 - 15 equivalents, entries 8-10) decreased the conversion down to 39% with a 15-fold excess of toluene after 10 hours (entry 10). Even more surprisingly, addition of toluene to the sodium or potassium isopropoxide catalyzed TH had zero effect on the reaction rate, underlying the unique role of lithium in this catalysis.

Table 3. TH of acetophenone with LiO^{i}Pr in the presence of various additives.[a]

Entry	Additive	Load	Time	Conversion[b]
1	Benzene	50%	10 h	83%
2	Toluene	50%	10 h	82%
3	Mesitylene	50%	10h	81%
4	Hexamethylbenzene	50%	10h	82%
5	THF	50%	10h	82%
6	Toluene	5%	10h	70%
7	Toluene	10%	10h	81%
8	Toluene	100%	10h	74%
9	Toluene	300%	10h	72%
10	Toluene	1500%	10h	39%

[a] Reaction conditions: acetophenone (50 μL), LiO^{i}Pr (2.8 mg), ligand (0.043 mmol), and 2-propanol (1.5 mL), 100°C; [b] conversions were determined by NMR analysis.

Mechanistic studies. The above data clearly show that alkali metal cations play the key role in the catalytic transfer hydrogenation and that ligands and additives can have significant impact on their performance, which is particularly noticeable in the case of lithium. For the traditional MVP reactions, three mechanistic pathways were considered: the hydridic route based on formation of a metal-hydride, a radical route, and a direct H-transfer from alkoxide to carbonyl via a six-membered transition state (most common).[6-7] For the alkali metal catalyzed reaction, the hydridic route can be reliably ruled out as the formation of MH species in alcoholic solutions is highly unlikely and because added hydrogen, the likely product of a reaction between transient MH and isopropanol, had no impact on catalysis. On the other hand, under water- and alcohol-free conditions, alkali metal hydrides can indeed become catalytically relevant.[21]

To get a further insight into the mechanism of catalytic action, kinetic studies under pseudo-first order conditions were performed by using large excess of isopropanol (10-25 equivalents). Cyclohexanone was chosen as the model substrate because its transfer hydrogenation can be considered as a virtually irreversible process at the start of the reaction (up to approximately 20% conversion). In all cases, first order kinetics in the substrate was observed. The dependence of the reaction rate on the catalyst was established by studying the variation of LiO^{i}Pr loading from 2 to 10 mol% in 1 mL of 2-propanol. A perfect linear plot of the effective reaction rate vs the amount of base was obtained (Figure S1), which shows that the reaction is also first order in the alkali metal catalyst. Further variation of the amount of 2-propanol at a fixed LiO^{i}Pr load (4 mol %), established that the reaction is also first order in the reducing agent to give an overall second order reaction, with the kinetic law being rate = k[catal][ketone][alcohol].

The effect of temperature was studied next by measuring the rate of reaction between 70°C and 90°C (Figure S3), which following use of the Van't Hoff equation (1) provided a temperature coefficient of 2.7.

$$r_2 = r_1 \gamma^{\frac{T_2 - T_1}{10}} \quad (1)$$

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Linearization of data in Arrhenius and Eyring coordinates (Figures S4 and S5), based on equations 2 and 3, respectively, allowed for the activation energy, enthalpy, and entropy be determined (Table 4). The relatively low enthalpy of activation and negative entropy of activation point to an organized transition state, which is consistent with a six-membered transition state commonly accepted for the aluminum-catalyzed MPV reaction.[6]

$$k = Ae^{\frac{-E_a}{RT}} \quad (2)$$

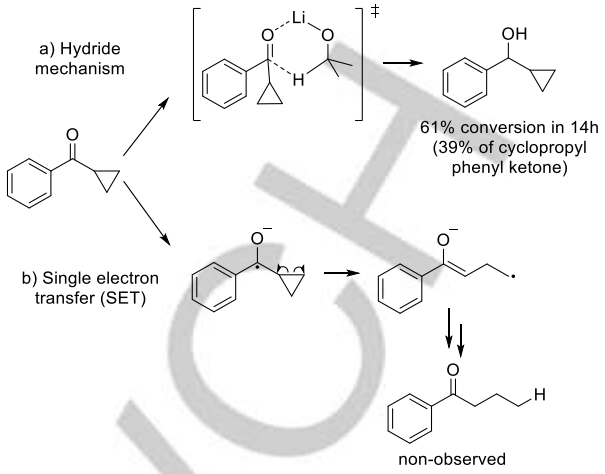
$$k = \frac{k_b T}{h} e^{\frac{-\Delta G^{\neq}}{RT}} \quad (3)$$

Table 4. Kinetic parameters found for the TH of cyclohexanone.[a]

Parameter	Value	Uncertainty
E^a	103.0 KJ/mol	0.5 KJ/mol
A	26.0 sec^{-1}	1.2 sec^{-1}
$\Delta H^{\neq}$	100.1 KJ/mol	0.6 KJ/mol
$\Delta S^{\neq}$	-38.7 J/mol	1.6 J/mol

[a] Reaction conditions: cyclohexanone (25.5 µL), LiO^{i}Pr (1.1 mg), and 2-propanol (1.0 mL), 70-90^{o}C.

