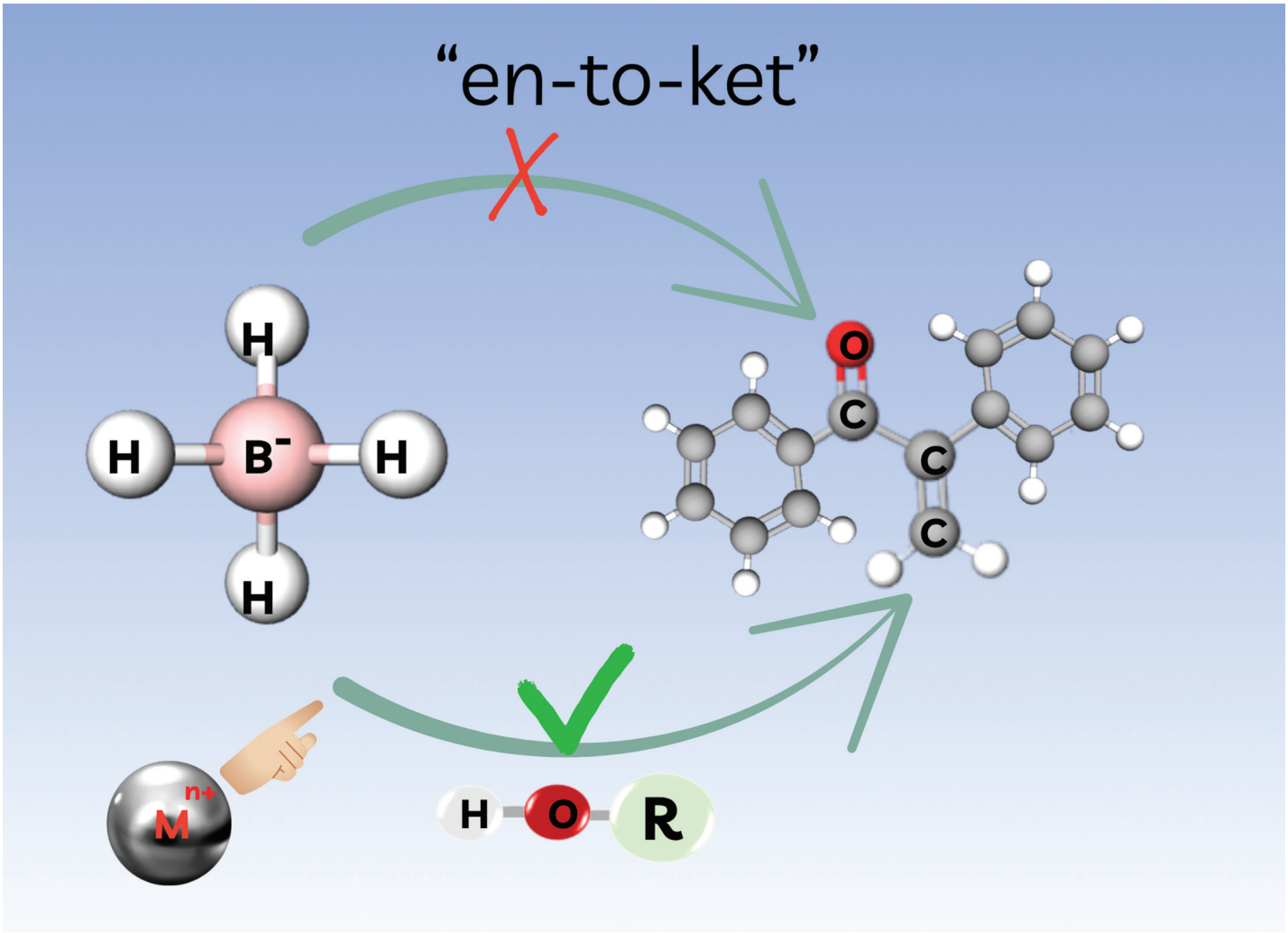


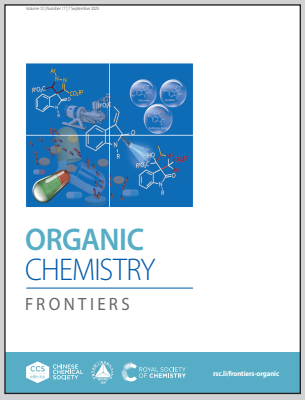
Showcasing research from Professor Leyva-Pérez's laboratory, Instituto de Tecnología Química (Universitat Politècnica de València–Agencia Estatal Consejo Superior de Investigaciones Científicas), Avda. de los Naranjos s/n, 46022 València, Spain.

Countercation- and solvent-controlled selective borohydride hydrogenation of alkenes in diaryl enones

Borohydride (i.e. $NaBH_4$) preferentially hydrogenates the ketone to the alkene group in diaryl enones under nearly standard and mild reaction conditions, using the appropriate alcohol solvent.

Image reproduced by permission of Miquel Molina–García and Antonio Leyva-Pérez from *Org. Chem. Front.*, 2025, **12**, 4708.

As featured in:



See Antonio Leyva-Pérez *et al.*, *Org. Chem. Front.*, 2025, **12**, 4708.

CCS 中国化学会 CHINESE CHEMICAL SOCIETY
SIOC 1950
ROYAL SOCIETY OF CHEMISTRY
rsc.li/frontiers-organic

ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2025, **12**, 4708

Countercation- and solvent-controlled selective borohydride hydrogenation of alkenes in diaryl enones†

Miguel Espinosa,‡ Miquel Molina-García,‡ Daniel Ciscares-Velázquez and Antonio Leyva-Pérez *

Borohydrides are considered benchmark reagents for the selective hydrogenation of ketones in the presence of alkenes, a reaction described in organic textbooks. However, the opposite, *i.e.* the borohydride-promoted hydrogenation of an alkene in the presence of a ketone, is barely described. Here we show that the alkene functionality in diaryl enones is preferentially hydrogenated to the ketone under standard uncatalyzed reaction conditions, after using a stoichiometric amount of a metal borohydride (*i.e.* $NaBH_4$). For *gem*-diaryl enones, mechanistic studies indicate that the combination of a suitably cation-substituted borohydride (from Li^+ to K^+) and the particular disposition of the highly-conjugated terminal alkene favors a highly selective 1,4-hydride addition, giving access to α-benzyl-substituted propiophenones in high yields, at room temperature and after just 30 min reaction time, without the assistance of any catalyst or additive. For *trans*-diaryl enones (chalcones), the simple change of the protic co-solvent from MeOH to electron-deficient and sterically-hindered alcohols triggers the selective hydrogenation of the alkene group. These results defy the established reactivity of borohydrides for enones and open a way to employ common borohydride reagents for selective alkene hydrogenation reactions, with potential application in synthetic chemistry.

Received 12th June 2025,
Accepted 10th July 2025

DOI: 10.1039/d5qo00883b

rsc.li/frontiers-organic

1 Introduction

Borohydrides ($M^+BH_4^-$, M = Li, Na, K, NR_4,...) are widely available inexpensive reagents, daily employed in academic and industrial facilities for the selective hydrogenation reaction of aldehydes and ketones to alcohols, in the presence of alkenes.[1,2] Alkenes and carbonyl compounds are considered the most common functional groups in natural and synthetic organic compounds,[3,4] which explains the widespread use of borohydride reagents in organic synthesis. Prominent industrial examples are the synthesis of blockbuster antibiotics (*i.e.* atorvastatin, levodopa, celecoxib and bupropion)[5] and antiviral (paxlovid)[6] drugs. Beyond that, $NaBH_4$ finds application in the paper and textile industries as a bleaching reagent[7] and in beer production as an anti-lightstruck effect agent,[8] and borohydrides are also profusely investigated as hydrogen carrier agents for the development of fuel cells,[9] by virtue of their high gravimetric hydrogen content (>10 wt%). All these data strongly suggest a sustained increase in the industrial production and use of borohydrides in the upcoming years.[10]

In this context, academic textbooks present any borohydride (particularly $NaBH_4$) as an example of a selective reagent for the hydrogenation reaction of aldehydes and ketones in the presence of other reducible functional groups, alkenes for instance,[11] as shown in Fig. 1. However, Fig. 1 also shows that soon after the description of the synthesis of $NaBH_4$ in the 1950s and its extraordinary ability to hydrogenate carbonyl compounds (although $NaBH_4$ was discovered in the 40s and kept a secret on war demands), it was shown that certain cyclic alkenes could independently be hydrogenated in the presence of carbonyl groups if both functionalities were conjugated (enones) and pyridine, PPh_3 or other amines were added to the reaction mixture (the amines were generally employed as the solvent for the reaction).[12] The fact that this procedure only worked for specific enones,[13] and that high amounts of $NaBH_4$ (*i.e.* 10 equivalents) and phosphines/amines (pyridine typically as a 1 M concentration solvent) were required,[14] discouraged the use of this reaction protocol, and later research on the selective hydrogenation of enones

Instituto de Tecnología Química (Universitat Politècnica de València-Agencia Estatal Consejo Superior de Investigaciones Científicas), Avda. de los Naranjos s/n, 46022 València, Spain. E-mail: anleyva@upv.itq.es

†Electronic supplementary information (ESI) available: Additional experimental and computational data, Fig. S1–S10, compound characterization with copies of NMR spectra, and additional references. See DOI: https://doi.org/10.1039/d5qo00883b

‡These authors contributed equally.

