Dalton Transactions

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

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Tandem Hydrogenation and Condensation of Fluorinated α,β-Unsaturated Ketones With Primary Amines, Catalyzed by Nickel

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***Keywords*:** α,β-unsaturated ketones / Fluorinated/ primary amines / nickel / transfer hydrogenation / condensation / tandem.

ABSTRACT

A simple homogeneous catalytic system based on nickel phosphine complexes has been developed for the transfer hydrogenation and condensation of α,β-unsaturated ketones to yield saturated ones and saturated imines using primary amines as hydrogen donors. Thus, a wide range of fluorinated 1,5-diaryl-1,4-pentadiene-3-ones were allowed to react with substituted benzylamines in the presence of the $[(dippe)Ni(\mu\text{-}H)]_2$ (dippe = 1,2-bis-(diisopropylphosphino)-ethane) using ethanol as solvent at 180 ºC to give the corresponding saturated carbonyl compounds, here hydrogenation of the C=C bond was preferred over the C=O bond. In the same reaction conditions but using an excess of benzylamine a tandem process is then favoured, starting also with the reduction of the C=C bond followed by a nucleophilic adidition of the primary amine to yield valuable saturated imines with good to excellent yields (62 % - 91 %).

INTRODUCTION

The transfer hydrogenation of α,β-enones is an important chemical transformation since these enones can be prepared by simple procedures[1] and the corresponding products from hydrogenation, such as saturated ketones, are of importance in the manufacture of value added chemicals for pharmaceuticals and fragrance industry.[2] The selective reduction of a carbonyl group in α,β-unsaturated compounds has been reported.[3] However, the transfer hydrogenation of the C=C bond in enones is relatively scarce.[4] The α,β-unsaturated ketones are widely used as substrates for a number of reactions, such as hydrogenation,[5] conjugate addition,[6] alkylation,[7] boration,[8] and epoxidation.[9] Specifically, 1,5-diaryl-1,4-pentadiene-3-ones and their analogs can be applied in biochemistry since these compounds have a conjugate system that is expected to be easily oxidized. Their general synthesis essentially involve an aldol condensation of the appropriate aromatic aldehyde with acetone in an alkaline medium at room temperature.[1a] Accordingly, 1,5-diaryl-1,4-pentadiene-3-ones are easily available either by isolation from natural products or by methods of classical organic synthesis.[1a-1e] Transfer hydrogenation of α,β-unsaturated ketones has been widely studied with a variety of different reducing agents. For example, the use of silanes,[10] alcohols,[11] water,[12] $NaBH_4$,[13] and Hantzsch esters[14] can promote reduction of α,β-unsaturated carbonyl compounds. However, although amines are one of the most versatile and inexpensive reagents in organic synthesis, relatively little attention has been paid to these compounds as hydrogen transfer reagents, and very few examples using amines in this type of reaction have been reported.[15-16] In 2011, Nakajima and co-workers demonstrated that the combination of bulky tertiary amines and trichlorosilyl triflate reduced α,β-unsaturated ketones to yield the corresponding saturated ketones in good yields.[15a] However, the conversion of 1,5-diaryl-1,4-pentadiene-3-ones substrates only provided partially reduced products in good

yields. Some other hydrogen transfer reagents containing N-H groups such as lithium amide, imidazoline, and thiazoline have been investigated in similar reduction reactions.[17-19] On the other hand, the conjugate reduction of α,β-unsaturated ketones using tosylhydrazine as a hydrogen source has also been investigated.[20] More recently, Chen *et al*. developed a reduction of chalcones to dihydrochalcones using tosylhydrazine as a hydrogen source.[20] This method does not require the use of transition metal; however, stoichiometric amounts of base (K_2CO_3) were used. Normally, the reaction between amines with α,β-unsaturated ketones resulted in α,β-unsaturated imines (1,2-addition of an amine to the corresponding carbonyl compound) or the competitive 1,4-addition product (Michael Addition).[21] Despite numerous studies on that chemistry, the reduction reaction of such enones using amines as hydrogen source has been scarcely studied. We envisaged the transfer hydrogenation from amines to α,β-enones as a feasible method of hydrogenation to yield saturated ketones and then with the use of additional amounts of amine to produce the corresponding saturated imines.[22] This tandem process requires of easily available starting materials and the produced saturated imines may be useful in the synthesis of anticancer and anti-inflammatory drugs, as well as in the preparation of building blocks for not naturally occurring α,β-amino acids.[23]

