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Controlling the selectivity and efficiency of the hydrogen borrowing reaction by switching between rhodium and iridium catalysts†

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The catalytic alkylation of ketones with alcohols *via* the hydrogen borrowing methodology (HB) has the potential to be a highly efficient approach for forming new carbon–carbon bonds. However, this transformation can result in more than one product being formed. The work reported here utilises bidentate triazole-carbene ligated iridium and rhodium complexes as catalysts for the selective formation of alkylated ketone or alcohol products. Switching from an iridium centre to a rhodium centre in the complex resulted in significant changes in product selectivity. Other factors – base, base loading, solvent and reaction temperature – were also investigated to tune the selectivity further. The optimised conditions were used to demonstrate the scope of the reaction across 17 ketones and 14 alcohols containing a variety of functional groups. A series of mechanistic investigations were performed to probe the reasons behind the product selectivity, including kinetic and deuterium studies.

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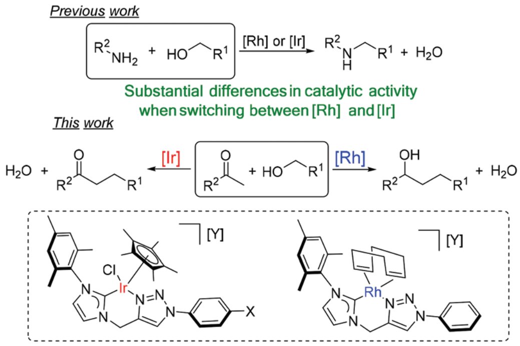
Introduction

Methodologies for promoting carbon–carbon bond formation play a key role in the area of organic synthesis, including pharmaceutical, agrochemical, natural product and other fine chemical synthesis processes.[1,2] While a number of methods exist, the use of mutagenic alkyl halides as the alkylating agent has a strong presence, leading to the formation of problematic toxic waste, thus limiting sustainable applications.[3–5] In alternative approaches, substantial efforts have been made to achieve C–C bond formation in a more effective, and sustainable manner for example C–C bond formation *via* catalytic cross-coupling reactions.[6] Another such C–C bond forming approach is the hydrogen borrowing (HB) reaction which is a highly efficient, low cost and eco-friendly approach with water being the only side-product formed. Thanks to these aspects, HB has seen increased interest over the past decade.[1,7–14]

This work, in particular, is concentrated on utilising the HB approach for the alkylation of ketones with alcohols to form new C–C bonds. The alkylation of ketones has been reported under transition metal free conditions[15,16] and also promoted by a number of different metal containing catalysts,[7] including Mn,[17–19] Ru,[20] Os,[8] Pd,[21–23] Rh,[24,25] Fe,[26,27] Co,[28,29] Ni,[30] and Ir.[31] Recently, Gülcemal and co-workers reported an iridium based system allowing for catalyst loadings as low as 0.05 mol% and TOF values of >900 h^{-1}.[31] However, a number of these approaches still suffer from high catalyst or base loadings, high reaction temperatures or in particular, poor product selectivity. For this catalytic C–C bond forming transformation the particularly challenging problems arise from the product selectivity, as during this HB process two different products can readily form; alkylated ketone and alkylated alcohol.[7,32]

Recently we reported a HB strategy for synthesising C–N bonds through coupling alcohols and amines (Scheme 1, previous work).[33] It was found that upon comparing the catalysis



Scheme 1 Previous work by Messerle and co-workers indicated that the analogous Rh and Ir catalysts can lead to different reactivity for the C–N bond forming hydrogen borrowing reaction. This work investigates the use of Rh and Ir complexes for product selectivity in C–C bond forming hydrogen borrowing reaction. X = H or CF_3, Y = $[BPh_4]^-$ or $[B(3,5\text{-}CF_3\text{-}C_6H_3)_4]^-$. H_2O is formed in all cases as a side-product.

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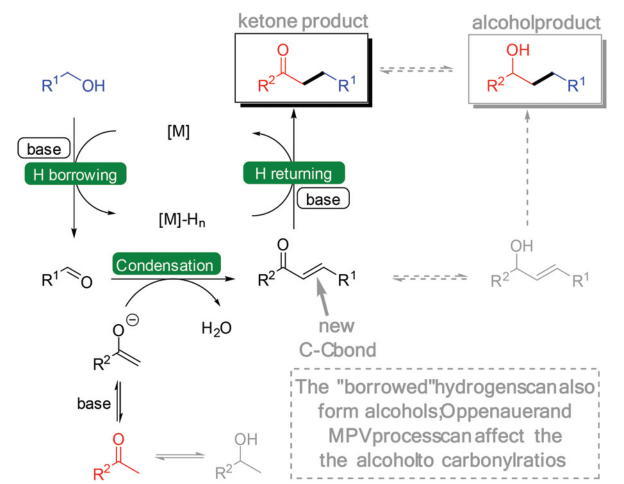
results when using rhodium or iridium complexes as the catalysts, in some instances substantially different catalytic activity was observed.[34] Based on these previous results, we were interested to investigate whether this difference in activity can be advantageous in product selectivity for the C–C bond formation and thus allow us to achieve control over the nature of the product formed (Scheme 1, this work).

The general mechanism for the HB mediated alkylation reaction that leads to the formation of C–C bonds relies on three main steps (Scheme 2). In the first step the alcohol reagent is oxidised to an aldehyde by the synergistic cooperation of metal catalyst and base. This can be seen as the hydrogen being captured or "borrowed" (*i.e.* dehydrogenation) from the alcohol to form the corresponding aldehyde. Next *via* the aldol condensation step the aldehyde forms a C–C bond with a nucleophilic enolate generated from the ketone in the presence of base. In the final step the unsaturated enol intermediate undergoes the hydrogen "returning" process (*i.e.* hydrogenation) resulting in the alkylated product which can be an alcohol or a ketone.

In addition to the synergistic transition metal and base mediated HB processes, the formation of the alkylated ketone and alcohol products can also be promoted by the presence of an alkali base alone.[15,16] Furthermore, the presence of a base in the reaction mixture can open the Oppenauer pathway to the oxidation of the alcohols to form carbonyls and the Meerwein–Ponndorf–Verley (MPV) pathway leading to the reduction of carbonyls to the corresponding alcohols.[16,35] These side reactions can significantly impact the product selectivity.[36]

The development of a catalyst that can control the product selectivity, even with the base present in the reaction mixture, is crucial. Such control could be highly significant for both, environment and industry, as using the most effective catalyst would substantially reduce the production cost, the waste formed and increase the overall viability of the process. Therefore, within this work we investigated the extent to which we can affect the product selectivity between the formation of ketone and alcohol products during the HB transformation by simply changing the metal centre of the complex used as the catalyst. In addition, other aspects of the reaction set-up were evaluated.