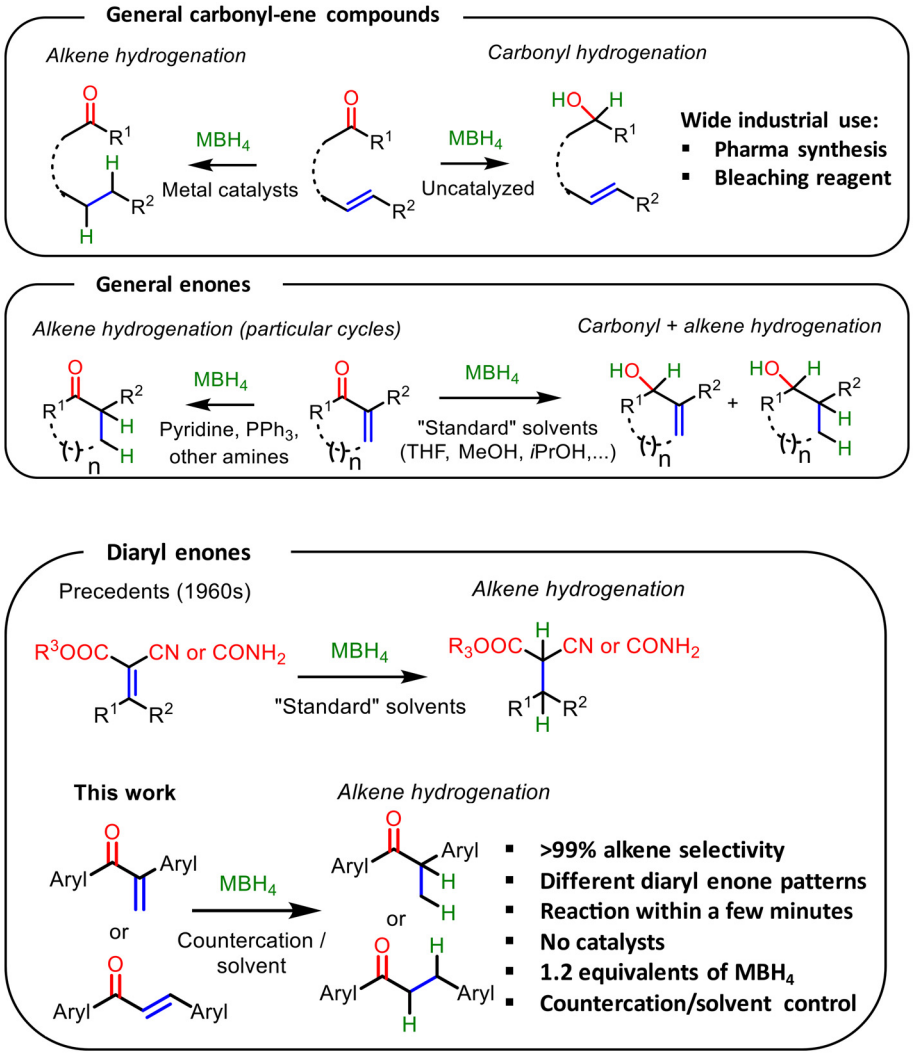


Fig. 1 MBH_4-mediated selective hydrogenation reactions of carbonyl–ene compounds. M = Li, Na, K, NR_4, ...; R^{1-3} = H, alkyl, aryl; n = 2, 3.

switched to catalytic methods. Today, not only the well-known Luche protocol (Ce catalyzed)[15] but also a plethora of other metal-catalyzed selective hydrogenation reactions of alkenes with borohydride reagents can be found in the literature, which include metal salts,[16] nanoparticles[17] and supported metal solids,[18] among others.[19,20] As a consequence, these catalytic methods have made bare borohydrides specific reagents for carbonyl hydrogenation reactions[21] in the organic reaction toolkit or, as much, uncontrolled hydrogenation reactants for both the alkene and the carbonyl groups, for certain enones.[22]

1,2-Diarylpropen-1-ones (here called *gem*-diaryl enones for the sake of simplicity and to emphasize the substitution pattern of the terminal alkene) are widely available substrates, achievable through different reaction sequences which include, for instance, the Baylis–Hillman reaction,[23,24] the methylenation reaction of α-arylacetophenones,[25] the cross-coupling reaction of substituted alkenes with acyl chlorides[26,27] and the sequential alkene metathesis/Wacker oxidation of stilbene derivatives,[28] among others.[29] Fig. 1 also shows that this family of enones has not been tested in a systematic manner for borohydride-mediated hydrogenation reactions, as far as we know; however, after digging into the literature, a potential selective hydrogenation of the alkene might be suggested. Already in the 1960s, it was reported that alkylidene malonates and malononitriles, in particular aromatic substituted and *gem*-alkenes, gave the corresponding alkanes without any reactivity of the carbonyl groups.[30] However, those carbonyl groups were protected as ester, amide and nitrile functionalities, much less reactive with borohydrides than ketones or aldehydes. These results were apparently never expanded to the latter, and only recently, a selective hydrogenation of the alkene group was reported for specific, highly-substituted enone examples in low yields (40%),[31,32] giving altogether the corresponding allyl alcohol and the fully hydrogenated compound (alkyl alcohol). These previous results encouraged us to study the possible hydrogenation of the alkene group in *gem*-aryl enones with $NaBH_4$, comparing with

other enones to find structural patterns in the reaction. The results here will show that under standard reaction conditions (a mixture of MeOH and THF as a solvent, room temperature), the alkene group will be preferentially hydrogenated *vs.* the ketone ("en-to-ket"), to give α-benzyl-substituted propiophenones in high yields, in a 1,4-reduction reaction of conjugated enones. Mechanistic studies will show the key role not only of the borohydride countercation but also of the protic solvent in the hydrogenation of the alkene, and with this in mind, we will also show here the selective hydrogenation of *trans*-diaryl enones (chalcones) after simply replacing MeOH with some electron-deficient and sterically-hindered alcohols as reaction media.

2 Results and discussion

2.1 Alkene hydrogenation in *gem*-diaryl enones

Fig. 2 shows the results obtained for the hydrogenation of a variety of enones, substituted or not in the three different positions of the alkene with either alkyl or aryl groups, employing "standard" reaction conditions for $NaBH_4$, *i.e.* 8 equivalents of the borohydride (4 molar excess of $NaBH_4$) in a mixed solution of anhydrous tetrahydrofuran and methanol (THF : MeOH, 1 : 1 v : v, 0.1 M) at room temperature (20 °C), without any catalyst. All the alkyl enones tested, including mono- (compounds **1** and **2**, *i.e.* methyl vinyl ketones), di- (compounds **3–5**, *i.e.* α-iso-methionine), tri- (compound **6**, carvone) and tetra-substituted (compound **7**, pulegone), underwent the hydrogenation reaction exclusively at the ketone and not the alkene, to yield the corresponding allyl alcohols in >99% after 16 h of magnetic stirring, according to combined gas chromatography (GC) and ^{1}H nuclear magnetic resonance (^{1}H NMR) measurements of the reaction mixture. Conversions and yields were double checked after the addition of external standard compounds and calibration with commercial products (if available), and product characterization studies were completed with ^{13}C nuclear magnetic resonance and distortionless enhancement by polarization transfer (^{13}C NMR and DEPT, respectively) measurements, and also with GC coupled to mass spectrometry (GC-MS; for details, see the ESI†).

The use of a chalcone (compound **8**) as a starting enone also gave the corresponding allyl alcohol as a single product after ketone hydrogenation, in quantitative yield, and the same occurred with different substituted chalcones (for preparation, see the ESI†), either symmetric and with electron donor groups (EDG, compound **9**) or asymmetric and with electron withdrawing groups (EWG, compounds **10–12**). When an aliphatic ketone conjugated to the styryl moiety was tested (benzylideneacetone, compound **13**), ketone hydrogenation was

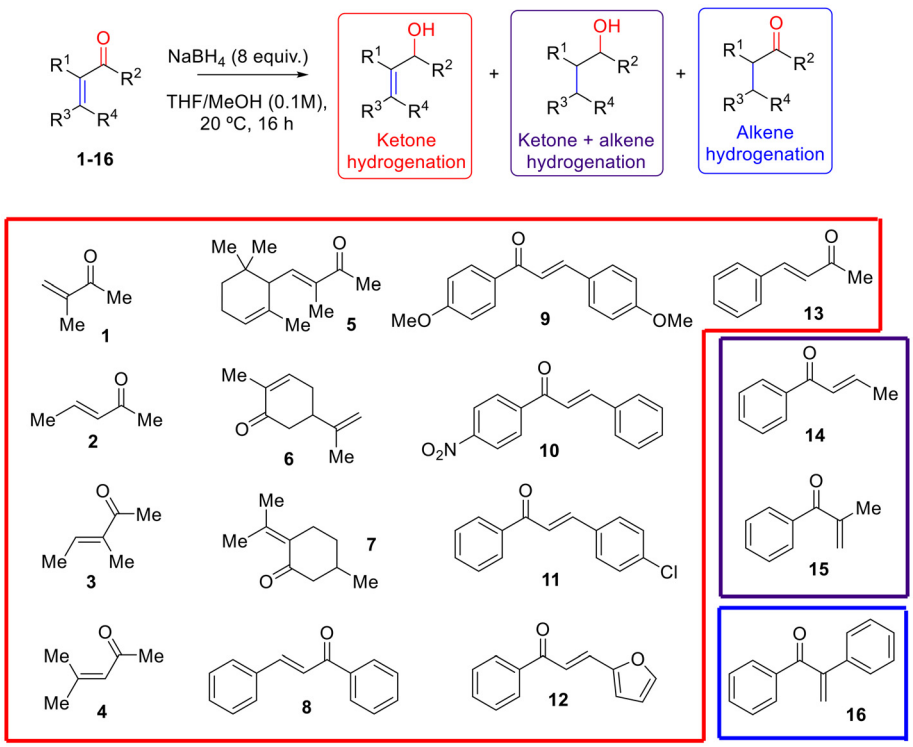


Fig. 2 Results for the hydrogenation reaction of the enone compounds **1–16** with $NaBH_4$ (8 equivalents, 4 molar excess of $NaBH_4$) under the indicated "standard" reaction conditions. Compounds marked in red: complete conversion to the corresponding allyl alcohol (ketone hydrogenation, typically >99%). Compounds marked in purple: complete conversion to the corresponding allyl + alkyl alcohol (ketone and ketone + alkene hydrogenation, <10% of the alkyl alcohol yield). Compound marked in blue: complete conversion to the corresponding alkyl alcohol (alkene hydrogenation, >99% yield). Yields were calculated and double checked by combined gas chromatography (GC) and ^{1}H nuclear magnetic resonance (^{1}H NMR), using, when possible, commercial products for calibration, to achieve an estimated accuracy >95%.