Transition metal catalyzed transfer hydrogenation of α,β-unsaturated ketones has attracted attention, and several reports have documented the use of organometallic complexes containing metals such as cobalt,[24] copper,[25] iridium,[26] palladium,[27] rhodium,[28] ruthenium,[29] and nickel [30] as catalysts in this type of reaction. Some of them present good regio-selectivity; for instance, palladium and rhodium were selective for the reduction of the C=C bonds of enones to yield saturated carbonyl compounds, and metals such as cooper and cobalt are particularly selective for carbonyl reduction (1,2-addition) to give allylic alcohols.[31] Recently, we reported the

synthesis and structure of the nickel complexes [{(dippe)Ni}n(η^2-Cα,Cβ-enone)] (dippe = 1,2-bis(di-isopropylphosphino)-ethane); n = 1,2; enone:1,5-diaryl-1,4-pentadiene-3-ones using complex ([(dippe)Ni(μ-H)]$_2$) with all of them containing symmetrical dienones, which were found to be an effective catalyst for the transfer hydrogenation and alkylation of α,β-unsaturated ketones that allow the selective reduction of C=C bonds and methanol which act as hydrogen donor and alkylating agent.[7a] Furthermore, our group recently disclosed the semihydrogenation and hydroamination of diphenylacetylene and 2-ethynylaniline using primary amines and aromatic N-heterocycles as hydrogen sources catalyzed by ([(dippe)Ni(μ-H)]$_2$).[16b] These findings prompted us to assess the activity of primary amines in the transfer hydrogenation of α,β-unsaturated ketones using a nickel catalyst to achieve this transformation. Herein, we report the reactivity of fluorinated 1,5-diaryl-1,4-pentadiene-3-ones with [(dippe)Ni(μ-H)]$_2$, which gives compounds of the type [{(P-P)Ni}n(η^2-Cα,Cβ-enone)] (P-P = bidentate phosphine ligand), and the catalytic activity of such compounds in the hydrogenation and subsequent condensation of α,β-unsaturated ketones using primary amines as hydrogen donors. A variety of substituents in the *ortho* and *para* position for the aryl ring were used to investigate the influence of steric and electronic effects in this tandem process.