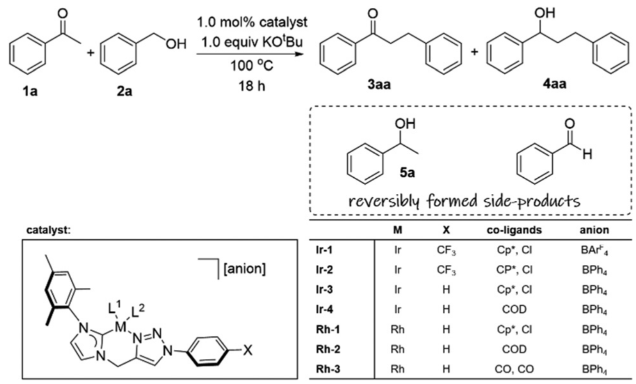
Scheme 2 General mechanistic pathway for coupling ketones with alcohols using the hydrogen borrowing methodology to form new ketone and alcohol products. MPV = Meerwein–Ponndorf–Verley pathway.

Results and discussion

Initial study of the benchmark reaction using Ir and Rh catalysts

The rhodium(I) and iridium(III) triazole-carbene complexes used in this investigation were designed based on the successful results obtained for the C–N bond forming HB reaction *via* the coupling of primary alcohols and amines (Scheme 1, previous work).[33,34] The benchmark reaction for the C–C bond formation work undertaken here was conducted with acetophenone (**1a**) and benzyl alcohol (**2a**) as the substrates (Scheme 3).

The benchmark reaction was probed using four iridium- and three rhodium complexes with varied catalyst parameters including oxidation state, co-ligands, ligand design and counter-ion (complexes **Ir-1–Ir-4** and **Rh-1–Rh-3**, Scheme 3). All iridium and rhodium catalysts led to 100% consumption of starting materials (**1a** and **2a**) within the 18 h reaction but with substantially different product selectivity (Table 1). Iridium catalysts displayed significant preference for the alkylated ketone product 1,3-diphenylpropan-1-one (**3aa**) over the alkylated alcohol product 1,3-diphenylpropan-1-ol (**4aa**) (**3aa** : **4aa** ratio of >7 : 1 for iridium(I) complexes, and 4 : 1 for the iridium(III) complex, Table 3, entries 1–4). Under the same reaction conditions, the rhodium catalysts yielded **3aa** and **4aa** at much lower preferences (**3aa** : **4aa** ratio of 2.6 : 1 for the rhodium(III) complex, and <1.3 : 1 in the case of rhodium(I) complexes,



	M	X	co-ligands	anion
Ir-1	Ir	CF_3	Cp*, Cl	BAr^F_4
Ir-2	Ir	CF_3	CP*, Cl	BPh_4
Ir-3	Ir	H	Cp*, Cl	BPh_4
Ir-4	Ir	H	COD	BPh_4
Rh-1	Rh	H	Cp*, Cl	BPh_4
Rh-2	Rh	H	COD	BPh_4
Rh-3	Rh	H	CO, CO	BPh_4

Scheme 3 Benchmark reaction for the hydrogen borrowing reaction using acetophenone (**1a**) and benzyl alcohol (**2a**) as the substrates and iridium and rhodium complexes (**Ir-1–Ir-4**, **Rh-1–Rh-3**) as catalysts. Ar^F_4 = 3,5-CF_3-C_6H_3. Toluene as solvent (1.0 mL). Substrates in 1 : 1 ratio (0.5 mmol). 0.5 mmol of KO^{t}Bu. In addition water is formed as a side-product.

Table 1 Comparison of different rhodium and iridium complexes as catalyst for the benchmark reaction depicted in Scheme 3

Entry	Catalyst	Base	Consumption of **2a**/%	Conversion/%			
				3aa	**4aa**	**5a**	**3aa : 4aa**
1	**Ir-1**	KO^{t}Bu	100	91	9	—	10 : 1
2	**Ir-2**		100	85	13	2	7 : 1
3	**Ir-3**		100	95	4	1	24 : 1
4	**Ir-4**		100	80	19	1	4 : 1
5	**Rh-1**	KO^{t}Bu	100	70	27	3	2.6 : 1
6	**Rh-2**		100	53	42	5	1.3 : 1
7	**Rh-3**		100	47	49	4	1 : 1
8	—	KO^{t}Bu	76	40	29	6	1.4 : 1
9	**Ir-1**	—	0	—	—	—	—
10	—	—	0	—	—	—	—

Reaction conditions: **1a** and **2a** in 1 : 1 ratio (1.0 mmol), with 1.0 molar equivalent of KO^{t}Bu as the base and 1.0 mol% catalyst loading. 100 °C for 18 h. Toluene as solvent (1.0 mL). Conversion measured by ^{1}H NMR spectral analysis.

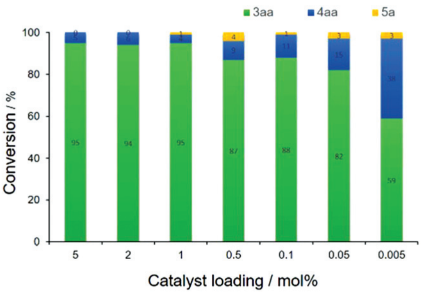


Fig. 1 The effect of catalyst loading to the product ratio of **3aa** and **4aa**. Reaction conditions: **1a** and **2a** in 1 : 1 ratio (1.0 mmol), with 1.0 molar equivalent of KO^{t}Bu as the base (1.0 mmol) and **Ir-3** as the catalyst. 100 °C for 18 h. Toluene as solvent (1.0 mL). The equivalent comparisons for all other catalysts are in the ESI section S1.5.†

Table 3, entries 5–7). For all catalysts in addition to **3aa** and **4aa**, small quantities (<5%) of 1-phenylethan-1-ol (**5a**) and very small amounts of benzaldehyde were observed during the reaction. Both of these additional species were expected to form reversibly *via* either the HB or the MPV/Oppenauer pathways.[16,35,36]

When the reaction was carried out with no metal complex in the reaction mixture, but with base (KO^{t}Bu) still present, only 76% of the starting materials was consumed, and the product ratio of 1.4 : 1 (**3aa** : **4aa**) was obtained, indicating only a slight preference for the ketone product (Table 3, entry 8). This matches the "base only" work reported by Xu *et al.* where similar yield and selectivity were seen for these substrates.[16] The control reaction with no base in the mixture led to no conversion to products (Table 3, entry 9). Similarly, no products formed when no iridium and no base were added to the reaction mixture (Table 3, entry 10).

The best product selectivity towards the alkylated ketone product **3aa** (24 : 1 ratio of **3aa** : **4aa**) was observed using the iridium(I) complex **Ir-3** as the catalyst and therefore the subsequent reaction condition screening for the formation of **3aa** was conducted using **Ir-3** as the catalyst.