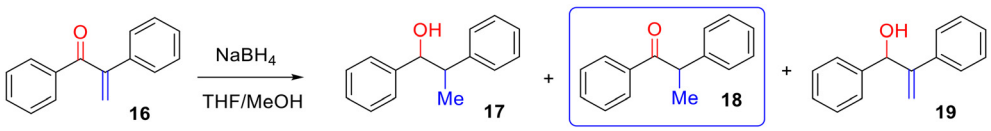
again the sole reaction observed. It is noteworthy that, for the sake of comparison, all the open-chain enones tested were in the *trans* configuration.

A different reactivity was observed when using *trans*-crotonophenone **14**. In this case, a mixture of the allyl alcohol (ketone hydrogenation) and the fully hydrogenated (ketone + alkene) products was obtained at the end of the reaction, although the latter in <2% amount, after complete conversion of **14**. This tiny but significant amount of the fully hydrogenated product was also observed after switching the methyl substituent to the α-position, *i.e.* in methacrylophenone (compound **15**), in this case with an ~10% yield. This result indicates that an aryl-substituted *gem* enone structure may favor the hydrogenation of the alkene bond, in good agreement with the precedents with malonic derivatives.[30] With these results in hand, we tested the hydrogenation of *gem*-diaryl substituted enone **16**, and the results showed a > 99% yield of the alkene hydrogenation + ketone hydrogenation product, showcasing the complete hydrogenation of the alkene in enone **16**. Thus, the possible selective hydrogenation of the alkene group, before ketone hydrogenation occurs, was further investigated.

Table 1 shows the optimized results for the hydrogenation reaction of 1,2-diphenylprop-2-en-1-one **16** with $NaBH_4$. A decrease in the amount of $NaBH_4$, from 8 to 1.2 equivalents, still yielded majorly the completely hydrogenated product **17** (entries 1–4); however, the desired alkene hydrogenated product **18** was observed in 20% yield when 1.2 equivalents of $NaBH_4$ were used (entry 4). The ketone hydrogenated product **19** was not observed in any case. Since the amount of $NaBH_4$ was already adjusted, and full use of the hydrides is being made, the reaction time was shortened to just 10 min, observing a 55% yield of **18** but still accompanied by a 45% yield of product **17**, after complete conversion (entry 5). The extreme fastness of the reaction despite using just a stoichiometric amount of $NaBH_4$ led us to decrease either the reaction temperature or concentration. Thus, on the one hand, the reaction was carried out at 0 °C, however, without improvement in the selectivity to **18** after 30 min reaction time (entry 6). On the other hand, the reaction was performed at five different concentrations, following in this case the conversion and yields with time by kinetic experiments, in order to accurately find the point when a better yield and selectivity to **18** was achieved. For the sake of comparison, the results at 20 min reaction time are indicated in Table 1 (for detailed results at different reaction times, see Fig. S1 in the ESI†), and it can be seen that a progressive increase in the selectivity to **18** with a decrease in the conversion of **16** occurs as the dilution of the reaction mixture increases (entries 7–10 and 12). The observed conversion/selectivity balance consistently resulted in an ~80% yield of **18** across all concentrations, with higher conversion and amounts of by-product **17** at higher concentrations and lower conversion but complete selectivity to **18** at lower concentrations (entries 11 and 13). Thus, a gamut of reaction conditions can be chosen here to achieve the alkene hydrogenated product **18** in up to 83% yield (entry 13). The use of THF alone as a solvent did not improve the selectivity of the reaction (entry 14).

In contrast to 1,2-diphenylprop-2-en-1-one **16**, neither *trans*-crotonophenone **14** nor methacrylophenone **15** gave the desired alkene hydrogenation products after decreasing the amount of $NaBH_4$ to 1.2 equivalents, but they gave only the corresponding allyl alcohol products in >95% yield (Fig. S2†). Further optimization was not carried out since the only products observed were the expected alcohols, coming from the selective hydrogenation of the ketone; in other words, ketone hydrogenation precedes alkene hydrogenation for enones **14**

Table 1 Optimization results for the hydrogenation reaction of 1,2-diphenylprop-2-en-1-one **16** with $NaBH_4$



Entry	$NaBH_4$ (equiv.)	Solvent[a] (concentration)	*T* (°C)	Time (min)	Conversion of **16**[b] (%)	**17**[b] (%)	**18**[b] (%)	**19**[b] (%)	Selectivity to **18** (%)
1	8	THF/MeOH (0.1 M)	20	960	>99	>99	—	—	—
2	2.4				>99	>99	—	—	—
3	1.6				>99	>99	—	—	—
4	1.2				>99	79	20	—	19
5				10	>99	45	55	—	45
6			0	30	>99	40	60	—	40
7		**THF/MeOH (0.02 M)**	**20**	**20**	**98**	**16**	**82**	**—**	**83**
8		THF/MeOH (0.016 M)		20	91	11	80	—	87
9		THF/MeOH (0.01 M)		20	91	14	77	—	85
10		**THF/MeOH (0.0075 M)**		20	60	—	60	—	>99
11				**960**	**77**	**—**	**77**	**—**	**>99**
12		**THF/MeOH (0.005 M)**		20	60	—	60	—	>99
13				**960**	**83**	**—**	**83**	**—**	**>99**
14		THF (0.1 M)		960	>99	42	58	—	58

[a] 1 : 1 (v : v) solvent mixture. [b] Calculated by combined GC and ^{1}H NMR.

and **15**. These results support the necessity of the *gem*-diaryl substituted enone structure for a native selective alkene hydrogenation reaction with $NaBH_4$ under standard conditions (THF/MeOH solvent).

2.2 Reaction scope for the hydrogenation of *gem*-diaryl enones: synthesis of α-benzyl-substituted propiophenones

The scope of the alkene hydrogenation reaction was then evaluated for different *gem*-diaryl substituted enones. The enones were synthesized in two steps by a reductive coupling of the benzaldehydes[33] **20–29** followed by a copper-catalyzed methylenation reaction[25] of the resulting ketones **30–39** (see Experimental and Fig. S3 and S4† for the individual reactions), as shown in Fig. 3. Other procedures such as the Wacker oxidation of stilbenes failed in our hands. The resulting *gem*-diaryl enones **40–49** were isolated in moderate to good yields after column chromatography.

Fig. 4 shows the results for the alkene hydrogenation reaction of the enones **40–48** (compound **49** did not react in our hands). It can be seen that excellent yields of the corresponding α-benzyl-substituted propiophenone (α-methyl aryl acetophenone) products **50** (85%) and **52–58** (60–96%) were obtained after just 30 min reaction time at room temperature, and the only *gem*-diaryl substituted enone that could not be stopped at the ketone product but at the hydrogenated alcohol product was the trifluoro-substituted enone **41**, which give alcohol **60** in 98% yield. This result suggests that electron acceptor groups in the aromatic rings may accelerate this reaction. In any case, different substituents in the aryl ring such as methyl (product **50**), methoxy (products **52** and **58**), chloride (product **53**), bromide (product **54**), fluoride (product **55**) and naphthalene (products **56** and **57**) are tolerated in the reaction.

2.3 The countercation effect in *gem*-diaryl enones

It is accepted that the nature of the cation in borohydride-mediated hydrogenations plays a fundamental role in the hydrogenation reaction of carbonyl compounds.[34–36] Thus, we