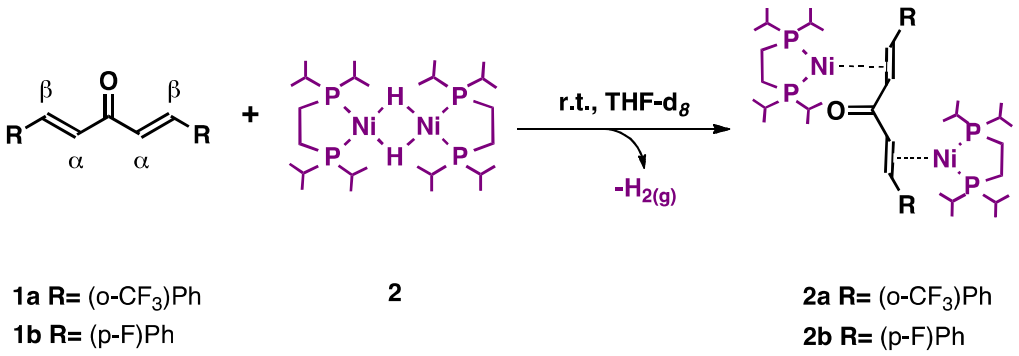
2. RESULTS AND DISCUSSION

2.1. Reactivity of Symmetrical Enones with [(dippe)Ni(μ-H)]$_2$

The reactivity of [(dippe)Ni(μ-H)]$_2$ (dippe = 1,2-bis(diisopropylphosphino)ethane) (**2**) in the presence of symmetrical enones was previously explored in our group (*vide supra*).[7a] In order to extend the scope of these results, particularly using aryl rings with *ortho*-CF_3 and *para*-F, i.e., to assess the reactivity of (**2**) in the presence of α,β-unsaturated enones containing electron

withdrawing groups in the aryl ring. In all cases, the reaction at room temperature of the nickel dimer with fluoro-enones (**1a**, $C_{19}H_{12}F_6O$ = 1,5-bis (2-(trifluoromethyl) phenyl) penta-1,4-dien-3-one and **1b**, $C_{17}H_{12}F_2O$ = 1,5-bis(4-fluorophenyl)-penta-1,4-dien-3-one) in THF-d_8 was fast and exhibited a color change from wine red to brown along with evolution of H_2 (**Scheme 1**). The isolated products contain two η^2-coordinated (dippe)Ni(0) moieties for each ligand to the Cα,Cβ- at the enone that were similar to those previously reported with nickel and palladium.[7a, 32]

Scheme 1. Reactivity **1a** and **1b** with **2**.



1a R= (o-CF_3)Ph
1b R= (p-F)Ph

2

2a R= (o-CF_3)Ph
2b R= (p-F)Ph

As depicted in **Scheme 1**, dinuclear complexes **2a-2b** were obtained as the main products on using 1 equiv of enone and 1 equiv of **2**. Nickel complexes **2a-2b** were fully characterized by NMR, X-ray crystallography, and EI^+-MS (see the Experimental Section). Complexes **2a-2b** typically display two broad doublet of doublets between 74-68 ppm with P-P coupling constants in the range of 51-57 Hz in their $^{31}P\{^1H\}$NMR spectra. The $^2J_{P\text{-}P}$ value is indicative of P bound to a Ni(0) center and is in agreement with a η^2-coordinated -Cα,Cβ-enone.[7a] In the $^{13}C\{^1H\}$ NMR spectrum, the corresponding signals for the coordinated carbons Cα,Cβ in **2a-2b** were assigned in the range of 60-45 ppm (the corresponding signals for the free ligand **1a-1b** were observed as singlets in the region of δ 142-130) with $^2J_{C\beta\text{-}P}$ = 15 Hz and $^2J_{C\alpha\text{-}P}$ = 15 Hz. The carbonyl signal in both compounds **2a-2b** are shifted to low field relative to the signals for the free enones **1a-1b**

(δ 189-188) and showed singlets in the range of 194 to 192 ppm. The ^{1}H NMR spectrum for the dinuclear complexes **2a-2b** showed the signals for the η^2-Cα, Cβ olefinic protons shifted to high field in the range of 4.4 - 4.2 ppm, while the olefinic protons of free enones typically resonate between 8.1 and 7.0 ppm.