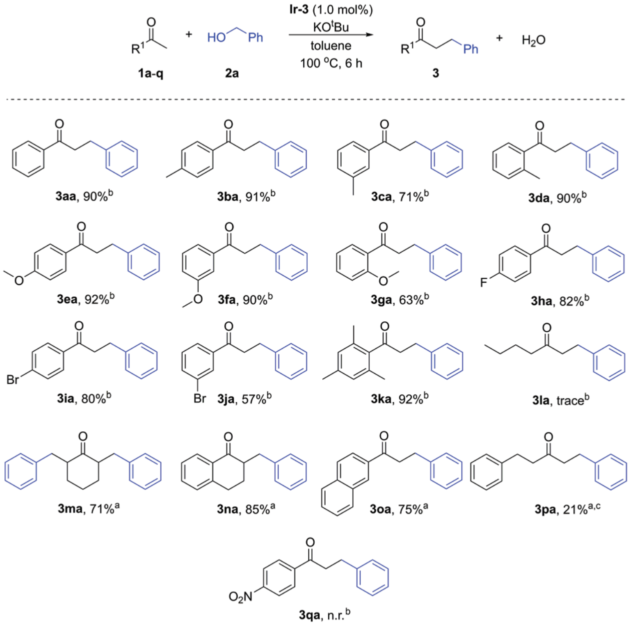
As both the transition metal catalyst and the base can affect the product selectivity of this HB reaction, the ratio of **Ir-3** to KO^{t}Bu was investigated. The benchmark reaction (Scheme 3) was conducted using **Ir-3** as the catalyst at different loadings, while the base (KO^{t}Bu) loading was kept at 1.0 molar equivalent (to substrate) (Fig. 1). When the catalyst loading was increased from the initial 1.0 mol% to 2.0 or 5.0 mol%, no substantial change was observed. When the catalyst loading was dropped to 0.5, 0.1 or even 0.05 mol%, the major product formed during the reaction was still **3aa** (for 0.05 mol% loading of **Ir-3**; 82%, 1640 turnovers). Only when the catalyst loading was reduced to 0.005 mol%, a substantial drop in the selectivity towards the formation of **3aa** resulted (59%), with **4aa** as the major side product (38%). This product ratio was similar to that achieved using base only (Table 1, entry 8), indicating that the limit of the base to catalyst ratio was breached, and the product selectivity gain from the catalyst was lost. When both, the catalyst loading and the base loading were lowered (0.005 mol% **Ir-3**, 0.5 mol% KO^{t}Bu), while keeping their relative ratio constant with respect to the 1.0 mol% catalyst loading reaction conditions, no product formed.

The base loading was evaluated at 1.0 mol% catalyst loading. The use of 0.5–1.0 molar equivalents of KO^{t}Bu to substrate resulted in >15 : 1 selectivity for the formation of **3aa** in all cases, whereas increasing the base loading to 1.5 molar equivalents of KO^{t}Bu led to 10 : 1 selectivity towards **3aa**. A series of different bases were screened. Analogous results were obtained when using KOH, while other bases led to lower yields and reduced selectivity (Table S1†). 100 °C was found to be optimal for high conversions (Table S1†). In addition, the reaction time was evaluated. The kinetic studies showed that the reaction reached completion in 6 hours.

Substrate scope for ketone formation

Using the catalyst (**Ir-3**) and the conditions that led to high selectivity towards the ketone product formation, the substrate scope of this reaction was evaluated. The first set of reactions was carried out between benzyl alcohol (**2a**) and a variety of ketone substrates (**1a–q**) (Scheme 4).

The coupling between benzyl alcohol and the ketone substrates with electron-donating groups resulted in good to excel-



Scheme 4 Conditions: **1** (0.5 mmol), **2** (0.5 mmol), **Ir-3** (1.0 mol%), KO^{t}Bu (0.5–0.8 equiv.), toluene (1.0 mL) at 100 °C for 6 h. Isolated yields of the ketones are given. ^{a}0.8 equiv. of KO^{t}Bu was employed, ^{b}0.5 equiv. of KO^{t}Bu was employed. ^{c}Conversion measured by ^{1}H NMR spectral analysis of crude product mixture using 1,1,2,2-tetrachloroethane (TCE) as the internal standard.

lent isolated yields (**3aa**–**3fa** and **3ka**) ranging from 71% to 92%. The one exception was **3ga** for which a lower yield to the ketone product was observed (63%) with the corresponding alcohol product as the main other species, and less than 5% of the starting materials remaining. This could be attributed to the additional steric bulk near the reactive site. In contrast, the ketone substrates bearing electron-withdrawing groups at the *para*-position led to a slight drop in the yield of the ketone product (**3ha**–**3ia**), and in the case of *meta*-bromo substituted **1j** the isolated yield was only 57% (with the alkylated alcohol product formed as the main side product). When the aliphatic ketone was used as a starting material, only traces of the product **3la** were observed, whereas, the incorporation of a phenyl ring to the starting material structure (**1p**), resulted in slightly higher conversion to the desired ketone (**3pa**), with the unreacted starting materials as the main species at the end of the reaction. Unprotected cyclohexanone **1m** was double alkylated in good yield. Interestingly, in this example no mono-alkylated ketone product formation was observed.[37] The 1-tetralone substrate **1n** was successfully alkylated in excellent yield (85%), and the more conjugated ketone **1o** bearing a naphthalene skeleton resulted in a 75% yield. The *para*-nitro-substituted ketone **1q** led to no product formation, likely due to catalyst decomposition indicated by dark particles precipitating during the reaction process.

In the second set of the scope evaluation for the formation of the ketone product, a series of alcohol substrates (**2b**–**o**) were investigated as starting materials in a reaction with acetophenone (**1a**) (Scheme 4).

Substituted benzyl alcohols were all readily converted to the corresponding ketones (**3ab**–**ah**) in good yields (77–88%), with the exception of 4-nitrobenzylalcohol **2i**, which led to catalyst decomposition, similar to what had been observed for the other nitro-substituted reagent, 4-nitroacetophenone (*cf.* **1q**, Scheme 3). Heterocycle containing substrates (**2j**–**2l**) resulted in the desired products in good yields (62–87%). In the case of **3ak**, the major side-product was the corresponding alcohol product. Aliphatic substrates of either cyclic (**2m**–**n**) or non-cyclic alcohols (**2o**) proved to be challenging and led to the formation of products in low to moderate yields (12–63%). The transformation of cyclopropylmethanol (**2m**) resulted in the formation of a mixture of products. The best conversion to the desired ketone (12% ^{1}H NMR spectral yield) was obtained upon using 0.2 molar equivalents of KO^{t}Bu, with the unreacted starting materials remaining as the major species at the end of the reaction. In the case of **3an** and **3ao**, the major side-products were the corresponding alcohols.

Catalyst and reaction conditions screening for forming alcohols

As the HB protocol can lead to two different products – alkylated ketones (**3**) or alcohols (**4**) (Scheme 1) even when the same substrates are used (**1** and **2**) – we were curious to investigate whether we can also selectively promote the alcohol (**4**) formation over the ketone (**3**). Based on the initial catalyst comparisons (Table 1), the best relative ratio for the formation of the alcohol product **4aa** was obtained when using the rhodium(I) complexes **Rh-2** or **Rh-3** as the catalyst (*ca.* 1 : 1 "selectivity" for **3aa** : **4aa**). Despite the **Rh-3** catalyst displaying slightly higher selectivity towards the ketone product **3aa**, the ease of synthesis of **Rh-2** compared to **Rh-3** outweighs this and further testing was carried out using **Rh-2** as the catalyst.