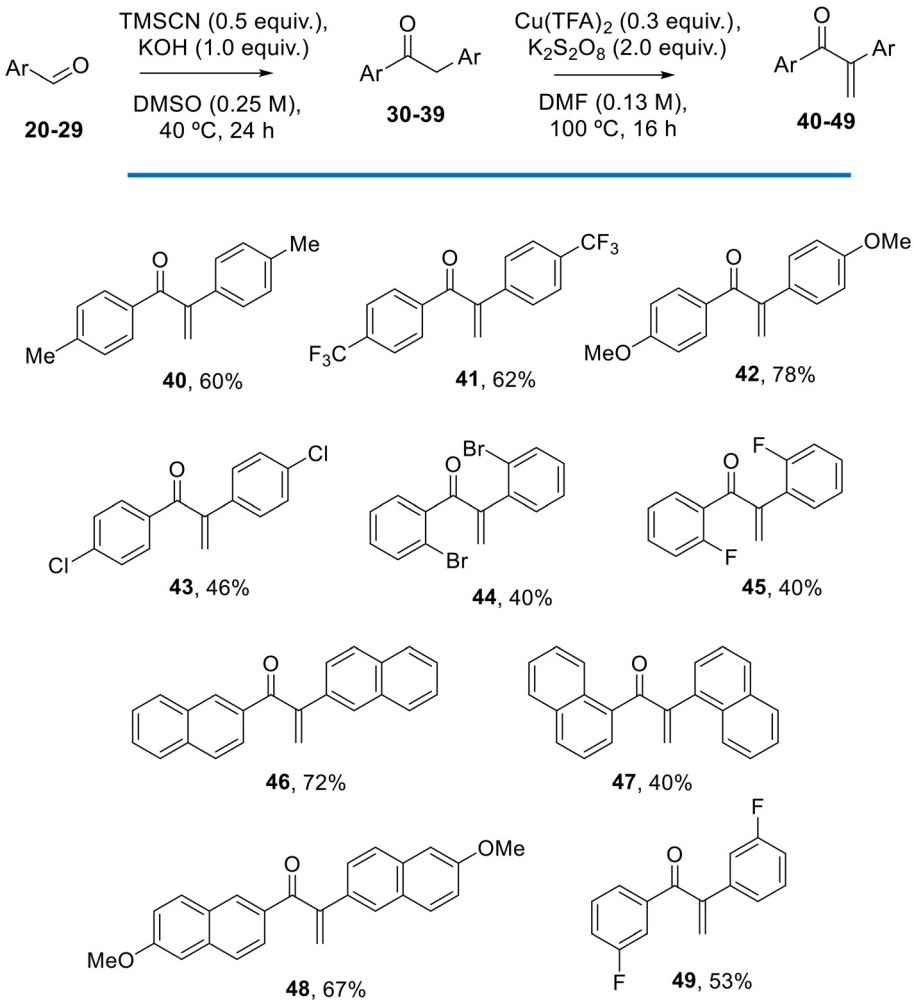


Fig. 3 Results for the two-step synthesis of the *gem*-diaryl substituted enones **40–49**, after reductive coupling of the corresponding aldehydes **20–29** and copper-catalyzed methylenation reaction of the resulting ketones **30–39**, under the indicated reaction conditions. Isolated yields after two-steps.

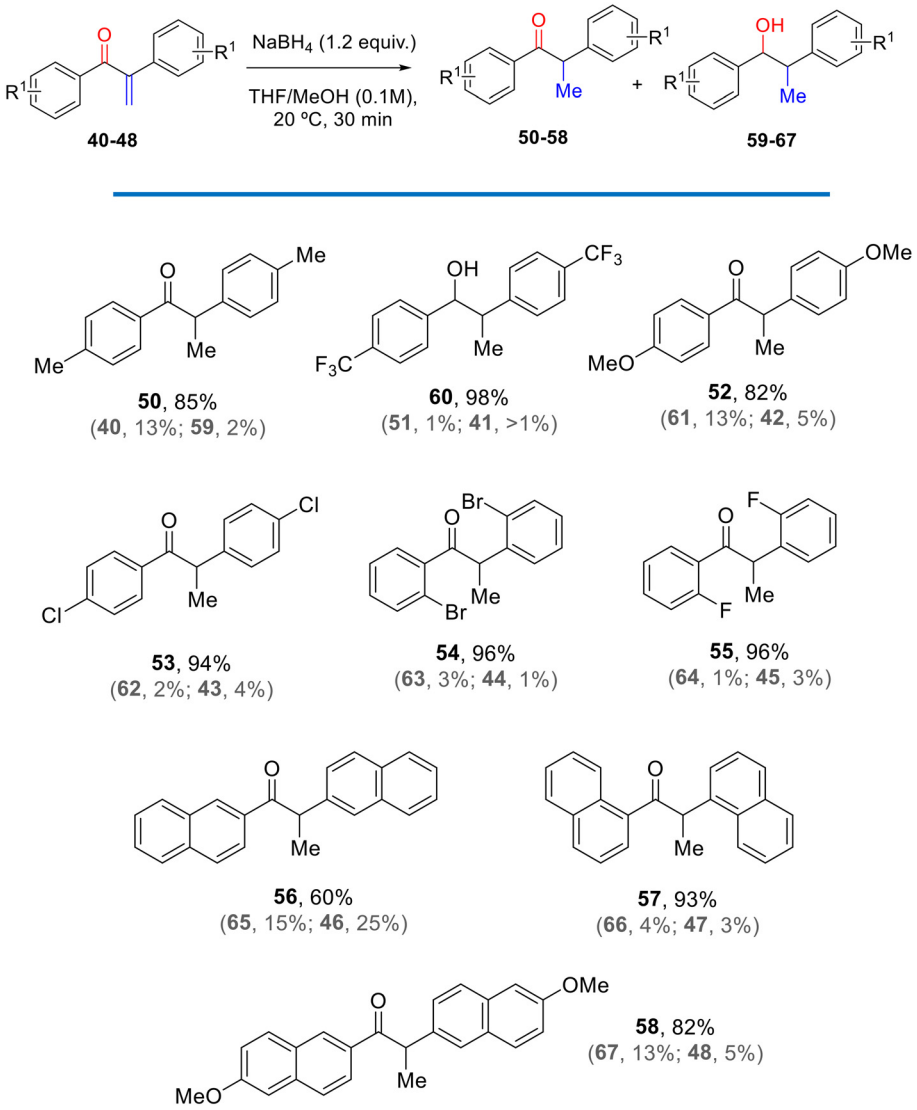


Fig. 4 Scope of the alkene hydrogenation reaction of 1,2-diarylprop-2-en-1-ones **40–48** with $NaBH_4$ under the indicated reaction conditions. Isolated yields.

wanted to know if the countercation also plays this decisive role[37] in the hydrogenation of the alkene group in *gem*-diaryl substituted enones. For that, the reactivity of different borohydrides MBH_4 (M = Li, K and NEt_4) was followed by kinetic experiments under the optimized reaction conditions but at 0.0075 M concentration, in order to slow down the reaction, and the initial rate was calculated and compared with that for $NaBH_4$. Fig. 5 shows that a positive linear trend arises for the initial rate of the reaction, from Li^+ to K^+, with ≥300 mol% h^{-1} higher activity for each 0.4 Å of solvated ionic radius.[38] In this way, the reaction goes from an initial rate of 84 h^{-1} with $LiBH_4$ to 744 h^{-1} with KBH_4, nearly one order of magnitude faster. A linear trend but in the opposite direction (negative) is observed for the selectivity to the desired alkene hydrogenation product **18**, calculated at 80% conversion in all cases (except for Li^+, maximum yield 34%), going from >99% for Li^+ and Na^+ to 73% with K^+. In other words, the results establish a clear linear relationship between the size of the solvated counterbalancing cationic radius and the reactivity of the borohydride. These results support the key role of the cation in the alkene hydrogenation of **16**.

The radius of the alkaline cation is directly related to its electronegativity; thus, in order to decouple these two factors (*i.e.* size and electronics), the borohydride Et_4NBH_4 was also employed as a hydrogenating reagent. The solvated radius of the organic ammonium cation Et_4N^+ is very similar to that of K^+ (≈4.5 Å),[39,40] however, with different electronegativity; thus the fact that the initial rate and selectivity to **18** are very similar for both KBH_4 and Et_4NBH_4 strongly supports that the cationic radius and not the metal electronegativity is what mainly influences the reaction outcome. If this is so, fine-tuning of the reaction rate and selectivity could be performed by mixing suitable cations during the reaction.[28,39,41] Indeed, Fig. 5 also shows that the use of an equimolar mixture of

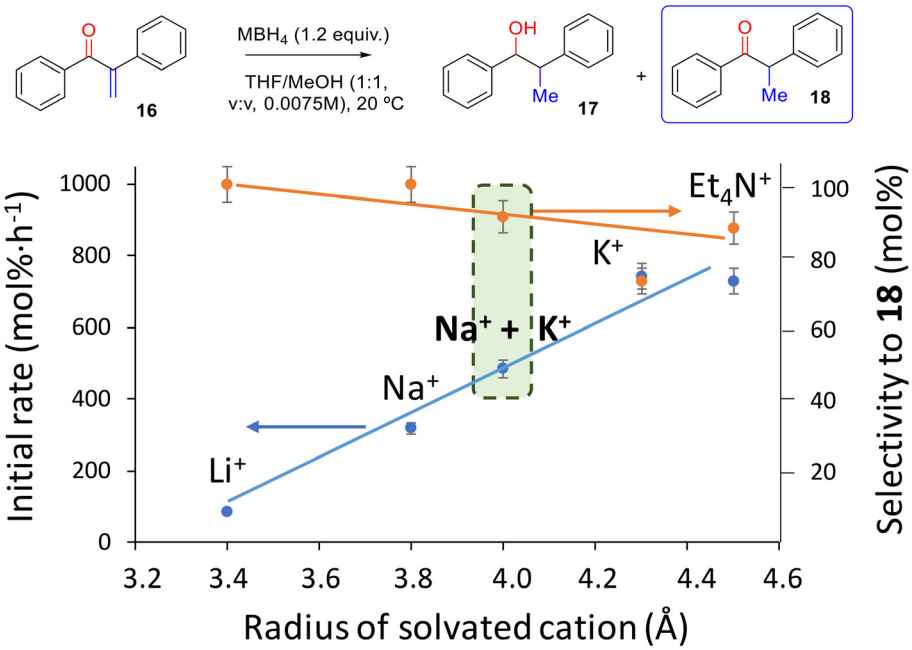


Fig. 5 Plots of the initial rate (blue points)/selectivity at 80% conversion (orange points) *vs.* the radius of the solvated cation for the hydrogenation reaction of 1,2-diphenylprop-2-en-1-one **16** with $NaBH_4$ under the indicated reaction conditions. Combined GC and ^1H NMR yields. Error bars indicate 5% uncertainty.