A thermolysis consisting of increasing the temperature from 25 to 100 ºC for 7 days and monitoring complex **2a** in THF-d_8 shows the signals assigned to the original binuclear complex and a singlet assigned to [(dippe)$_2$Ni], δ 51.9, and light formation of metallic nickel (**Scheme 2**). Compound **2a** was also characterized in the solid state using single-crystal X-ray crystallography. The ORTEP representation of complex **2a** (**Figure 1**) confirmed the double nickel coordination to the enone moiety in a η^2-Cα,Cβ way The C-C bond length of the olefin in the unsaturated ketone is enlarged by 0.115 Å upon coordination in compound **2a** (1.445 Å) relative to the free ligand (1.330 Å). The C(15)-C(16) and C(18)-C(19) bond distances and the C(15)-Ni-C(16) and C(18)-Ni-C(19) bond angles of the 1,5-bis(2-(trifluoromethyl)phenyl)penta-1,4-dien-3-one ligand are similar to those observed previously in the [(dippe)$_2$Ni(η^2-(Cα,Cβ-DBA)] complex.[7a] The two metal moieties [(dippe)Ni(0)] are arranged in a mutually *trans* position with respect to the plane of ligand; each nickel center has a slightly distorted trigonal-planar geometry. An ORTEP representation of compound **2b** is included in the Supporting Information (See Figure S19). The planarity of the η^2-Cα,Cβ–1,5-bis (2-(trifluoromethyl) phenyl) penta-1,4-dien-3-one ligand is significantly affected by the coordination to nickel(0) atoms. In the supramolecular network, the intermolecular contacts of the van der Waals type F···H–C with $R_2^2(6)$ motif for C13–F(3)···H(46B)–C46–H(46A)···F(2), $D_1^1(7)$ motif for C3–H3···F(1) and $D_1^1(10)$ H(25B)···F(5)–C14 mainly lead to infinite chains aligned with a axis.

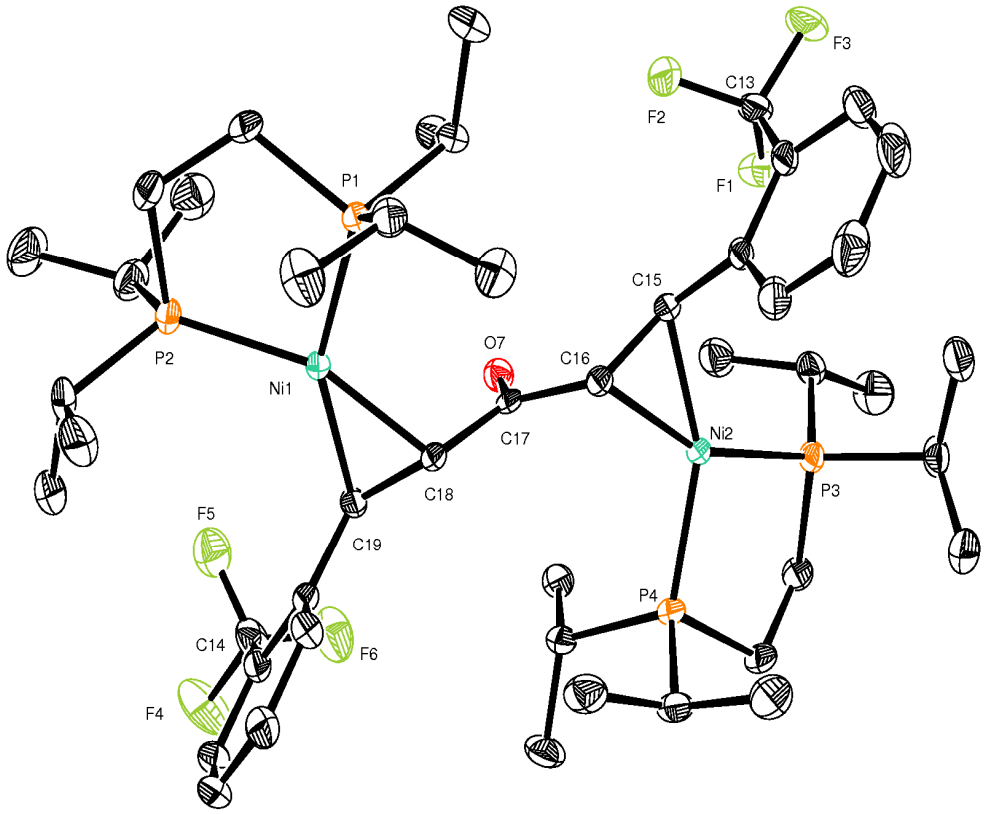
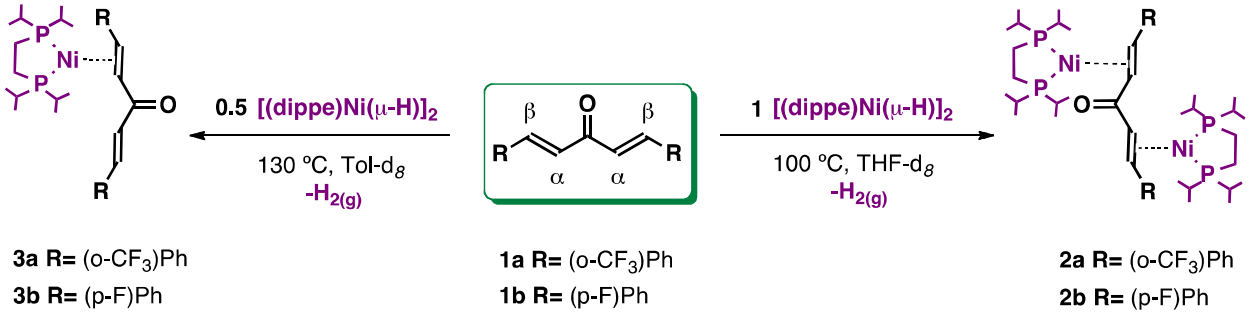