Although the rhodium complexes led to higher selectivity towards the alcohol product than the iridium catalysts, the selectivity was still limited (Table 1). This was rationalised by the need for two "extra" H atoms to form the alcohol product.[16] To overcome this limitation, additional alcohol was introduced to the system by using an excess of the alcohol substrate (two molar equivalents of **2a**, Scheme 6). This change resulted in a substantially higher conversion to the desired alkylated alcohol product. The direct comparison of the substrate ratio, using **Rh-2** as the catalyst, demonstrated that one molar equivalent of **2a** (to **1a**) resulted in 1.3 to 1 ratio of ketone to alcohol products **3aa** and **4aa**, whereas two molar equivalents of **2a** led to a significant improvement for the alcohol product selectivity with 1 to 13.3 ratio of **3aa** to **4aa** (Scheme 6).

To confirm that this selectivity towards the alcohol product was not solely due to the increased alcohol presence (2.0 equivalence), the iridium catalyst **Ir-3** that was previously employed for selective ketone formation was evaluated under the conditions employing the higher alcohol equivalence. When the iridium(III) complex **Ir-3** was used as a catalyst, the alcohol product (**4aa**) was still formed as a major product, but the selectivity was lower by approximately a factor of 3, compared

Table 2 Screening of the catalysts and reaction conditions for the selective formation of the alcohol product **4aa**

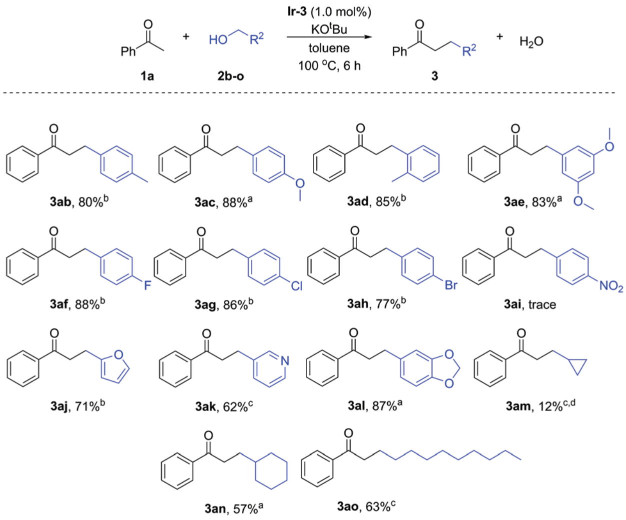
Entry	Catalyst	**2a**/equiv.	Base	Base equiv.	Temp/°C	Conversion/% **3aa**	**4aa**	**5a**	**3aa : 4aa**
1	**Rh-2**	1.0	KO^{t}Bu	1.0	100	53	42	5	1.3 : 1
2	**Rh-2**	2.0	KO^{t}Bu	1.0	100	7	92	—	**1 : 13.3**
3	**Rh-2**	2.0	KO^{t}Bu	2.0	100	10	90	—	1 : 9
4	**Rh-2**	2.0	KO^{t}Bu	0.8	100	36	64	—	1 : 1.8
5	**Rh-2**	2.0	KOH	1.0	100	11	84	5	1 : 7.6
6	**Rh-2**	2.0	KOH	2.0	100	6	91	3	1 : 15.2
7	**Rh-2**	2.0	KOH	2.0	120	8	92	—	**1 : 11.5**
8	**Ir-3**	2.0	KO^{t}Bu	2.0	100	18	82	—	1 : 4.6
9	**Ir-3**	2.0	KOH	2.0	120	16	84	—	1 : 5.3

Reaction conditions: **1a** and **2a** in 1 : 1 molar ratio, catalyst (1.0 mol%), base and toluene-d$_8$ (0.5 mL) were placed to the 4 mL glass vial sealed with PTFE cap. Preparations were operated under air. The reactions were stirred at 100 °C for 18 h. Determined by ^{1}H NMR spectral analysis of crude product mixture using 1,1,2,2-tetrachloroethane (TCE) as the internal standard.

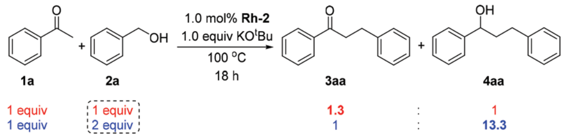
to that seen upon using the rhodium(I) complexes (Table 2, entries 8 and 9). This result confirms the initial hypothesis that the difference in the catalysis activity seen when comparing rhodium and iridium for the C–N bond formation *via* HB[34] could be used as a basis for achieving different product selectivity for forming C–C bonds.

The reaction conditions to promote the alcohol production as the main product were further screened using **Rh-2** as the catalyst (Table 2, entries 3–7). By changing the base (KO^{t}Bu) loading from 1.0 to 2.0 molar equivalents relative to **1a**, a small drop in selectivity was observed (**3aa** : **4aa** product ratio of 1 : 9), whereas when the base loading was dropped to the level suitable for ketone formation (0.8 molar equivalents relative to **1a**), product selectivity dropped to a **3aa** : **4aa** product ratio of 1 : 1.8. Similarly to what had been observed during the ketone formation screening results, KOH was also found to be a suitable base for these transformations. With one equivalent of KOH added, a product ratio of 1 to 7.6 (**3aa** : **4aa**) was seen. However, upon comparing KO^{t}Bu and KOH a different trend was observed and the increase of the base loading to two equivalents of KOH led to increased selectivity towards the alcohol product (1 : 15.2 of **3aa** : **4aa**). In both cases when using KOH as the base, small amounts of 1-phenylethan-1-ol (**5a**) (≤5%) formed. The use of KOH did allow for simpler reaction work-up and ^{1}H NMR spectra interpretation.

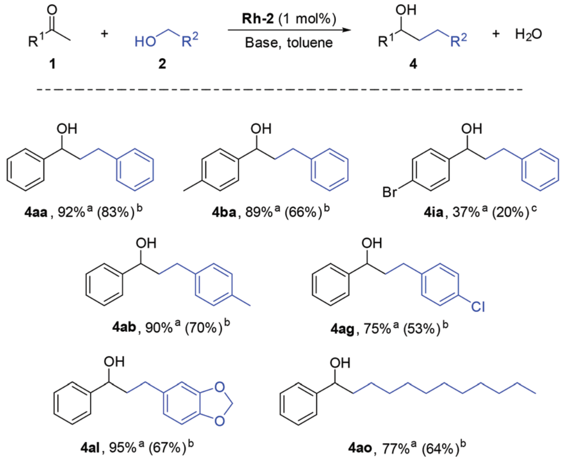
The substrate scope study for the formation of the alcohol product (**4**) was carried out using **Rh-2** as the catalyst, 1 : 2 ratio of the substrates **1** and **2**, 2.0 molar equivalents of KOH, 120 °C and toluene as the solvent. For assessing the scope of the reaction, a representative set of ketone and alcohol substrates was used. Typical electron-donating and electron-withdrawing groups of both substrates resulted in moderate to good yields (Scheme 7, **4aa**, **4ba**, **4ab** and **4ag**). Interestingly, the brominated ketone **4ia** was an exception, with only 37% conversion seen after 18 hours. In the case of both halogenated species (**4ia** and **4ag**) the main other product formed was the ketone product, indicating that the substrate can also have an effect on the product selectivity. This relative preference for the ketone product can also be seen by the good conversions observed in Schemes 4 and 5. The biologically relevant piperonyl alcohol proved to be a suitable substrate leading to the formation of **4al** in a 95% conversion. A relatively high boiling aliphatic alcohol decanol allowed for a good