We then probed the possibility of a radical mechanism by studying the TH of cyclopropyl phenyl ketone, employing the cyclopropyl group as a radical probe (a "radical clock"). Although earlier studies by von Doering and Aschner ruled out a radical mechanism,[13] some later work supported the possibility of one electron transfers to substrates prone to stabilize radicals. For example, the ketyl radical were detected in the MPV reduction of benzophenone.[27] Cyclopropyl phenyl ketone would give different products, depending on the mechanism of the reduction process. When an MPV-like transfer of hydrogens occurs, only the C=O bond undergoes transformation to the hydroxyl functionality (Scheme 3a). But if a radical is generated during the reaction, it can cause intramolecular isomerization, which would be triggered by the steric strain of the cyclopropyl ring (Scheme 3b). In the case of cyclopropyl phenyl ketone reduction under the alkali metal catalyzed TH, only cyclopropyl(phenyl)methanol was observed, suggesting an MPV mechanism and not a single electron transfer. Further insight into the mechanism of transfer hydrogenation of ketone was provided by kinetic isotope effect measurements carried out in isopropanol with 10 mol% lithium isopropoxide and 10% TMEDA. Benzophenone, a non-enolizable ketone, was chosen as a substrate to avoid any side effects, which can be caused by enolization. Comparison of the rates obtained in $HOCHMe_2$ and $DOCHMe_2$ fetched a small KIE of 1.1, indicating that proton transfer is not involved in the rate determining step (RDS). On the other hand, a significant KIE of 3.6 was obtained for the reaction carried out in the fully deuterated isopropanol $DOCD(CD_3)_2$, which is consistent with the C-D bond cleavage in the RDS. This result corroborates further the suggestion that reaction proceeds via direct hydrogen transfer from the alkoxide to carbonyl.



Scheme 3. a) Direct hydride transfer mechanism and b) single electron transfer mechanism for the lithium-catalyzed transfer hydrogenation of cyclopropyl phenyl ketone.

The effect of substitution in the phenyl ring of acetophenone was probed then and the resulting Hammett plot is presented in Figure 3. The positive slope shows that the reaction accelerates when electron-withdrawing substituents in the para position of the phenyl ring are present. This implies that a negative charge is developed at the carbonyl group during the rate determining step (RDS), which is more effectively stabilized by electron-withdrawing rather than electron-donating groups. This result is consistent with the hydride transfer to the substrate in the RDS.

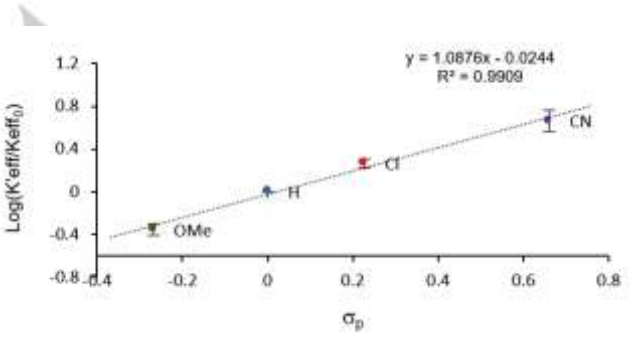


Figure 3. Hammett plot for lithium cation-catalyzed transfer hydrogenation of acetophenones in isopropanol.

Taken together, these kinetic data underpin the Woodward's proposal[12] that alkali base-catalyzed transfer hydrogenation proceeds via a six-membered cyclic transition state similar to the conventional mechanism of Meerwein–Ponndorf–Verley reduction mediated by aluminum alkoxides.

Discussion of experimental results

The understanding of alkali metal catalyzed reduction is very important in the context of development of more benign and

sustainable synthetic processes that would circumvent the use of toxic and expensive transition metals and minimize the production of waste. The latter aspect is of great concern in the traditional aluminum-based MPV catalysis which usually requires stoichiometric amounts of aluminum alkoxide or alkyl reagents.[7] So far, the use of alkali metals in the MPV reactions has been very limited because of the low activity and the need of using increased amounts of the catalyst.[7a] In this study we show that this problem can be mitigated by the application of ligands and promoters.

Before discussing the alkali metal catalysis, one question should be addressed: Is it possible that catalysis is triggered by traces of transition metals? The detailed study by Ouali et al. shows that transition metals are not responsible for the observed base catalysis and, in fact, their addition has a detrimental effect.[19a] This finding may explain why large excess of alkali base is required in some "transition metal-catalyzed" transfer hydrogenations.

The main puzzle of the alkali metal-catalyzed MPV reduction is that the reactivity order in the transfer hydrogenation of acetophenone, the most common model substrate for the TH, is Na > K > Li. This order is counterintuitive because MPV requires the presence of a strong Lewis acid to polarize and activate the C=O bond, whereas the order of Lewis acidity of alkali metals is Li > Na > K. Ouali et al. explained this reactivity order by the need to balance the substrate activation step with the rate of product de-coordination, which requires a weaker Lewis acid, so that the maximum activity is observed with sodium.[19a] However, the ligand exchange for alkali metal ions is known to be very fast.[7a] The lack of reactivity by the application of ylide $H_2C{=}PPh_3$ alone versus the productive catalysis in the case of a combined action of ylide and LiCl illustrates the need of a Lewis acid. So, how can one explain the abnormal reactivity order for alkali metals? The change of the reactivity order to the expected Li > Na> K in the case of cyclohexanone shows conclusively that the reactivity is substrate-dependent and therefore the abnormal behavior should be caused by the presence of the arene ring in acetophenone.