Figure 1. ORTEP drawing of **2a**, [{(dippe)Ni}$_2$(η^2-C_α ,C_β –$C_{19}H_{12}F_6O$)], showing 50% probability ellipsoids. Selected bond distances (Å): C(19)-C(18) 1.445(3), C(18)-C(17) 1.475(3), C(17)-C(16) 1.477(3), C(16)-C(15) 1.437(3), C(15)-Ni(2) 1.9860(19), Ni(2)-P(3) 2.1554(6), Ni(1)-C(19) 1.9933(19) Ni(1)-P(2) 2.1644(6). Selected bond angles (deg): C(16)-Ni(2)-P(4) 112.08(6), C(16)-Ni(2)-C(15) 42.54(8), P(4)-Ni(2)-P(3) 91.96(2), C(15)-Ni(2)-P(3) 112.91(6), C(19)-Ni(1)-P(2) 117.02(6), C(19)-Ni(1)-C(18) 42.75(8), C(18)-Ni(1)-P(1) 108.93(6), P(2)-Ni(1)-P(1) 91.44(2).

On the other hand, the reaction of complex **2** with fluorinated enones **1a-1b** in a 0.5:1 ratio dimer-to-enone at room temperature (RT) resulted in the formation of mononuclear complexes **3a-3b**. However, the dinuclear complexes **2a-2b** were still observed at RT. The use of Tol-d_8 instead of THF-d_8 allowed reaching a higher temperature to yield the mononuclear complexes **3a-3b** heating at 130 ºC for 15 hours (**Scheme 2**).

Scheme 2. Formation of mono- and binuclear [(dippe)Ni(η^2-Cα,Cβ-1,4-pentadiene-3-one)] complexes.



3a R= (o-CF_3)Ph
3b R= (p-F)Ph

1a R= (o-CF_3)Ph
1b R= (p-F)Ph

2a R= (o-CF_3)Ph
2b R= (p-F)Ph

The ^{1}H NMR spectra for the monometallic complexes **3a-3b** displayed signals shifted to high field assigned to the two protons in the η^2-Cα=Cβ coordination and displayed two doublets in the region of 6.3 ppm and 5.5 ppm with $^2J_{H\text{-}P}$ of 15 Hz. The $^{31}P\{^1H\}$ NMR spectra displayed two doublets located between δ = 75 - 68 with P-P coupling constants of 39 Hz, which is consistent with two non-equivalent phosphorous coordinated to a Ni(0). Single crystals for **3a** were obtained by cooling a Toluene-d_8 solution to -26 ºC. The corresponding ORTEP diagram of the mononuclear complex **3a** is shown in **Figure 2**.