$NaBH_4$ and KBH_4 leads to higher reactivity than when $NaBH_4$ was employed alone, and also to better selectivity to **18** than when KBH_4 was employed alone. These results show that the selective hydrogenation of alkenes in *gem*-diaryl enones could be further optimized by employing a suitable combination of different borohydrides.

2.4 Reaction mechanism for *gem*-diaryl enones

Reactivity and isotopic experiments were carried out to get insight into the reaction mechanism of the alkene hydrogenation reaction of enone **16**, and they are shown in Fig. 6. First, the more reactive hydrides in $NaBH_4$ (1.2 equivalents) were quenched by adding acetophenone **68** (0.5 equivalents) to the reaction medium, prior to **16**. After leaving the reaction to proceed overnight, the formation of the expected ketone hydrogenated product phenylethanol **69** was observed in high yield, and at this point, **16** (0.5 equivalents) was added to the mixture. The results in Fig. 6A show that the selective hydrogenation of the alkene in **16** was still observed, in good yields. These results indicate that all the hydrides in $NaBH_4$ are able to hydrogenate the alkene, ruling out a key role of the hydride strength in the reaction. This result also explains the complete hydrogenation of the trifluoro-substituted enone **41** (see Fig. 4). The same reactivity test was carried out with chalcone **8**; however, the hydrogenation product of the ketone (**70**) was the major product observed under these reaction conditions (90%), in agreement with the results shown in Fig. 2.

Isotopically-labelled $NaBD_4$ (>95% labelling extension) was then used as the reactant for enone **16**. Fig. 6B shows that the kinetic isotopic effect (KIE = k_H/k_D) value observed under optimized conditions is 1.2(8), suggesting that the hydride addition plays a significant role in the reaction rate. The KIE could be due to the formation of new C–D bonds or the breaking of the B–H/D bonds. An equimolar yield of the different deuterated products, *i.e.* **17** and **18**, after complete conversion of **16**, was found, in accordance with the results obtained under non-isotopic reaction conditions (entry 5 in Table 1). The first deuterium atom incorporates in the terminal position (C_β) of the *gem*-alkene in product **18**, and after further hydrogenation, the second deuterium atom incorporates in the carbonyl position of **17**. Complementarily, if deuterated solvents (THF-d^8 and CD_3OD) are used in combination with $NaBH_4$, the first deuterium atom incorporates in the internal position (C_α) of the *gem*-alkene, and after further hydrogenation, the second deuterium atom is found in the final alcohol group. Kinetic experiments with different *para*-substituted *gem*-diaryl enones enable the drawing of a Hammett plot (Fig. S5†), which shows a good correlation ($R^2 > 0.95$) and gives a $\rho = +0.15$, which indicates that the build-up of a slight negative charge on the conjugated system increases the reaction rate; in other words, the electron acceptor groups accelerate the reaction. These results strongly suggest a first 1,4-hydride addition to the unsaturated alkene of enone **16** and a second 1,2-hydride addition to the carbonyl group in ketone **18**, after reaching the corresponding enol equilibrium.

Fig. 7 shows the proposed mechanism for the selective alkene hydrogenation of *gem*-diaryl substituted enones with MBH_4 (M = Li–K and Et_4N), compared with the ketone hydrogenation in chalcones, on the basis of the experimental results obtained and also of some computational calculations

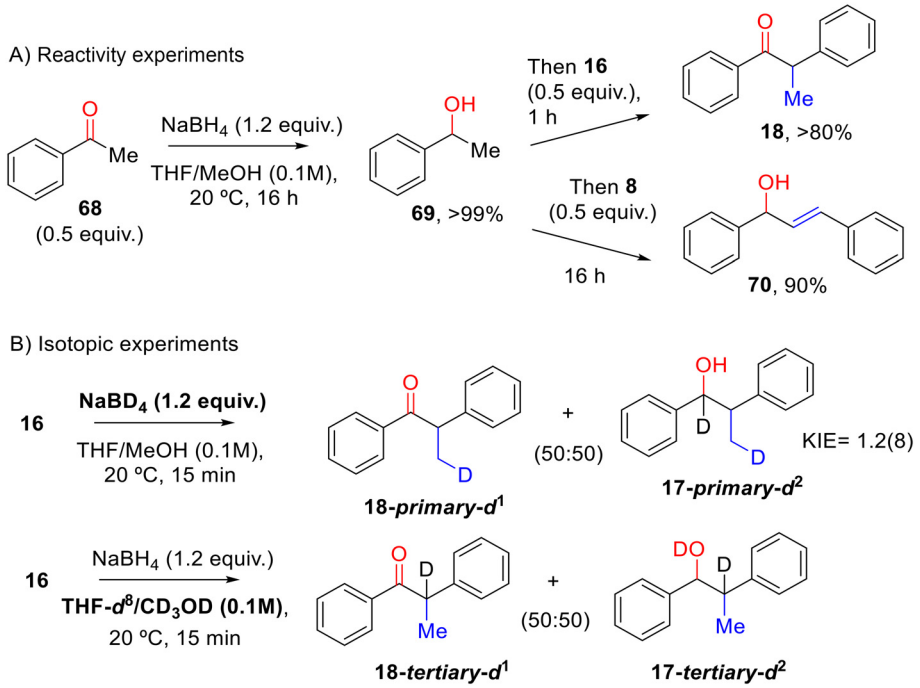


Fig. 6 (A) Reactivity experiments for the hydrogenation reaction of acetophenone **68** with $NaBH_4$ and later hydrogenation of either 1,2-diphenyl-prop-2-en-1-one **16** or chalcone **8**; (B) isotopic experiments for the hydrogenation of **16**, under the indicated reaction conditions. Deuterium incorporation was >95% in all cases, as assessed by combined GC-MS and ^{1}H NMR; the conversion was >99% and the equimolar final yields of deuterated **17** and **18** were obtained, calculated by combined GC and ^{1}H NMR measurements.

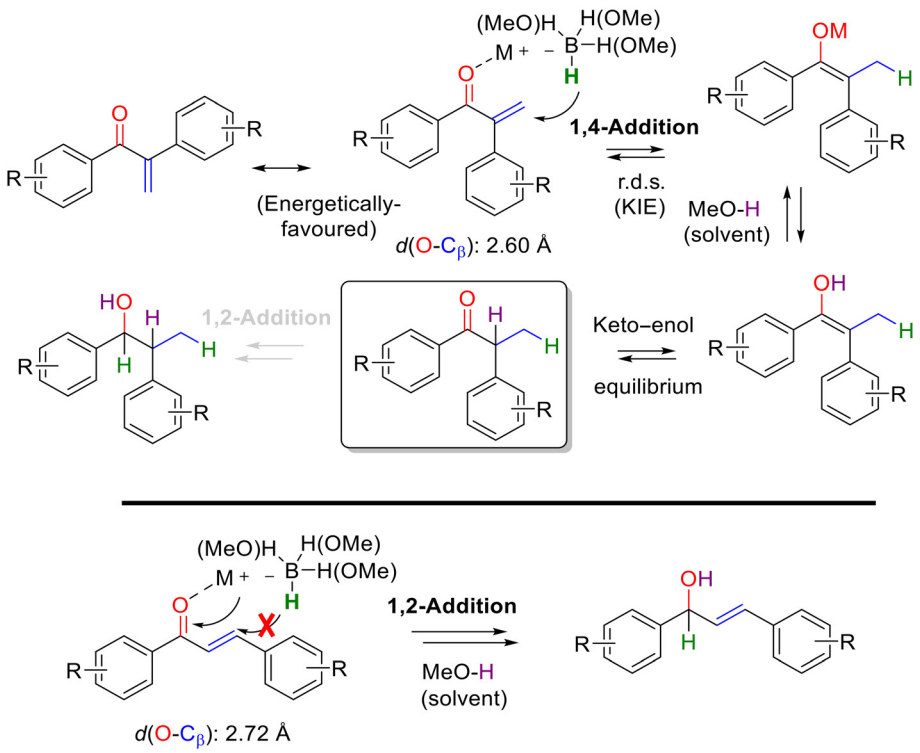


Fig. 7 Proposed mechanism for the selective alkene hydrogenation of *gem*-diaryl substituted enones with MBH_4 (M = Li–K and Et_4N), compared with the ketone hydrogenation of structurally parent chalcones under the same reaction conditions (THF : MeOH solvent, bottom). r.d.s.: rate-determining step; KIE: kinetic isotopic effect.