Scheme 5 Conditions: **1** (0.5 mmol), **2** (0.5 mmol), **Ir-3** (1 mol%), KO^{t}Bu (0.5–0.8 equiv.), toluene (1.0 mL) at 100 °C for 6 h. Isolated yields of the ketones are given. ^{a}0.8 equiv. of KO^{t}Bu was employed. ^{b}0.5 equiv. of KO^{t}Bu was employed. ^{c}0.2 equiv. of KO^{t}Bu was employed. ^{d}Conversion measured by ^{1}H NMR spectral analysis of the crude product mixture using 1,1,2,2-tetrachloroethane (TCE) as the internal standard.



Scheme 6 Hydrogen borrowing reaction with the amount of the alcohol substrate **2a** varied between 1.0 and 2.0 molar equivalents. The relative amount of **1a** was fixed to 1.0 molar equivalent in both reactions. Toluene as solvent. In addition water is formed as a side-product.



Scheme 7 Scope study of coupling various methylene ketones (**1**) with primary alcohols (**2**) for alkylated alcohols (**4**). [a]Conditions: **1** (0.5 mmol), **2** (1 mmol), **Rh-2** (1 mol%), KOH (2.0 equiv.), toluene (1.0 mL) at 120 °C for 18 h. Conversions based on ^{1}H NMR spectral data are given. [b]Isolated yields of the alcohols are given after 18 h. [c]Conversions measured by ^{1}H NMR spectral analysis of crude product mixture using 1,1,2,2-tetrachloroethane (TCE) as the internal standard. ^{1}H NMR spectral data after 6 h[a]: **4aa** (94%), **4ba** (85%), **4ia** (36%), **4ab** (97%), **4ag** (63%), **4al** (93%) and **4ao** (84%).

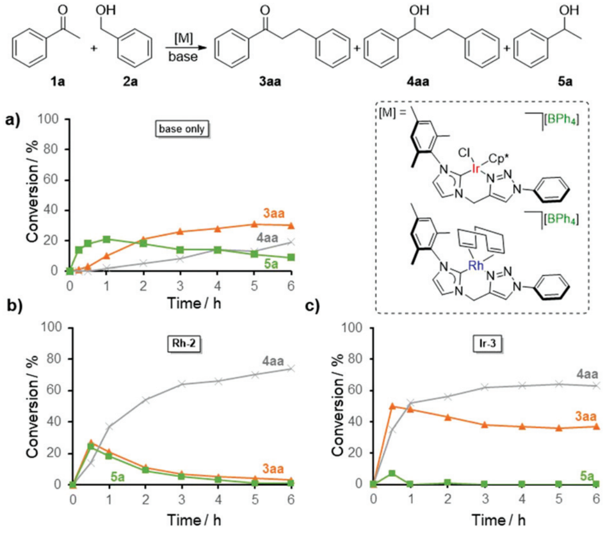


Fig. 2 Time course of the hydrogen borrowing reaction using **1a** and **2a** as the substrates in 1 : 2 ratio, KO^{t}Bu (1 molar equivalent), toluene (1.0 mL) at 100 (°C), (a) no transition metal catalyst, (b) **Rh-2** (1.0 mol%), (c) **Ir-3** (1.0 mol%). In addition water is formed as a side-product.

conversion to the corresponding product, resulting in 77% conversion to **4ao.** In most cases, a reaction time of 6 hours was also found to be sufficient to obtain the same conversions as seen after 18 hours (Scheme 7). In all cases no remaining traces of substrate **1** were observed at the end of the reaction.

Mechanistic investigations

The mechanistic investigation was conducted based on our previous HB work on the C–N bond formation[33] and the recently reported fundamental computational studies using density functional theory (DFT).[38–40] In particular, the following aspects were probed: (1) understanding the origin of the selectivity between the formation of alkylated ketone and alcohol products, (2) understanding the roles of the base and the metal catalyst in the catalytic process, and (3) understanding the formation and the fate of the reaction intermediates during the catalysis. To this end, an NMR study was conducted using ^{1}H NMR, ^{2}H NMR and *in situ* NMR spectroscopy.

Kinetic study

The reaction between **1a** and **2a** was monitored over time to probe the relative product ratios at different time points. This was carried out using three different reaction set-ups: (a) no transition metal catalyst, (b) a rhodium catalyst (**Rh-2**) and (c) an iridium catalyst (**Ir-3**) present in the reaction mixture. In all cases the substrates **1a** and **2a** were used in 1 : 2 ratio to promote the formation of both products (**3aa** and **4aa**), one molar equivalent of KO^{t}Bu in toluene at 100 °C (Fig. 2).

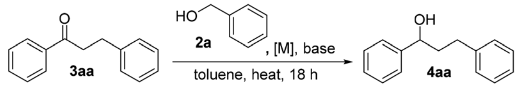
Under all three reaction conditions (Fig. 2a–c) the same three main products (**3aa**, **4aa** and **5a**) formed during the catalytic transformation, however, some clear trends were observed. While the reaction with no transition metal catalyst in the mixture gradually led to the production of both coupling products (**3aa** and **4aa**), both transition metal containing reactions resulted in the fast initial formation of **3aa** (within the first 30 minutes), which was consumed over time – presumably converted to **4aa.** Interestingly, during the 6 hours reaction, **Rh-2** led to the full consumption of **3aa**, whereas **Ir-3** resulted in the formation of a mixture of both products. In addition to the formation of the two coupling products, the reversible formation of the secondary alcohol **5a** was also observed in all cases. After 6 hours, the reaction was effectively complete, with no significant change in the product ratios seen after 24 hours. In addition to the mentioned species forming, traces of benzyl aldehyde were observed in the ^{1}H NMR spectra.

Besides the different product ratios, a clear difference in the reaction rates was observed. Both metals promote faster product formation than the base only, with **Ir-3** resulting in particularly fast initial rate. While this fast initial rate can shed some light on the difference in product selectivity when compared to the base only reaction, we don't think that the enhanced product selectivity is simply due to the transition metal catalyst outrunning the base catalysed reaction, as even at very low catalyst loading (0.05 mol%) significant product selectivity was still observed (*cf.* Fig. 1).

When the reagent ratio was changed to a 1 : 1 ratio of the substrates **1a** and **2a**, reversible formation of **5a** was still observed, however, no conversion of **3aa** to other products was detected, indicating that the limited availability of substrate **2a** (*i.e.* 1 *vs.* 2 equivalents) in the reaction mixture inhibits the conversion of **3aa** to **4aa** (see ESI, section S1.6†).