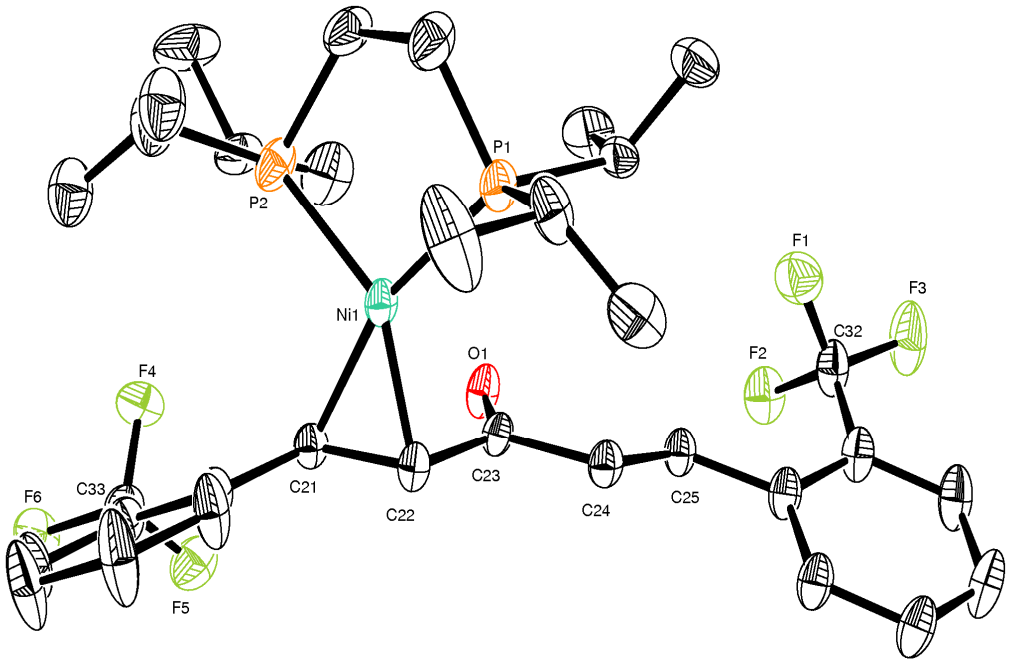


Figure 2. ORTEP drawing of **3a**, [(dippe)Ni(η^2-C_α,C_β –$C_{19}H_{12}F_6O$)], showing 50% probability ellipsoids. Selected bond distances (Å): C(25)-C(24) 1.330(6), C(22)-C(21) 1.421(5), C(22)-Ni(1) 1.984(4), Ni(1)-P(1) 2.1743(14), C(21)-Ni(1) 2.027(4), Ni(1)-P(2) 2.1548(13). Selected bond angles (deg): C(22)-Ni(1)-P(1) 119.39(12), C(22)-Ni(1)-C(21) 41.48(16), C(21)-Ni(1)-P(2) 107.52(12), P(1)-Ni(1)-P(2) 91.72(5).

As expected, the structure confirms a lengthening of the η^2-coordinated Cα=Cβ bond (1.421(5) Å) due to coordination to nickel compared with the free ligand Cα=Cβ bond (1.330(6) Å) and turns out to be intermediate between a typical C=C double bond (1.32 Å) and a single bond (1.54 Å).[33]

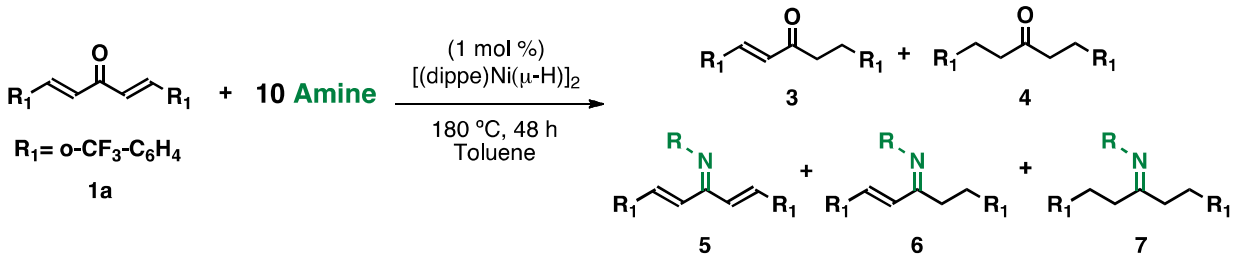
2.2. Catalytic Transfer Hydrogenation of Symmetrical Enones using Amines as Hydrogen Donors