(*vide infra*). The first step is a 1,4-addition reaction of the hydride atom of MBH_4 (or the corresponding partially reacted intermediates, as experimentally confirmed by the reactivity experiments in Fig. 6A) to the terminal alkene bond (C_β), to generate the corresponding enolate. This step has been unambiguously confirmed by the experimental deuteration experiments in Fig. 6B, and it can be considered the rate-determining step (r.d.s.) of the reaction, taking into account the KIE value found [1.2(8)] and the Hammett plot. Then, the enolate intermediate tautomerizes to the ketone by taking a H atom from the solvent, as demonstrated by the deuteration experiments in Fig. 6B and also by the necessary presence of protic solvents during the reaction (see Table 1).[42] The countercation in MBH_4 probably exerts a structural stabilization effect on the reactive intermediate during the hydride addition, on the basis of the different reactivities observed in Fig. 5 and of the extensive literature on this topic.[43] Finally, the ketone hydrogenation can also occur on the desired product, following a classical 1,2-hydride addition assisted by the protic solvent.[44] The lack of steric hindrance at the beta-carbon atom in these substrates together with the formation of kinetically stable enols could also be the reason behind their particular reactivity here.[45]

Chalcone **8** and its derivatives only react through the ketone under the same reaction conditions (THF : MeOH solvent) despite its structural similarity with enone **16**, as shown above. Computational calculations were carried out to get some insights into these reactive differences. Both density functional theory (DFT) and molecular mechanics (MM2) support that the electronic density distribution in the C_β terminal double bond of **16** (Bader charges) is >0.2 e^- higher than that in chalcone **8** (Fig. S6†), and that the electronic densities in the carbonyl groups of **16** and **8** only differ by 0.02 e^-, one order of magnitude less. These results rule out a native electronic effect to explain the preferred addition of the hydride to the terminal alkene rather than to the ketone group in **16**. In contrast, the computational calculations show that the *gem* disposition of alkene **16** favors the parallel arrangement of the ketone and the terminal alkene groups, with the aryl groups twisted 35° with respect to the planar position, enabling a calculated spatial C_β–O distance of 2.60 Å, while chalcone **8** stays in a completely *trans* planar configuration (the calculated aryl group twist is 0°) with a calculated C_β–O spatial distance of 2.72 Å. Besides, the DFT computations also show that the hydrogenation of the *gem* alkene in **16** with $NaBH_4$ releases an energy of 24.4 kcal mol^{-1}, to give ketone **18**, while the (theoretical, not experimentally determined) associated energy for the hydrogenation of the alkene in chalcone **8** is 22.1 kcal mol^{-1}, 2.3 kcal mol^{-1} less than that for **16** (Fig. S7†). These computational results further support that the particular steric disposition of *gem*-diaryl enones is behind the unique alkene reactivity with MBH_4.

2.5 Switching from ketone to alkene hydrogenation in *trans*-diaryl enones (chalcones)

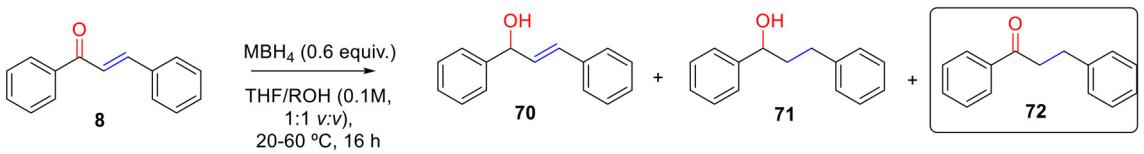
The results above clearly demonstrate that chalcones react through the expected carbonyl group in the presence of $NaBH_4$ under standard reaction conditions (THF : MeOH solvent, room temperature). However, the study also indicates that not only the countercation but also the protic solvent plays a key role in the reaction; thus varying these two factors might drive a selective hydrogenation of the alkene group in the widespread chalcone (*trans*-diaryl enone) family.

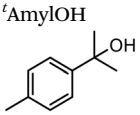
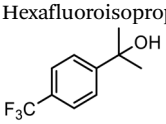
Table 2 shows the results for the hydrogenation reaction of chalcone **8** with different borohydrides (MBH_4) and protic solvents (ROH). We could see from the above discussion (Fig. 6A) that the hydrogenation of **8** with $NaBH_4$ proceeded to afford the allyl alcohol **70** in 90% yield, and a close inspection of the crude NMR showed us that the 10% remaining corresponded to the completely hydrogenated alcohol **71**. Indeed, it can be seen from Table 2 that when varying the borohydride countercation from Li^+ to K^+ and then to NEt_4^+, the selectivity for the hydrogenation of the alkene increases (products **71** + **72**, entries 1–4), to finally obtain some selectivity for the alkyl ketone **72** with NEt_4BH_4, although with moderate conversion after 16 h (64%). Thus, at this point, we changed the alcohol co-solvent, increasing the steric hindrance around the alcohol group (entries 5–12). The results clearly show that an increase in the hydrogenation of the alkene occurs with an increase in the steric hindrance, to give product **71**, and that the desired ketone **72** could be formed in 36% yield after complete conversion of **8** when a tri-substituted benzyl alcohol **73** was used as a co-solvent with THF (entry 12).

Fig. 8 shows the plots of the different yields for products **70–72** *vs.* the Taft or Hammett values for the different alcohols tested. The Taft values are a measure of how the steric hindrance affects the reaction, while the Hammett values refer to the electronics. It can be seen that an inverse linear correlation appears for the classical ketone hydrogenation reaction (product **70**) for both the Taft and Hammett parameters, in accordance with the better action of borohydrides in the presence of small nucleophilic alcohol co-solvents such as MeOH. In contrast, a linear correlation appears for the non-classical alkene hydrogenation reaction (products **71** and **72**), in accordance with a better alkene hydrogenation with hindered and electron-deficient alcohol co-solvents.[43] Indeed, the correlation is more pronounced for the desired product **72** in the Hammett plot, indicating that electron-withdrawing groups (in a sterically crowded alcohol) would be beneficial for the alkene hydrogenation.

NEt_4^+ was then used as the countercation of borohydrides with alcohol **73** as the co-solvent; however, the selectivity to **72** did not improve compared to that of Na^+ in this case, although it was still reasonably good (31%, entry 13). At this point, it seems that the solvent effect prevails over the countercation effect. In order to confirm if the better formation of ketone **72** mainly comes from the electron withdrawing effect or the steric hindrance around the alcohol group, diphenylmethanol, triphenylmethanol and phenol were tested as alcohols in THF, and the results show a significant selectivity for the alkene hydrogenation (entries 14–16), but not higher than that with the tri-substituted benzyl alcohol **73**. Fluorinated solvents were then tested, including the trifluoromethylated derivative of

Table 2 Results for the hydrogenation reaction of chalcone **8** with different borohydrides (MBH_4) and protic solvents (ROH)



Entry	MBH_4 (equiv.)	Solvent (THF/ROH)	T (°C)	Conversion of **8** (%)[a]	**70** [a] (%)	**71** [a] (%)	**72** [a] (%)	Selectivity to **72** (%)
1	Na	MeOH	20	>99	90	10	—	—
2	Li			25	25	—	—	—
3	K			>99	86	14	—	—
4	NEt_4			64	50	9	5	8
5	Na	EtOH		>99	77	23	—	—
6		^{i}PrOH		>99	66	34	—	—
7		*n*-BuOH		>99	74	26	—	—
8		2-BuOH		>99	64	36	—	—
9		^{i}BuOH		>99	68	32	—	—
10		^{t}BuOH		>99	57	39	4	4
11		^{t}AmylOH		>99	59	40	1	1
12				**>99**	**38**	**26**	**36**	**36**
13	NEt_4			>99	27	42	31	31
14	Na	Diphenylmethanol		>99	53	47	—	—
15		Triphenylmethanol		83	51	16	16	19
16		Phenol		87	69	15	3	3
17		Trifluoroethanol		87	81	3	3	4
18		Hexafluoroisopropanol		25	19	2	4	16
19				75	46	13	16	21
20		*o*,*m*-Tetrafluorophenol		1	0	0	1	>99
21		^{t}BuOH	60	>99	55	41	4	4
22		**73**		>99	28	40	32	32
23		4-Chlorophenol		43	39	0	4	9
24		**Pentachloro-phenol**		**57**	**0**	**0**	**57**	**>99**

[a] Calculated by combined GC and ^{1}H NMR.

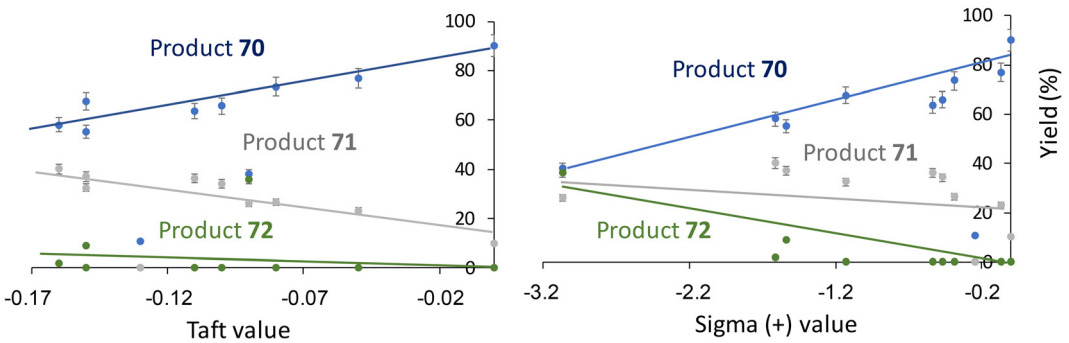


Fig. 8 Plots of Taft (left) and Hammett (right) values *vs.* yield for the hydrogenation reaction of chalcone **8** under the reaction conditions indicated in Table 2 and with different alcohols (entries 5–12). Yields were calculated by combined GC and ^{1}H NMR. Error bars indicate 5% uncertainty.

alcohol **73** (compound **74**, entries 17–20), but they did not improve the results, although, perhaps as a curios case, a fluorinated phenol (entry 20) gave very low yield but complete selectivity to ketone **72**. Thus, at this point, we increased the reaction temperature to 60 °C, testing different alcohols and including a perchlorinated phenol (the fluorinated phenol is extremely odorous and difficult to handle). The results (entries 21–24) show that alcohol **73** does not improve the selectivity to ketone **72** after heating but the perchlorinated phenol does, to achieve complete selectivity and a 57% yield of ketone **72**