A seemingly obvious explanation is that the change of reactivity is caused by specific interactions between the alkali metal ion and the aromatic ring. Indeed, alkali cation-π interactions are very well established, so that alkali cations can be solvated by aromatic molecules through interaction with π-electrons.[28] However, Kochi et al. conclusively demonstrated that the strength of alkali metal/aromatic interactions increases down Group 1, with the sodium cation (the smallest studied) showing no sign of Na+…π-interactions.[29] Therefore, it is unlikely to play any major role in the lithium catalysis, and if this effect were operating, the activity in the TH should have changed monotonously down the group.

Since Lewis acidity of the lithium cation is not a decisive factor in impeding the reduction of acetophenone, we envisaged that it could be caused by the different stabilization of the product, 1-phenylethanol, in solution and in complex. Because 1-phenylethanol is a relatively large molecule, it disrupts the hydrogen bonding network of the solvent (isopropanol). On the other hand, placing two or more molecules of 1-phenylethanol in the coordination sphere of a lithium ion may allow for additional stabilization through the π-π stacking interactions or charge-transfer interactions between the aromatic rings in the intermediates $[(PhMeC{=}O)Li(HOCHMePh)_2(OCHMePh)]$ and $[Li(HOCHMePh)_3(OCHMePh)]$. Indirectly supporting this idea is the observation that Li-catalyzed reduction noticeably slows down at about 40% conversion, which corresponds to four molecules of the product per the alkali metal ion (at the 10% catalyst load). If this hypothesis is correct, the stabilizing aromatic interactions are weakened in the case of sodium and potassium because their larger size places the aromatic groups of ligated 1-phenylethanol farther away. This stabilizing effect should be absent in the case of cyclohexanone which is reduced quicker on the lithium center because of its high Lewis acidity and stronger activation of the carbonyl function.

The inhibiting influence of 1-phenylethanol was studied next. TH of acetophenone was performed with addition of 40 mol% of 1-phenylethanol before the reaction was launched at reflux. The process was much slower comparing to the reaction without additional 1-phenylethanol (Figure S6).

The ligand effect in the case of acetophenone is then explained by a dual phenomenon. First, strong ligands, and in particular chelating ligands, can coordinate to lithium, thus preventing the accumulation of 1-phenylethanol in the coordination sphere of the cation. The enhanced activity of soft ligands, e.g. carbene, versus hard nitrogen- and oxygen-based donors is likely caused by the same reason: the former type of ligands are stabilized worse by the polar media than the latter and tend to bind the lithium cation better. Second, the need to stabilize the product, 1-phenylethanol, in solution is nicely illustrated by the effect of aromatic additives. Small amounts of toluene and other aromatics (and likely Ph-containing ligands, such as dppe) solvate 1-phenylethanol more effectively than isopropanol, likely by means of π-π interactions and help the product leave the coordination sphere of lithium, thus freeing the catalyst.

Another way to break the proposed arene/arene π-interactions is to increase the temperature. This allows for the need of very high temperature (180 °C) in the lithium isopropoxide-catalyzed reduction of ketones reported by Adolfsson et al.[18] At such temperatures, nearly quantitative formation of targeted alcohols is achieved.

To test further our hypothesis, we carried out reduction of acetophenone in the presence of 10 mol% lithium isopropoxide and a stoichiometric amount of LiCl. Fast reduction was observed, reaching 79% conversion after only 2 h versus 60% conversion in the absence of this additive (the equilibrium value was accomplished within 3 h). The tendency for acceleration of transfer hydrogenation of other aromatic substrates (Scheme 4) was similar to the one with the addition of dppe. And no reaction rate improvement was observed for cyclohexanone.

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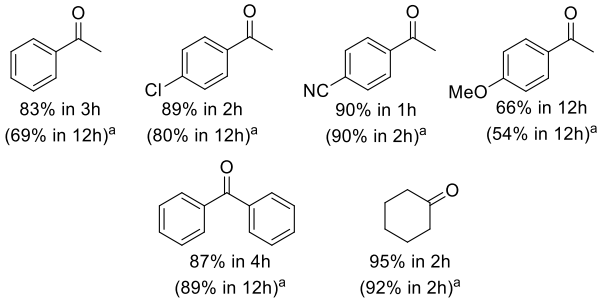

Scheme 4. Reaction conditions: 10 mol% LiO^{i}Pr, 1eq. LiCl in isopropanol (1 ml). [a] No LiCl was added.

DFT calculations

To shed additional light on the mechanism of these alkali-metal catalyzed transfer hydrogenations, DFT calculations exploring a reaction pathway involving direct H-transfer via a cyclic six-membered transition state were performed. Emerging from these calculations were pathways initiating from tetra-coordinated alkali metal complexes $\mathbf{4}_{Li,Na,K}$ (Figure 4). From this complex, hydride transfer by cyclic transition states $\mathbf{TS1}_{Li,Na,K}$ ensues with modest activation barriers of 12.5 kcal mol^{-1}, 10.1 kcal mol^{-1}, and 11.2 kcal mol^{-1}, respectively, to afford complex $\mathbf{5}_{Li,Na,K}$. Notably, these calculated barriers are in line with the observed $Na^+ > K^+ > Li^+$ order of reactivity found experimentally for the ligand/additive-free catalytic processes (*vide supra*). The salient features of these transition states included nearly equivalent bond forming C(1)•••H(2) and bond breaking C(3)•••H(2) distances of 1.33-1.37