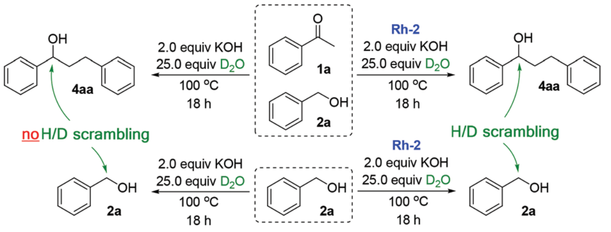
As the presence of base can lead to the interchange of the formed products **3aa** and **4aa** (*cf.* MPV-O reactions), and we saw changes in the product ratios during the HB reaction

Table 3 Cross experiments of reactions using **3aa** as the starting material



	Conversion to **4aa**/%		
	Ir-3[a]	**Rh-2**[b]	N/A[c]
KO^{t}Bu	36	62	13
KO^{t}Bu (no **2a**)	n.r.	n.r.	n.r.
KOH	62	61	29
KOH (no **2a**)	n.r.	n.r.	n.r.

Reaction conditions: Only other product in the mixtures is the starting **3aa** (and **2a** when added). n.r. = no reaction. [a] 1.0 equiv. of **3aa**, 1.0 equiv. of **2a**, 1.0 mol% **Ir-3**, 0.8 equiv. of KO^{t}Bu/2.0 equiv. of KOH, 100 °C, 18 h. [b] 1.0 equiv. of **3aa**, 1.0 equiv. of **2a**, 1.0 mol% **Rh-2**, 0.8 equiv. of KO^{t}Bu/2.0 equiv. of KOH, 120 °C, 18 h. [c] For KO^{t}Bu at 100 °C 18 h, for KOH, 120 °C, 18 h. 1,1,2,2-tetrachloroethane (TCE) was used as the internal standard.



Scheme 8 Deuterium incorporation from D_2O into the alcohol product (**4aa**) and into the alcohol substrate (**2a**) with and without the presence **Rh-2**. The ratio of 1 : 2 of **1a** to **2a** was used. In addition water is formed as a side-product.

(Fig. 2), we were intrigued to understand the stability of the alkylated products once they formed. For this **3aa** was used as the starting material under three sets of reaction conditions; (i) **Ir-3**, (ii) **Rh-2** and (iii) no transition metal catalyst present in the reaction mixture. All three reaction conditions were tested using both bases KO^{t}Bu and KOH, and the alcohol substrate quantity was modified (no **2a** *vs.* one molar equivalent of **2a**, Table 3).

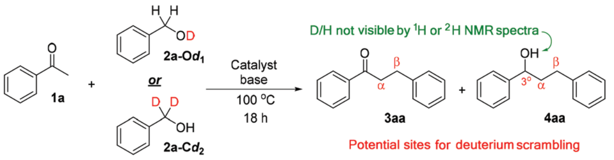
When **2a** was present in the mixture, 36–62% conversion from **3aa** to the alkylated alcohol (**4aa**) was observed in the presence of transition metal catalysts, and 13–29% conversion under the "base only" conditions, demonstrating that the exchange between alcohols and carbonyls does not simply proceed *via* MPV-O processes. However, the lack of **2a** in the reaction mixture completely halted the conversion of **3aa** to **4aa** under all reaction conditions. Evidently, excess alcohol plays an important role in the formation of the alkylated alcohol products. This means that any excess alcohol substrate in the catalytic mixture can significantly reduce the selectivity for **3aa**, while the excess of the alcohol substrate does aid the formation of **4aa**.

Isotopic labelling experiments

To probe the product selectivity further, deuterium was introduced to the reaction mixture at the beginning of the reaction. In particular, we were interested in comparing the outcome of the incorporation of deuterium atoms to understand whether the reaction undergoes two mechanisms in parallel – transition metal catalysis and base-dictated catalysis, or whether a mechanism involving both the transition metal catalyst and the base simultaneously was occurring.

As the first test, a very simple reaction was designed – deuterated water was added to the reaction mixture. D_2O can promote the formation of $C_6H_5CH_2OD$, $C_6H_5CD_2OD$ and KOD,[41,42] which in turn would allow for the deuterium incorporation into the reaction products. In addition, the control reaction of adding 25.0 molar equivalents of H_2O to the reaction mixture was tested and this had no effect on the reaction outcome. Therefore, 25.0 equivalents of D_2O was added to different reaction mixtures and the deuterium incorporations were inspected by ^1H and ^2H NMR spectroscopy (see ESI, section S1.7.1†). In the case of **1a** and **2a** as the substrates in 1 : 2 ratio and **Rh-2** as the catalyst, deuterium was incorporated onto the tertiary carbon of the alcohol product, consistent with the HB process (Scheme 1, reversible hydrogen borrowing; Scheme 8, top). Presumably the deuteration of the alcohol unit also occurred, but we were not able to observe the OH/D peaks by ^1H or ^2H NMR spectra, likely due to the interaction with the base in the reaction mixture. When the same reaction was carried out without **Rh-2**, no H/D scrambling occurred. This verifies the presence of a different mechanism when a transition metal is present in the reaction mixture. The control reactions with no ketone (**1a**) in the reaction mixture resulted in analogous results, with H/D scrambling occurring in the alcohol substrate **2a** when **Rh-2** was included into the reaction mixture, but no scrambling when no **Rh-2** was added (Scheme 8, bottom).

The deuteration study was extended to using more sophisticated reagents instead of D_2O – two deuterated versions of the alcohol substrate **2a**: $C_6H_5CH_2OD$ (**2a-Od$_1$**) and $C_6H_5CD_2OH$ (**2a-Cd$_2$**) (Scheme 9). The catalysis reactions were carried out using the two different transition metal catalysts (**Ir-3** and **Rh-2**) and under the ketone and alcohol promoting reaction conditions (1 : 1 *vs.* 1 : 2 substrate ratio of **1a** and **2a**) to investigate the fate of the deuterium atoms in both products (**3aa** and **4aa**). In addition, the transition metal free conditions under the same sets of substrate ratios were conducted (see ESI, section S1.7.2†).



Scheme 9 Deuterium labelled substrates in hydrogen borrowing reactions. In addition water is formed as a side-product.

Upon reacting benzyl alcohol **2a-Cd_2** and **1a**, the iridium and rhodium catalysts (**Ir-3** and **Rh-2**) led to the formation of the ketone product **3aa** with the deuterium atom mostly incorporated on the α-carbon regardless of the substrate ratio used. In the case of the alcohol product (**4aa**) both reaction conditions led to the deuterium mainly being incorporated at the β-carbon and at the tertiary carbon. Small amounts of deuterium also ended up on the α-carbon, likely due to interactions with the H_2O in the mixture. When no transition metal catalyst was present in the reaction mixture, the reaction did not go to completion after 18 hours, and for both products (**3aa** and **4aa**) the deuterium ended up in the β-position.