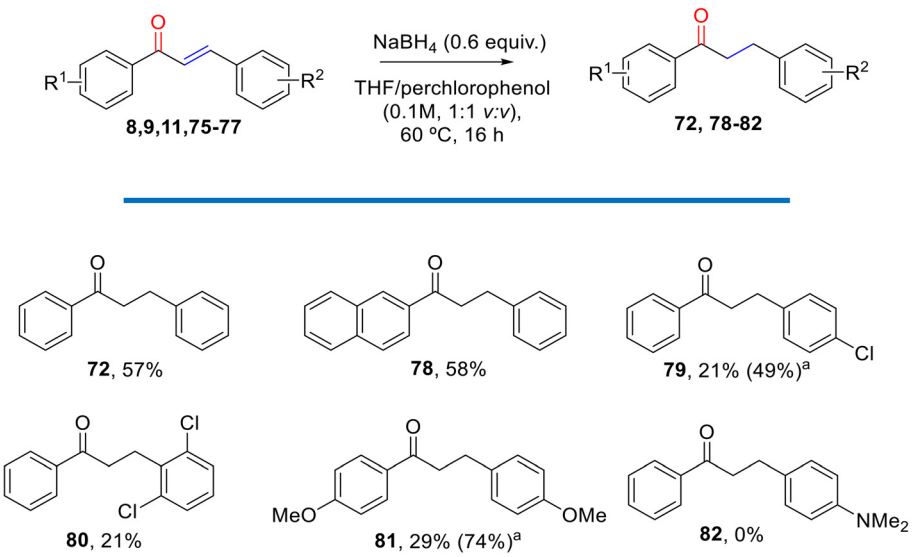


Fig. 9 Scope of the alkene hydrogenation reaction of chalcones **8**, **9**, **11** and **75–77** with $NaBH_4$ under the indicated reaction conditions, giving ketones **72** and **78–82**. Isolated yields. [a]In parentheses, results for 1.2 equivalents of $NaBH_4$ and 72 h reaction time. The mass balance is completed with unreacted material.

(entry 24). This result is remarkable, since it is difficult to find in the literature a procedure to exclusively hydrogenate alkenes in the presence of ketones (moreover conjugated) with $NaBH_4$. It is true that the perchlorinated phenol is odorous and relatively toxic; however, it stays liquid at 60 °C and precipitates at room temperature, even when mixed with THF, thus enabling its easy separation and recovery. With this observation in mind, more chalcones were prepared (compounds **75–77**, Fig. S8†) and tested under the optimal reaction conditions for the selective hydrogenation of the alkene group. The results in Fig. 9 show that naphthalene (product **78**), chloride (products **79** and **80**) and methoxy groups (product **81**) are tolerated during the selective hydrogenation reaction, to give the desired ketones in good yields, with complete selectivity to the ketone (the mass balance is completed with unreacted material). In some cases, double the amount of $NaBH_4$ and a longer reaction time (72 h) were necessary to increase the reaction yield, however, without any hydrogenation of the ketone in any case. The dimethylamino group (product **82**) completely stopped the reaction, with the recovery of the whole starting material, and this lack of reactivity when a basic group is present in the reaction medium is in line with the necessity of a relatively acidic proton for the polar solvent to trigger the selective hydrogenation reaction of the alkene group.

For comparison purposes, the reactions with the chalcones were repeated with ^{t}BuOH instead of perfluorophenol as a co-solvent, to check that the substrate structure did not influence the final outcome of the employed alcohol. Indeed, the product selectivity found for the new chalcones with ^{t}BuOH as a co-solvent is essentially the same as that observed for chalcone **8** (entry 21, Table 2), with not more than 18% yield of the ketone products (Fig. S9†). However, the unreactive chalcone **77** indeed reacted with ^{t}BuOH as a co-solvent, to give the expected alcohol products, confirming that the selective hydrogenation of the alkene group with EWG-containing alcohols is at the expense of the high reactivity of $NaBH_4$. Following this rationale, the use of the commercially-available sodium triacetoxyborohydride reagent was tested under optimized reaction conditions. Acetic acid has a similar pK_a to pentafluorophenol (pK_a = 5.5); thus one would guess that the former may produce a similar effect on the reaction. However, conversion of chalcone **8** was not obtained (Fig. S10†), which highlights the subtlety of the reaction conditions to selectively hydrogenate the alkene bond.

3 Conclusions

Commercial borohydrides selectively hydrogenate the alkene group in enones under the reaction conditions reported here, without any catalyst required and making full use of the hydride atoms. The specific structural pattern of *gem*-diaryl substituted enones enables the selective hydrogenation reaction of the alkene group with different MBH_4 borohydrides under standard reaction conditions (*i.e.* THF/MeOH solvent at room temperature), while any other enones tested under these reaction conditions mainly gave the expected ketone hydrogenation reaction. The lack of steric hindrance at the beta-carbon atom in these substrates together with the formation of kinetically stable enols could also be the reason behind their particular reactivity here.[45] The variation of the cation in MBH_4 allows fine-tuning of the reactivity of the system, and a series of α-aryl substituted propiophenones could be synthesized in this way. Mechanistic studies support a native 1,4-addition of the hydride to the terminal alkene carbon of the *gem*-diaryl enone, with the assistance of the alcohol co-solvent, which

provides the second H atom. With these results in mind, the selective hydrogenation of the alkene group in widespread *trans*-diaryl enones (chalcones) could be achieved after changing the counterbalancing cation from Na^+ to Et_4N^+ and the alcohol co-solvent from MeOH to electron-deficient alcohols, since electron withdrawing substituents in a sterically crowded alcohol lead to the selective alkene hydrogenation.[46] These "en-to-ket" transformations open a way to investigate catalyst-free hydrogenation reactions of unsaturated carbon–carbon bonds with borohydrides, which considering the multiple options available for the reactants (alkynes, allenes, ...; different cations and substituents on the B atom, ...),[47–49] together with some reports on catalyst-free hydrogenation reactions of unsaturated carbon–carbon bonds with other typical hydrides such as $LiAlH_4$,[50–52] may stimulate this chemistry in the near future.

Author contributions

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

Conflicts of interest

There are no conflicts of interest to declare.

Data availability

The data underlying this study are available in the published article and its ESI.†

Acknowledgements

This work is part of the project PID2023-148441NB-I00. Financial support from the Severo Ochoa Centre of Excellence program (CEX2021-001230-S) is gratefully acknowledged. The work has also been funded by Generalitat Valenciana (Prometeo Grupos de Investigación de Excelencia PROMETEU/2021/054). M. E. thanks the Universitat de València (PROMETEU/2021/054) for the concession of a contract. M. M.-G. thanks ITQ, UPV-CSIC, for the concession of a contract (PAID 01-23).

References

1 J. P. Adams, Sodium borohydride in organic chemistry, *Org. React.*, 1999, **51**, 345–477.
2 M. Zaidlewicz and M. M. Pakulski, Reduction of carbonyl groups: transfer hydrogenation, hydrosilylation, catalytic hydroboration, and reduction with borohydrides, aluminum hydrides, or boranes, in *Science of Synthesis, Stereoselective Synthesis*, ed. J. G. De Vries, G. A. Molander and P. A. Evans, 2011, vol. 2, pp. 59–131.
3 P. Ertl and T. A. Schuhmann, Systematic cheminformatics analysis of functional groups occurring in natural products, *J. Nat. Prod.*, 2019, **82**, 1258–1263.
4 S. Sanz-Navarro, M. Mon, A. Doménech-Carbó, R. Greco, J. Sánchez-Quesada, E. Espinós-Ferri and A. Leyva-Pérez, Parts–per–million of ruthenium catalyze the selective chain–walking reaction of terminal alkenes, *Nat. Commun.*, 2022, **13**, 2831.
5 E. Burkhardt and K. Matos, Boron reagents in process chemistry: Excellent tools for selective reductions, *Chem. Rev.*, 2006, **106**, 2617–2650.
6 C. Shekhar, R. Nasam, S. R. Paipuri, P. Kumar, K. Nayani, S. Pabbaraja, P. S. Mainkar and S. Chandrasekhar, Total synthesis of antiviral drug, nirmatrelvir (PF-07321332), *Tetrahedron Chem*, 2022, **4**, 100033.
7 M. Hey, Paper bleaching: Its simple chemistry and working procedures, *Pap. Conserv.*, 1977, **2**, 10–23.
8 P. L. Ting and D. S. Ryder, The bitter, twisted truth of the hop: 50 years of hop chemistry, *J. Am. Soc. Brew. Chem.*, 2017, **75**, 161–180.
9 J. Zhang, H. Li, X. Xiao and L. Ouyang, Preparation and regeneration of metal borohydrides for high-density hydrogen supply: Progress, challenges, and perspectives, *J. Alloys Compd.*, 2023, **951**, 169887.
10 B. Richter, J. B. Grinderslev, K. T. Møller, M. Paskevicius and T. R. Jensen, From metal hydrides to metal borohydrides, *Inorg. Chem.*, 2018, **57**, 10768–10780.
11 L. Rodney, A. Fernandes and A. B. Ingle, Synthetic studies on C_{14} cembranoids: Synthesis of C_{4-12} fragment of sarcophytonolides E-G and L and C_{5-11} fragment of sarcophytonolide, *Tetrahedron Lett.*, 2011, **52**, 458–460.
12 K. Adank, H. A. Pfenninger, W. G. Stoll and M. Viscontini, Über pyrrolizidinchemie: 3. mitteilung) eigenschaften und chemisches verhalten der 2,5-dioxo-5H-pyrrolo-[2,1-a] isoindole, *Helv. Chim. Acta*, 1963, **46**, 1030–1041.
13 D. Kupfer, Altered selectivity of reduction of steroidal carbonyls, *Tetrahedron*, 1961, **15**, 193–196.
14 S. Raucher and K.-J. Hwang, A convenient procedure for the preparation of dihydrocarvone, *Synth. Commun.*, 1980, **10**, 133–137.
15 J. L. Luche, Lanthanides in organic chemistry. Selective 1,2 reductions of conjugated ketones, *J. Am. Chem. Soc.*, 1978, **100**, 2226–2227.
16 A. J. MacNair, M.-M. Tran, J. E. Nelson, G. U. Sloan, A. Ironmonger and S. P. Thomas, Iron-catalysed, general and operationally simple formal hydrogenation using $Fe(OTf)_3$ and $NaBH_4$, *Org. Biomol. Chem.*, 2014, **12**, 5082–5088.
17 S. Bulut, Z. Fei, S. Siankevich, J. Zhang, N. Yan and P. J. Dyson, Aqueous-phase hydrogenation of alkenes and arenes: The growing role of nanoscale catalysts, *Catal. Today*, 2015, **247**, 96–103.
18 S. Yakabe, M. Hirano and T. Morimoto, Hydrogenation of alkenes with sodium borohydride and moist alumina cata-