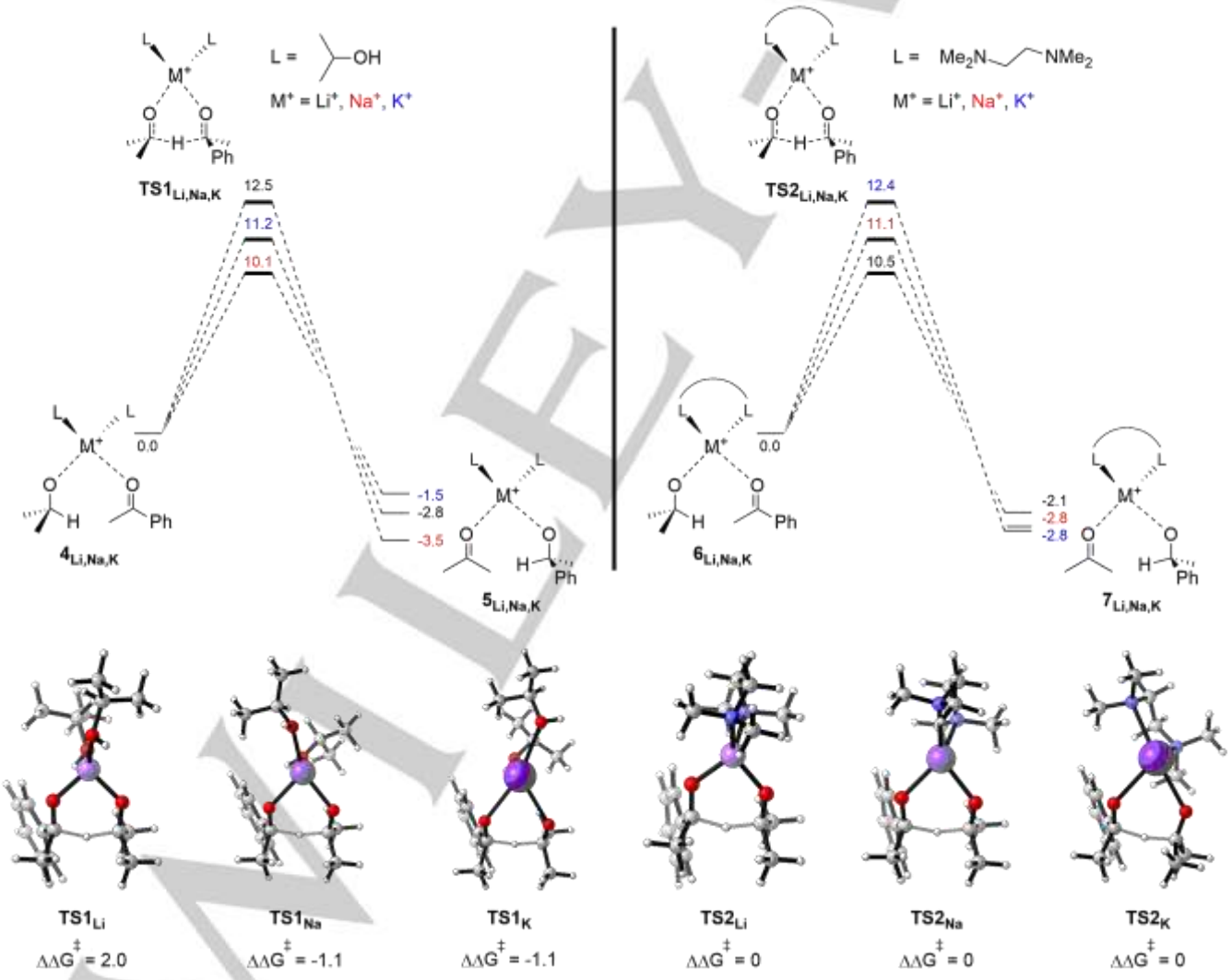

Figure 4. Energy profile corresponding to concerted model for H-transfer from isopropoxy groups to acetophenone with the incorporation of TMEDA ligand. Calculated relative free energies (kcal mol^{-1}) at SMD(Isopropanol)/B3LYP-D3//6-31+G(d,p) level of theory are shown for transitions states with TMEDA ligand and with isopropanol ligand.

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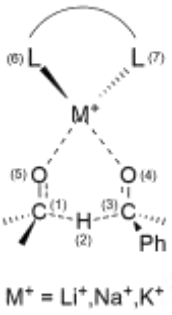
Table 5. Bond making, bond breaking and metal cation heteroatom coordination distances of **TS1$_{Li,Na,K}$** and **TS2$_{Li,Na,K}$** computed at SMD(Isopropanol)/B3LYP-D3//6-31+G(d,p) level of theory. All bond distances are reported in ångströms.

L = Isopropanol

Structure	**TS1$_{Li}$**	**TS1$_{Na}$**	**TS1$_{K}$**
C(1)•••H(2)	1.33	1.34	1.34
C(3)•••H(2)	1.35	1.35	1.37
O(5)•••M$^+$	1.89	2.26	2.63
O(4)•••M$^+$	1.89	2.24	2.75
L(6)•••M$^+$	2.14	2.47	2.94
L(7)•••M$^+$	2.11	2.46	2.96



L = TMEDA

Structure	**TS2$_{Li}$**	**TS2$_{Na}$**	**TS2$_{K}$**
C(1)•••H(2)	1.33	1.34	1.35
C(3)•••H(2)	1.36	1.37	1.36
O(5)•••M$^+$	1.90	2.25	2.68
O(4)•••M$^+$	1.90	2.28	2.71
L(6)•••M$^+$	2.00	2.33	2.75
L(7)•••M$^+$	1.96	2.32	2.79

Å with little dependence on the alkali metal cation (Table 5). In contrast, there was visible elongation of the alkali metal-ligand bonds (to L(6) and L(7)) from 1.96 Å to 2.79 Å upon descending the group I series. Likewise, the distances between the metal cation and carbonyl oxygen O(4) of the substrate increased from 1.90 Å to 2.71 Å.