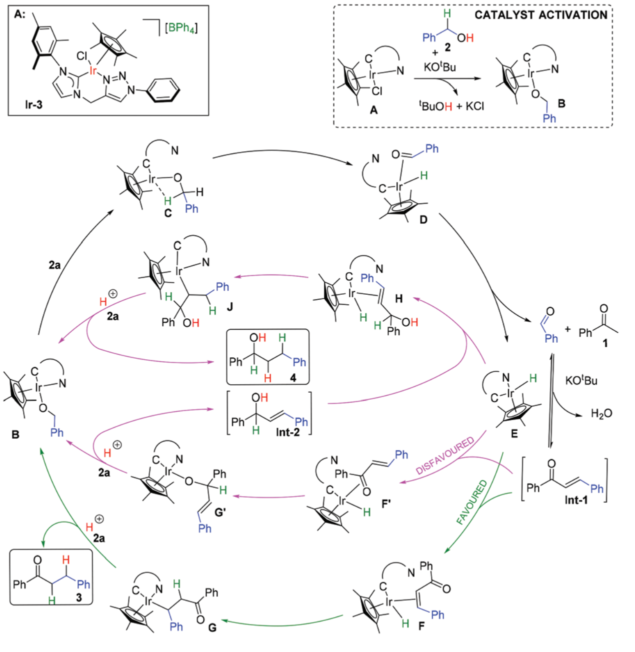
By changing the alcohol reagent from **2a-Cd_2** to **2a-Od_1** the opposite trend was observed. Only deuterium scrambling to the β-carbon of the ketone product **3aa** was observed under the ketone formation condition (**1a** and **2a-Od_1** at the ratio of 1 : 1). When the higher ratio of **2a-Od_1** was employed (2.0 equivalents), both, **Ir-3** and **Rh-2** led to the deuterium ending up on the α-carbon of the alcohol product **4aa**. In addition, deuterium migration to the CH_2 unit of **2a-Od_1** was observed, indicating that reversible hydrogen borrowing occurred. These trends in the deuterium allocations when using **2a-Od_1** as a substrate were analogous to the D_2O addition experiments, indicating that in the D_2O addition experiments, the H/D-scrambling into the OH group was much faster than into the CH_2 unit of benzyl alcohol starting substrate. Under the base only conditions, deuterium incorporation was only observed at the β-carbon of **3aa** when the substrate ratio was 1 : 1.

Overall, these deuterium reactions once again suggest that the role of the base is significantly altered when there is a transition metal catalyst (rhodium or iridium) present in the reaction mixture during the HB transformation.

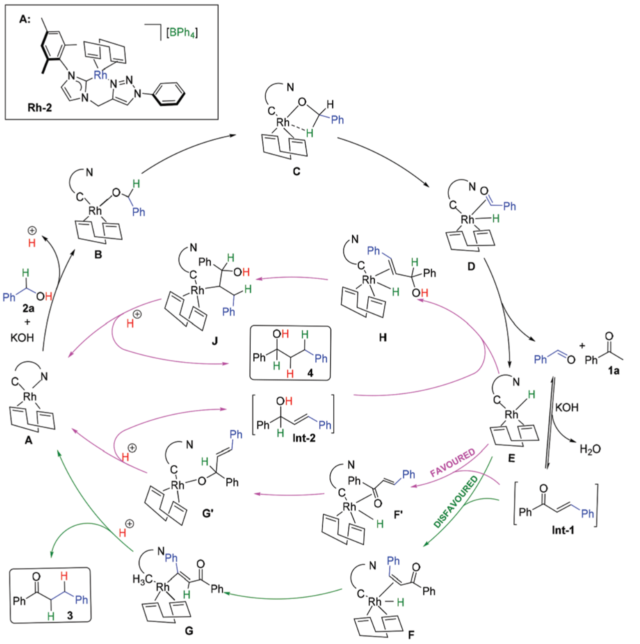
Reaction mechanism

Based on the catalysis results, the deuterium incorporation and the reported mechanistic studies, we postulated a mechanism to explain the formation of each product *via* the HB methodology using **Ir-3** or **Rh-2** as the catalyst.[39,40,43–45]

We propose that the first half of the catalytic cycle (Schemes 10 and 11, black arrows) is very similar for both metals, and analogous to the one reported for C–N bond formation *via* HB.[33] For both **Ir-3** (Scheme 10) and **Rh-2** (Scheme 11), the first step is the coordination of the alkoxide to **A**, with the help of the base, forming the metal-alkoxido complex **B**. This is followed by the β-hydride elimination of a hydrogen from the benzylic CH_2, leading to the metal-hydride intermediate **D**. Both of these steps are aided by the de-coordination of the nitrogen arm of the ligand. In addition to opening up a coordination site, the dissociation of the nitrogen arm could provide an additional benefit through interactions with the substrate.[46] The reaction proceeds by the release of the benzaldehyde, to form the metal-hydride intermediate **E** as previously demonstrated for the analogous C–N bond formation reaction mechanism.[33] *In situ* ^{1}H NMR spectroscopy indicated that once formed, the benzaldehyde was rapidly consumed even when higher quantities (2.0 molar equivalents) of the starting alcohol substrate (**2a**) were used. This was expected, as the formed aldehyde undergoes aldol



Scheme 10 Proposed reaction mechanism of **Ir-3** catalysed C–C bond formation of alcohols with ketones *via* hydrogen borrowing. In addition, conversion from **3** to **4** can occur (*cf.* Table 3). It is proposed that throughout the catalytic cycle the iridium centre remains as Ir(III), and the +1 charge of the complex is retained.



Scheme 11 Proposed reaction mechanism of **Rh-2** catalysed C–C bond formation of alcohols with ketones *via* hydrogen borrowing. In addition, conversion from **3** to **4** can occur (*cf.* Table 3). It is proposed that throughout the catalytic cycle the rhodium centre remains as Rh(I), and the +1 charge of the complex is retained.

condensation with acetophenone (**1a**) in the presence of the base to form the enone (**Int-1**) and one molar equivalent of water.

Once formed, the enone (**Int-1**) enters the catalytic cycle through the coordination to the metal hydride **E**. This coordination opens up two different reaction pathways, dependant on whether the coordination of the C=C or C=O bond occurs (depicted as a green and a pink pathway, respectively, in Schemes 10 and 11). This coordination strongly influences whether the formation of **3aa** or **4aa** will be favoured. Both metal complexes can promote either pathway, but clear preferences were observed.

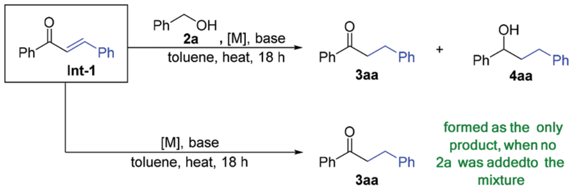
The coordination of the C=C double bond (favoured by **Ir-3**, Scheme 10, green pathway) leads to the formation of the intermediate **F**, and sequentially the formation of **G** *via* the 1,2-migratory insertion. The intermediate **G** then reacts with another equivalent of **2a** regenerating the metal-alkoxide intermediate **B** and the ketone product **3aa** is formed upon "picking up" the H-atom abstracted by the base during the first step.