lyzed by nickel chloride, *Tetrahedron Lett.*, 2000, **41**, 6795–6798.
19 R. C. Wade, Some industrial processes using borohydride–reduced catalysts, *Chem. Ind.*, 1981, **5**, 165–179.
20 T. Shimbayashi and K.-i. Fujita, Metal–catalyzed hydrogenation and dehydrogenation reactions for efficient hydrogen storage, *Tetrahedron*, 2020, **76**, 130946.
21 R. Ravichandran and S. Divakar, Cyclodextrin and its derivatives directed axial attack of hydride ion in the reduction of (R)–(+)–pulegone and (2S,5R)–(−)–menthone, *J. Mol. Catal. A: Chem.*, 1996, **109**, 201–208.
22 W. R. Jackson and A. Zurqiyah, The occurrence of 1,2– or 1,4–addition in the reduction of some unsaturated ketones with metal hydrides, *J. Chem. Soc.*, 1965, 5280–5287.
23 M. Shi, C.-Q. Li and J.-K. Jiang, Different reaction patterns in the Baylis–Hillman reaction of aryl aldehydes with phenyl vinyl ketone, phenyl acrylate and phenyl thioacrylate, *Molecules*, 2002, **7**, 721–733.
24 A. Corma, H. García and A. Leyva, Heterogeneous Baylis–Hillman using a polystyrene–bound 4–(N–benzyl–N–methylamino)pyridine as reusable catalyst, *Chem. Commun.*, 2003, 2806–2807.
25 J. Liu, H. Yi, X. Zhang, C. Liu, R. Liu, G. Zhang and A. Lei, Copper–catalysed oxidative Csp^3–H methylenation to terminal olefins using DMF, *Chem. Commun.*, 2014, **50**, 7636–7638.
26 N. Asao, P. Liu and K. Maruoka, 1,8–Bis(allylstannyl) naphthalene derivatives as neutral allylation agents: Rate acceleration by chelation induced Lewis acidity, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2507–2509.
27 F. Garnes-Portolés, R. Greco, J. Oliver-Meseguer, J. Castellanos-Soriano, M. C. Jiménez, M. López-Haro, J. C. Hernández-Garrido, M. Boronat, R. Pérez-Ruiz and A. Leyva-Pérez, Regioirregular and catalytic Mizoroki–Heck reactions, *Nat. Catal.*, 2021, **4**, 293–303.
28 P. Mingueza-Verdejo, S. Rodríguez-Nuévalos, J. Oliver-Meseguer and A. Leyva-Pérez, Alkene cross–metathesis with 2,5–dimethyl–2,4–hexadiene enables isobutylenyl/prenyl functionalizations and rubber valorization, *Chem. – Eur. J.*, 2024, e202400860.
29 J. Esquivias, R. G. Arrayás and J. C. Carretero, Copper–catalyzed enantioselective conjugate addition of dialkylzinc reagents to (2–pyridyl)sulfonyl imines of chalcones, *J. Org. Chem.*, 2005, **70**, 7451–7454.
30 S. B. Kadin, Reduction of conjugated double bonds with sodium borohydride, *J. Org. Chem.*, 1966, **31**, 620–622.
31 S. Rodríguez-Nuévalos, M. Espinosa and A. Leyva-Pérez, Soluble individual metal atoms and ultrasmall clusters catalyze key synthetic steps of a natural product synthesis, *Commun. Chem.*, 2024, **7**, 76.
32 J. L. García-Ruano, M. A. Fernández-Ibáñez, J. A. Fernández-Salas, M. C. Maestro, P. Márquez-López and M. M. Rodríguez-Fernández, Remote stereocontrol mediated by a sulfinyl group: Synthesis of allylic alcohols via chemoselective and diastereoselective reduction of γ–methylene *δ*–ketosulfoxides, *J. Org. Chem.*, 2009, **74**, 1200–1204.
33 G. Zhang, Q. Liang, W. Yang, S. Jiang, Z. Wang, C. Zhang and G. Zhang, One Pot Synthesis of 1,2–disubstituted ethanones by base–mediated reductive homocoupling of aldehydes, *Adv. Synth. Catal.*, 2022, **364**, 2951–2956.
34 S. Tomoda and T. Senju, Origin of π–facial stereoselectivity of hydride reduction of cyclohexanones. A new interpretation based on quantitative analysis of exterior frontier orbital extension, *Tetrahedron*, 1997, **53**, 9057–9066.
35 Y. Suzuki, D. Kaneno and S. Tomoda, Theoretical study on the mechanism and diastereoselectivity of $NaBH_4$ reduction, *J. Phys. Chem. A*, 2009, **113**, 2578–2583.
36 R. S. Glass, D. R. Deardorff and K. Henegar, Highly stereoselective reductions of α–alkoxy–β–keto esters. Aspects of the mechanism of sodium borohydride reduction of ketones in 2–propanol, *Tetrahedron Lett.*, 1980, **21**, 2467–2470.
37 Y. Zheng, A. Vidal-Moya, J. C. Hernández-Garrido, M. Mon and A. Leyva-Pérez, Silver–exchanged zeolite Y catalyzes a selective insertion of carbenes into C–H and O–H bonds, *J. Am. Chem. Soc.*, 2023, **145**, 24736–24745.
38 Y. Marcus, Ionic radii in aqueous solutions, *Chem. Rev.*, 1988, **88**, 1475–1498.
39 C. M. Armstrong, Interaction of tetraethylammonium ion derivatives with the potassium channels of giant axons, *J. Gen. Physiol.*, 1971, **58**, 413–437.
40 H. Moldenhauer, I. Díaz-Franulic, F. González-Nilo and D. Naranjo, *Sci. Rep.*, 2016, **6**, 19893.
41 P. Mingueza-Verdejo, J. C. Hernandez-Garrido, A. Vidal-Moya, J. Oliver-Meseguer and A. Leyva-Perez, *Catal. Sci. Technol.*, 2023, **13**, 2308–2316.
42 D. C. Wigfield and F. W. Gowland, Limited alkoxy group exchange in tetraalkoxyborohydrides: Evidence against the four–centre transition state in the borohydride reduction of ketones, *Tetrahedron Lett.*, 1976, **17**, 3373–3376.
43 Y.-D. Wu, J. A. Tucker and K. N. Houk, Stereoselectivities of nucleophilic additions to cyclohexanones substituted by polar groups. Experimental investigation of reductions of *trans*–decalones and theoretical studies of cyclohexanone reductions. The influence of remote electrostatic effects, *J. Am. Chem. Soc.*, 1991, **113**, 5018–5027.
44 C. T. Meta and K. Koide, *Trans*–Selective conversions of γ–hydroxy–α,β–alkynoic esters to γ–hydroxy– α,β–alkenoic esters, *Org. Lett.*, 2004, **6**, 1785–1787.
45 H. Hart, Simple enols, *Chem. Rev.*, 1979, **79**, 515–528 (please read first, in particular, the fragment about transformation of 6 into 7).
46 J. Ballesteros-Soberanas, J. A. Carrasco and A. Leyva-Pérez, Parts–per–million of soluble Pd0 catalyze the semi–hydrogenation reaction of alkynes to alkenes, *J. Org. Chem.*, 2023, **88**, 18–26.
47 A. Leyva, X. Zhang and A. Corma, Chemoselective hydroboration of alkynes vs. alkenes over gold catalysts, *Chem. Commun.*, 2009, 4947–4949.
48 J. Oliver-Meseguer, A. Leyva-Pérez and A. Corma, Very small (3–6 atoms) gold cluster catalyzed carbon–carbon and carbon–heteroatom bond–forming reactions in solution, *ChemCatChem*, 2013, **5**, 3509–3515.

49 M.Á Rivero-Crespo, M. Tejeda-Serrano, H. Pérez-Sánchez, J. P. Cerón-Carrasco and A. Leyva-Pérez, Intermolecular carbonyl–olefin metathesis with vinyl ethers catalyzed by homogeneous and solid acids in flow, *Angew. Chem., Int. Ed.*, 2020, **59**, 3846–3849.

50 D. S. Hays, M. Scholl and G. C. Fu, Organotin hydride–catalyzed conjugate reduction of *alpha*,*beta*–unsaturated ketones, *J. Org. Chem.*, 1996, **61**, 6751–6752.

51 L. Grigorjeva, A. Kinens and A. Jirgensons, Unsaturated *syn*– and *anti*–1,2–amino alcohols by cyclization of allylic bis–trichloroacetimidates. Stereoselectivity dependence on substrate configuration, *J. Org. Chem.*, 2015, **80**, 920–927.

52 X. Ren and Z. Lu, Cobalt–catalyzed asymmetric 1,4–-hydroboration of enones with HBpin, *Org. Lett.*, 2021, **23**, 8370–8374.