Intrigued by the role of supporting ligands in these reductions, we next examined the effect of exchanging the coordinated isopropanols for a chelating TMEDA ligand, which notably resulted in more stable complexes. Thus, substitution of two molecules of isopropanol in complexes **4$_M$** results in complexes **6$_M$** (M= Li, Na, K), with respective relative free energies of -50.87, -50.95 and -49.10 kcal mol^{-1}. Like in the case of isopropanol ligand, reduction of acetophenone in the presence of TMEDA complexes exhibited qualitatively similar geometrical trends with respect to the cyclic six-membered transition state subassembly (Table 5, right). For instance, in transition states **TS2$_{Li,Na,K}$**, derived from complex **6$_{Li,Na,K}$** and affording complex **7$_{Li,Na,K}$**, the bonds from the acetophenone and isopropoxide oxygen atoms to the alkali metal cations, O(4)•••M$^+$ and O(5)•••M$^+$ (M$^+$ = Li$^+$, Na$^+$, K$^+$) were comparable for each cation (Figure 4). Further, there was a steady elongation from 1.89 Å to 2.75 Å in going from lithium to potassium (Figure 5). Meanwhile, the alkali metal cation to TMEDA nitrogen atom bond distances, N(6)•••M$^+$ and N(7)•••M$^+$, varied from 1.96 Å to 2.79 Å. By the same token, the bond forming C(1)•••H(2) and bond breaking C(3)•••H(2) distances were nearly equivalent 1.33-1.37 Å, and very close to the distances observed with isopropanol ligands. Despite these structural similarities between the isopropanol and TMEDA series, the $\Delta G^{\neq}$ values for the hydride transfer transition states progressively increased down group I in the order 10.5 kcal mol^{-1}, 11.1 kcal mol^{-1}, and 12.4 kcal mol^{-1}, in excellent agreement with our experimental observation. The lower activation barrier in the presence of TMEDA relative to isopropanol ligands in the case of lithium cation, i.e., $\Delta\Delta G^{\neq}$ = 2.0 kcal mol^{-1}, is noteworthy. Contributing to this difference, in part, were unfavorable eclipsing interactions as seen from the O(5)C(1)•••C(3)O(4) dihedral angles of **TS2$_{Li}$** and **TS2$_{K}$** ($\phi_{O(5)\text{-}C(1)\text{-}C(3)\text{-}O(4)}$ = 11.7° vs 27.4°) ascribed to the larger ionic radius of the potassium cation allowing for greater flexibility in the cyclic six-membered transition state fragment. However, in **TS2$_{K}$** the larger dihedral angle creates steric contacts as seen by an H•••H distance of 2.37 Å, resulting in transition state destabilization. Further, the relative free energies of transition states **TS1$_{Li,Na,K}$** and **TS2$_{Li,Na,K}$** revealed the later series of first-order saddle points were energetically more stable (see SI).

To better understand the origin of this intriguing divergence in reactivity, a distortion/interaction (D/I) analysis was applied. In this context, D/I analysis is a useful tool for analyzing activation barriers in terms of the energy required to distort the reactants to their transition state geometries and the affinities to bring together these fragments, which in turn provides insights into the factors controlling reactivity.[30] The energy, namely the distortion energy or activation strain, constitutes the major component of the activation energy. To overcome the distortion energy leading to the products, there is the requirement for strong bonding interactions between the two reactants, referred to as the interaction energy.

Turning to the case at hand, the D/I analysis for **TS1$_{Li,Na,K}$**/**TS2$_{Li,Na,K}$** was broken down as follows: equation 4 describes the distortion energy (ΔE_{dist}) arising from ligand (**TMEDA** or **HO^{i}Pr**) association to the acetone-acetophenone complex **8$_{Li,Na,K}$** as found in their transition state geometries. This can be further broken down into three components, ΔE_1 is the distortion imposed by ligand dissociation from the precomplex **4$_{Li,Na,K}$** or **6$_{Li,Na,K}$** (Figure 5). The next components, ΔE_2 and ΔE_3, represent the strain incurred by perturbing the acetone-acetophenone metal complex and the ligand fragments, respectively, from their minimized geometries to the transition state geometries. Equation 5 describes the relationship between the distortion energy ΔE_{dist} and the interaction energy ΔE_{int} of the ligand chelation to the acetone-acetophenone complex to give the transition state structure. The interplay of the distortion energy and interaction energy results in the activation energy ΔE_{act}.