As discussed above, **Int-1** can also coordinate to the metal centre *via* the C=O bond (favoured by **Rh-2**, Scheme 11, pink pathway).[47] This coordination results in the formation of **F′** which undergoes 1,2-migratiory insertion, with the H-atom ending up on the carbonyl-carbon, forming **G′** (*cf.* **G**, where the H-atom migrated to the α-position). **G′** then reacts with another equivalent of **2a** leading to the formation of **Int-2**. No build-up of the concentration of **Int-2** was observed, indicating that once formed the intermediate readily coordinates to the hydrido-complex **E**, availability of which is also linked to the relative concentration of **2a**. This coordination is now limited to the C=C bond, hence the formation of **H** occurs (analogously to the formation of **F**). Once again *via* 1,2-migratory insertion the H-atom is delivered to the double bond. Interestingly, based on the H/D-scrambling data, this migration step (**H** to **J**) has different selectivity compared to that of **F** to **G**. The migration to the β-position occurs, (*cf.* migration to α-position for **F** to **G**). This is likely due to the changed coordination of the substrate to the metal; carbonyl *vs.* alcohol. With the assistance of the base, **J** releases **4aa** as the product and the catalyst is returned for the next cycle through formation of **B**. In addition, as demonstrated in Table 3, the formation of **4aa** can also occur from **3aa**, as long as some **2a** is present in the reaction mixture.

As water is formed during the HB reaction, we are unsure of the reversibility of the individual steps during the catalytic cycle, as any H/D-scrambling that could stem from reversible steps, could also arise from interactions with water.

As the formation of **Int-1** is the same for both metals, and **Int-1** is the intermediate for the formation of both **3aa** and **4aa**, we probed the mechanism further by using **Int-1** as the starting material instead of **1a** and **2a**. Once again, the reactions were carried out under three different reaction conditions; (a) **Ir-3**, (b) **Rh-2** and (c) no transition metal catalyst present in the reaction mixture. Additionally, the amount of **2a** added to the reaction mixture was varied from 1 molar equivalent of **2a** added to no **2a** being added (Table 4).

Table 4 Product selectivity (**3aa** *vs.* **4aa**) when using **Int-1** as the starting material



	Ir-3[a]		**Rh-2**[b]		N/A[c]	
	Conversion to:/%		Conversion to:/%		Conversion to:/%	
	3aa	**4aa**	**3aa**	**4aa**	**3aa**	**4aa**
KO^{t}Bu (no **2a**)	7	0	13	0	6	0
KO^{t}Bu	41	12	26	26	19	35
KOH (no **2a**)	17	0	100	0	20	0
KOH	59	21	39	61	67	33

Conditions: [a] 1.0 equiv. of **Int-1**, 1.0 equiv. of **2a**, 1.0 mol% **Ir-3**, 0.8 equiv. of KO^{t}Bu/2.0 equiv. of KOH, 100 °C, 18 h. [b] 1.0 equiv. of **Int-1**, 1.0 equiv. of **2a**, 1.0 mol% **Rh-2**, 0.8 equiv. of KO^{t}Bu/2.0 equiv. of KOH, 120 °C, 18 h. [c] For KO^{t}Bu at 100 °C, 18 h, for KOH, 120 °C, 18 h. 1,1,2,2-tetrachloroethane (TCE) was used as the internal standard. In addition water is formed as a side-product (top).

When no **2a** was added, in all cases, mixtures of the starting **Int-1** and the methylated ketone product (**3aa**) were observed, however, no formation of the methylated alcohol product (**4aa**) was seen. This matches well with the results observed when attempting to convert **3aa** to **4aa** without the presence of **2a** (Table 3). These results indicate that the presence of the alcohol substrate is important as a hydrogen source for the reduction of the carbonyl group. This means that the **G′** to **Int-2** step as depicted in the reaction mechanisms (Schemes 10 and 11) occurs only if enough **2a** is present in the reaction mixture. However, the presence of **2a** is not crucial for the reduction of the C=C double bond. Particularly impressive activity was seen when using **Rh-2** and KOH to reduce **Int-1** to **3aa.** Under those conditions quantitative conversion to **3aa** was observed, while the same reaction using **Ir-3**/KOH or just KOH resulted in <20% conversion to **3aa.** While not crucial, the presence of **2a** did improve the reduction of the double bond, seen in the lower amounts of starting **Int-1** remaining at the end of the reaction, matching well with our proposed catalytic cycle.

Upon comparing the resulting product ratios of **3aa** to **4aa** when using **Int-1** as the substrate, to the ratios from the reactions using **1a** and **2a** as substrates, significant differences were observed. For the reactions starting with **Int-1**, substantially lower product selectivity was observed. However, once again, these results demonstrate that low concentrations of the alcohol substrate **2a**, as would be the case under the ketone formation conditions, strongly inhibit the formation of the alkylated alcohol product **4aa.** Therefore it is not surprising that the product ratios change when starting from **Int-1** *vs.* **1a** and **2a.** This is valuable knowledge for designing the alkylated ketone reaction conditions, as any excess of the alcohol has a deleterious effect on the desired selectivity. Also, the results showed that the combination of the base and transition metal is key. The highest relative amount of **3aa** was formed from **Int-1** when the combination of **Ir-3** and KO^{t}Bu was used, while the highest amount of **4aa** was observed when **Rh-2** and KOH were used, corresponding well with the optimised conditions used in the scope study.

Clearly, the mechanism is highly nuanced and it is extremely hard to discern the processes occurring at any given moment. However, the combination of the mechanistic studies and catalysis results presented in this work provide a solid ground for determining how C–C bond formation *via* the HB methodology is affected by different aspects, such as the choice of transition metal catalyst, the base, and the relative loadings of substrates and catalysts. In turn, this knowledge is important for considering how to improve the catalytic approaches to advance this high potential HB methodology.

Conclusions

In this work, we were able to carry out the alkylation of ketones with alcohols *via* the hydrogen borrowing (HB) methodology using triazole-carbene ligated on rhodium(I) and iridium(III) complexes. It was demonstrated that the nature of the products that form from these HB reactions was strongly affected by the reaction conditions. In addition to the reaction conditions (choice of base, relative amounts of reagents and base, and reaction temperature), the choice of the transition metal catalyst can play a significant role in tuning the product selectivity between alkylated ketone and alcohol products. Being able to select the product outcomes enables this highly useful HB reaction to become even more viable as an approach for new C–C bond formation for the selective synthesis of alkylated ketones and alcohols.

The scope studies showed that this methodology could be used for a range of substrates to selectively lead to either the ketone products, or the alcohol products in moderate to excellent yield. The catalyst screening, time course and deuterium studies showed that although a number of different processes could occur during the catalytic transformation, leading to different product ratios, it is ultimately the transition metal catalyst that determines the product selectivity.

Conflicts of interest

There are no conflicts to declare.

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