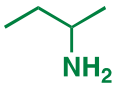
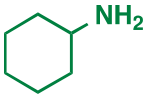
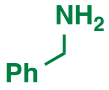
Considering the potential formation of dinuclear **2a** and mononuclear **3a** compounds in the reaction of **1a** with **2**, the transfer hydrogenation process was initially investigated using a variety of aliphatic amines. Thus, the treatment of **1a** with catalytic amount of **2** with an excess

of amine in toluene at 180 ºC for 48 h yielded the reduction products **3** and **4.** This and other selected results are summarized in **Table 1**. Compound **3** was obtained in low yield (14 %, entry 2) with the use of *n*-butylamine. That yield was improved by using benzylamine (32 %, entry 4). Additionally, with the use of benzylamine, a product derived from a dehydrogenation-transamination process was also produced (SI section, Figure S23).[16b, 34] The condensation products **5-7** were also produced (entries 1-4). Generally, α,β-unsaturated imines are prepared by 1,2-addition of an amine to the analogous α,β-unsaturated carbonyl compound. It is noteworthy that high amounts of saturated imine **7** were obtained (53 %, entry 4). The formation of saturated imine **7** produced by this method has been relatively unexplored.[21, 24b]

A complete conversion of the starting material with the use of cyclohexylamine and benzylamine was achieved (entries 3-4) but only with moderate selectivity. Therefore, we decided to investigate the effect of solvents and other reaction conditions in this tandem process and to extend the scope to other α,β-unsaturated ketones.

Table 1. Reduction of 1a by [(dippe)Ni(μ-H)]$_2$ Using Amines [a]



Entry	Amine	Conv 1a (%)	Yield (%) [b]				
			3	4	5	6	7
1		61	21	-	-	8	32
2		74	42	14	18	-	-
3		100	-	22	10	35	33
4		100	-	32	-	15	53

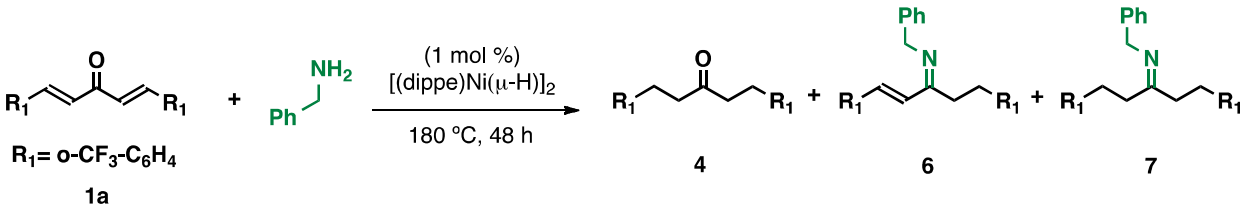
[a] Reaction Conditions: **1a** (0.15 mmol), **Amine** (1.5 mmol), **2** (1 mg, 1.55*10^{-3} mmol), toluene (3 mL), 180 ºC, 48 h. [b] All yields were measured by GC-MS.