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$$\Delta E_{dist} = \Delta E_1 + \Delta E_2 + \Delta E_3 \quad (4)$$
$$\Delta E_{act} = \Delta E_{dist} + \Delta E_{int} \quad (5)$$

Figure 6 shows the distortion-interaction analysis for transition states **TS1$_{Li,Na,K}$** and **TS2$_{Li,Na,K}$**. Evident from this analysis were similar ΔE_{dist} energies for each metal cation. What is more, the ligand distortion energy ΔE_3, irrespective of isopropanol or TMEDA as the ligand, was consistently smaller than the distortion energy ΔE_2 for the acetone-acetophenone fragment or ΔE_1. Further, ΔE_2 was greater for lithium relative to sodium or potassium cation for both isopropanol and TMEDA coordinated complexes. For example, the distortion energies ΔE_2 for **TS2$_{Li,Na,K}$** were 16.3 kcal mol^{-1}, 13.5 kcal mol^{-1}, and 14.3 kcal mol^{-1}, while those for **TS1$_{Li,Na,K}$** were 17.0 kcal mol^{-1}, 14.2 kcal mol^{-1}, and 13.9 kcal mol^{-1}, respectively. By comparison, the distortion energies ΔE_1 were similar for both lithium and sodium cation-based systems, whereas with potassium the energy was ~5.0 kcal mol^{-1} lower.

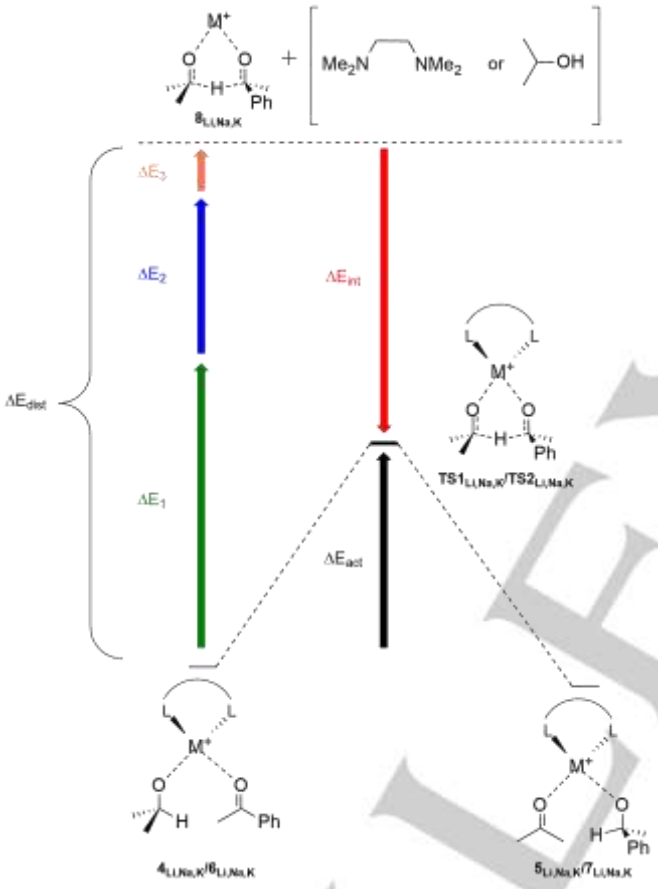

Figure 5. Distortion/interaction analysis for **TS1$_{Li,Na,K}$/TS2$_{Li,Na,K}$**. Activation energy (black arrow); interaction energy (red arrow); distortion energy (ΔE_1) for ligand dissociation from precomplex **4**$_{Li,Na,K}$**/6**$_{Li,Na,K}$ (green arrow); distortion energy (ΔE_2) of the acetone-acetophenone metal complex **8**$_{Li,Na,K}$ (blue arrow); distortion energy (ΔE_3) of the ligand (orange arrow). Calculated energies are shown in kcal mol^{-1}. M$^+$ = Li$^+$, Na$^+$, K$^+$.

The interaction energy ΔE_{int} of **TS1$_{Li}$** was lower than **TS2$_{Li}$** by 2.2 kcal mol^{-1}, while for sodium and potassium cation the interaction energies decreased chromatically. Ultimately, this manifests in a lower activation barrier (ΔE_{act}) for the reduction of acetophenone in the presence of lithium cation and ligand TMEDA, thus correlating with the experimentally observed rate acceleration in the presence of an additive. Conversely, an analogous ligand-based trend on ΔE_{int} energies (isopropanol vs TMEDA) was not observed for sodium or potassium cation catalysis, which is again consistent with the experiment. From these energetics it is clear that the lower activation barrier for lithium cation catalysis derives in large part from larger interaction energies relative to sodium or potassium cation catalysis, which is likely caused by the higher charge density of the smaller lithium cation. It is also meaningful to note that the observed rate acceleration conferred by ligand TMEDA relative to isopropanol is accounted for by the 2.2 kcal mol^{-1} difference in ΔE_{int} values.

As for the deceleration of lithium cation catalysis in the absence of additional ligands, we attribute this to specific interligand interactions between 1-phenylethanol and acetophenone. Consistent with this was the fact that Li-catalyzed reductions noticeably slowed down at about 40% conversion, corresponding to about four molecules of the product per the alkali metal ion (at the 10% catalyst load), while Na$^+$ and K$^+$ catalyzed reductions slowed gradually. This divergency is ascribed to a decreased rate of product de-coordination and/or ligand exchange at the metal center of Li$^+$ complexes relative to Na$^+$ and K$^+$ complexes. To probe this hypothesis, non-covalent interaction (NCI) plots were computed of complexes **9**$_{Li,Na,K}$ corresponding to the lowest energy structures of product coordination (Figure 7). Clear from these plots was greater phenylethanol coordination to the alkali metal ion and greater shielding of the metal cation in the case of **9**$_{Li}$ relative to **9**$_{Na}$. [31] Contributing to this in part were non-covalent interactions between the aryl moiety of 1-phenylethanol and the carbonyl group of acetophenone in Li$^+$ complex **9**$_{Li}$. Conversely, in the cases of Na$^+$ and K$^+$ complexes, **9**$_{Na,K}$, because of their larger ionic radius the aromatic groups reside farther away from the alkali metal resulting in attenuated π-orbital and CH/π interactions between coordinated phenylethanol molecules (see SI for select interaction distances).

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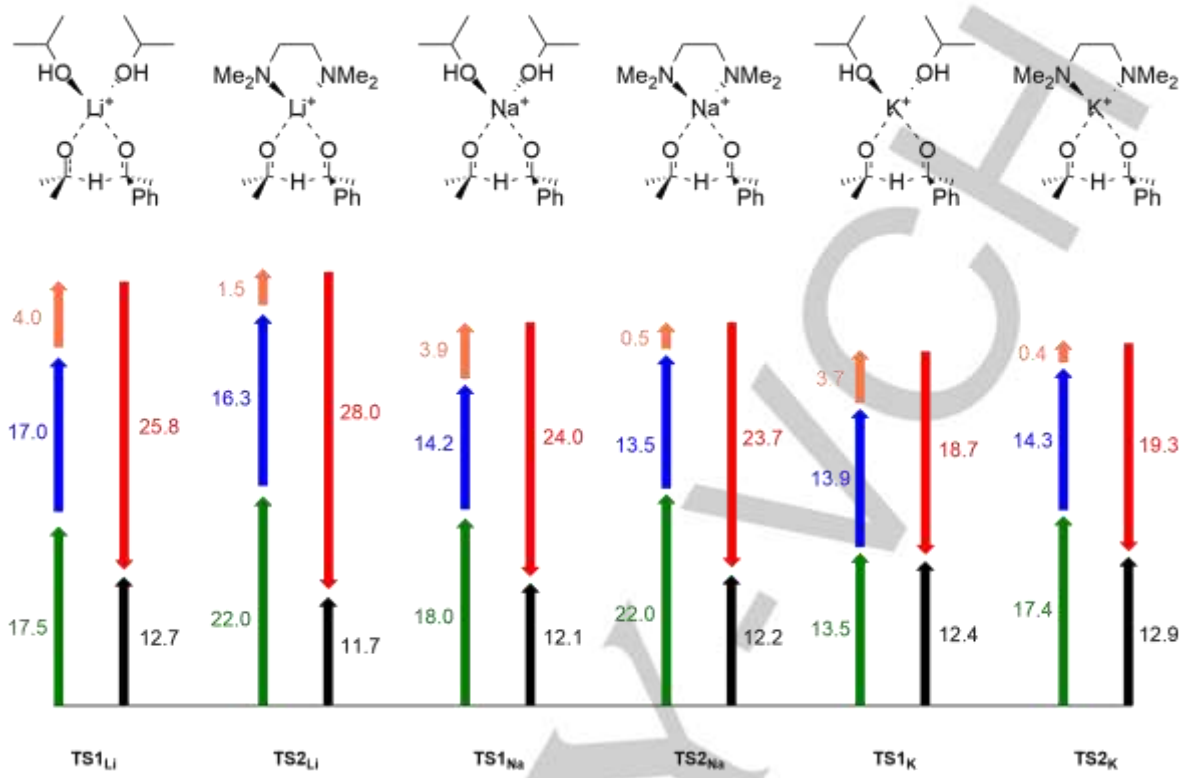

Figure 6. D/I analysis for transition states **TS1**$_{Li,Na,K}$ and **TS2**$_{Li,Na,K}$. Activation energy (black arrow); interaction energy (red arrow); distortion energy (ΔE_1) for ligand dissociation from the precomplex (green arrow); distortion energy (ΔE_2) of the acetone-acetophenone metal complex (blue arrow); distortion energy (ΔE_3) of the ligand (orange arrow). Calculated energies are shown in kcal mol^{-1}.

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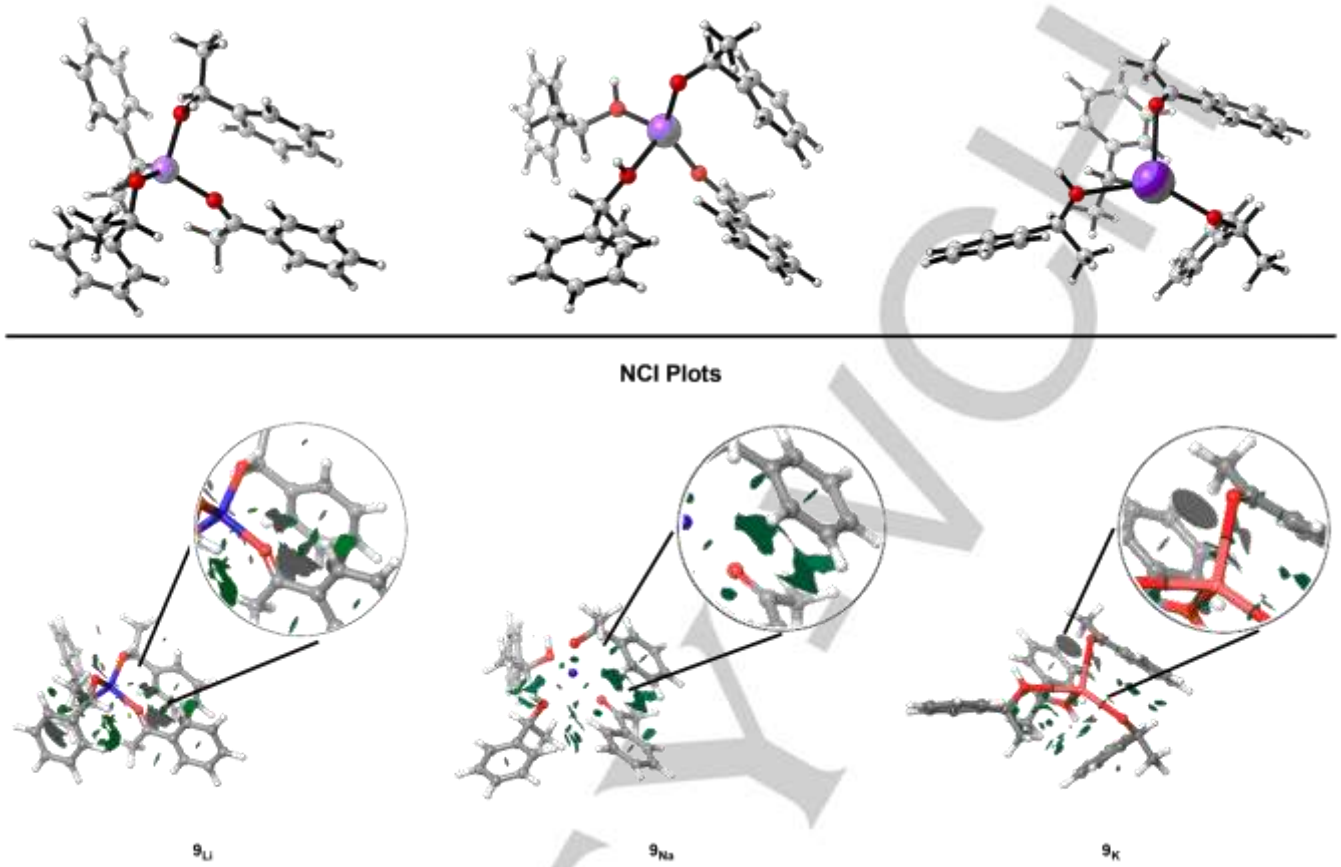

Figure 7. Non-covalent interaction (NCI) plots for structures $\mathbf{9}_{Li,Na,K}$ displaying interactions between the aryl moiety of 1-phenylethanol and the carbonyl group of acetophenone.

Conclusions

In conclusion, our combined experimental and computational study of the alkali metal base-catalyzed transfer hydrogenation of ketones revealed an important dependency on the alkali metal cation employed and offered insights into the mechanism of these reactions. In particular, the counterintuitive reactivity order for catalytic reduction of acetophenone, $Na^+ > Li^+ > K^+$, can be changed to the expected reactivity pattern $Li^+ > Na^+ > K^+$ by adding ligands and additives. These additives accelerate the transfer hydrogenation significantly in the case of aromatic substrates, but not for aliphatic ketones, which usually react fast and show the expected decrease of activity down Group 1. The reaction can be also easily accelerated by adding excess of a cheap and benign reagent, LiCl. Kinetic, labelling, and competition experiments, supported by DFT calculations, point to a concerted direct hydride transfer mechanism, originally suggested by Woodward, as the principle reaction pathway. The experimentally observed deceleration of lithium cation-catalyzed reaction at ~40% conversion was explained by the presence of specific non-covalent interactions, such as charge transfer, between the aryl moiety of 1-phenylethanol product and the carbonyl group of acetophenone, which hampers product dissociation from the catalytic center. This observed ligand/additive effect is likely a combination of several factors, including a change in activity of alkali metal cations and the relative stabilization of reagents and substrates in solution and the coordination sphere of the metal. For the case of isopropanol and diamine ligands, the D/I calculations revealed a noticeable decrease of activation energy of ligation by a diamine (TMEDA), while in the cases of sodium and potassium cations there was only a marginal impact. Other additives can likely stabilize better the product in solution by solvation (e.g. excess toluene) or initiate a new reaction center (the case of LiCl).

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding Sources

This research was supported by NSERC (Discovery Grants DG 2012-326899 and 2017-05231 to G.I.N. and 2014-04410 to T.D.)

Acknowledgements

We thank SHARCNET (Shared Hierarchical Academic Research Computing Network: www.sharcnet.ca) and Compute/Calcul Canada for computing resources.

Keywords: lithium • transfer hydrogenation • ligands • DFT calculation

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10.1002/chem.201902240

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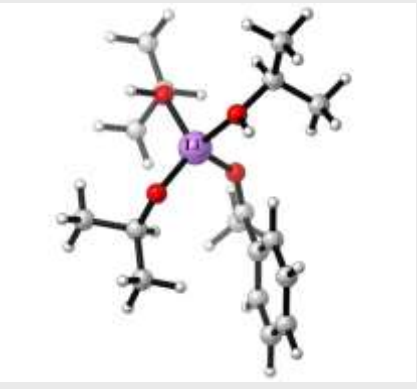
This paper unveils the reactivity patterns, as well as ligand and additive effect on alkali metal base catalyzed transfer hydrogenation of ketones. Kinetic, labelling, and competition experiments and DFT calculations suggested that the reaction proceeds via a concerted direct hydride transfer mechanism.



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Ligand Effect in Alkali Metal-Catalyzed Transfer Hydrogenation of Ketones