The effect of the solvent and amount of benzylamine were assessed; the main results for these experiments are summarized in **Table 2.** As shown, initial studies were carried out at 180 ºC, 48 h, and using 1 mol % of catalytic precursor **2**. All reactions produced the saturated imine **7** in low to high yields (5% to 80 %, entries 1-8) along with low yields of saturated ketone **4** (9 % to 32 %, entries 1-8). Toluene was again a useful solvent for the hydrogenation and condensation of

enone **1a**; however, we found that decreasing the amounts of benzylamine to 100 equivalents in Toluene produced a low yield of saturated products (entry 1). When the amounts of benzylamine were increased to 500 equivalents (entry 2), a better yield of saturated imine **7** was produced (68 %, entry 2). Note that the catalytic conversion and yield of saturated products are enhanced with a more polar solvent such as ethanol (entry 5) to produce **7** in a good yield (80 %, entry 5). Nevertheless, the yield of saturated product **7** decreases dramatically when increasing the amount of amine (22 %, entry 6) probably due to coordination of this amine to nickel.[35] Additionally, the use of alcohols as a hydrogen source for the reduction of α,β-unsaturated enones is well known[11] where they are oxidized to the corresponding aldehydes.[7a] In these experiments, the crude was analyzed by ^{1}H NMR and GC-MS, acetaldehyde was not detected.

Thus, ethanol was chosen as the optimal solvent since the reaction in this solvent led to complete conversion in 48 h and exhibited an improved selectivity of **7** (80 %, entry 5). Other solvents, (e.g., THF, water, or neat benzylamine) proved to be less efficient in this reaction (entries 3, 4 and 8); under these conditions, the products **4**-**7** were obtained in low yields.

Table 2. Optimization of Reaction Conditions in Reduction and Condensation of Enone 1a with Benzylamine [a]

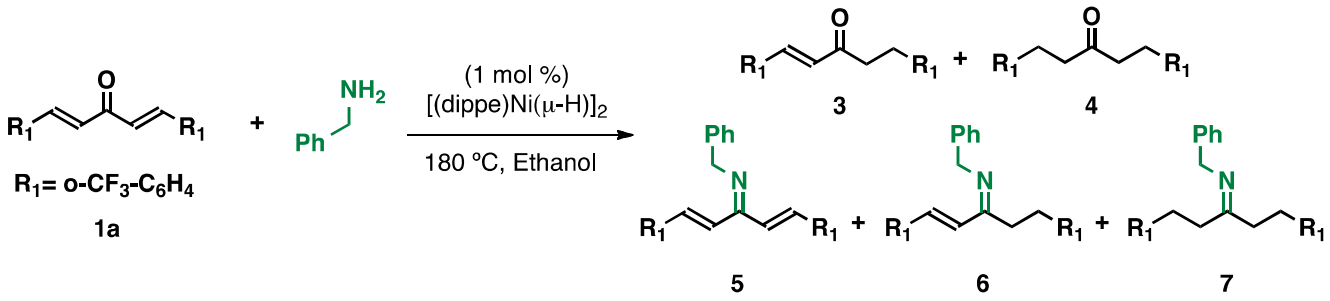


Entry	Solvent	Equivalents Amine	Conv 1a [d] (%)	Yield (%) [b]		
				4	6	7
1	Toluene	100	14	9	-	5
2	Toluene	500	100	11	21	68
3	THF	500	100	-	-	33
4	Water	500	94	25	-	16
5	Ethanol	500	100	14	6	80
6	Ethanol	1000	100	13	10	22
7	Toluene	1000	100	32	15	53
8 [c]	Neat	10000	100	-	8	29

[a] Reaction Conditions: **1a** (0.15 mmol), **2** (1 mg, $1.55*10^{-3}$ mmol), **Solvent.** (3 mL), 180 ºC, 48 h. [b] All yields were measured by GC-MS. [c] Benzylamine (2 mL). [d] Complete conversion of **1a** is calculated by summing **4, 6, 7** and additional product **5** (α,β-unsaturated imine).

We further investigated the formation of saturated products to understand the relative rates and selectivity of saturated ketone **4** *vs.* saturated imine **7** (**Table 3**). Simple reaction time monitoring proved to be useful for this purpose (**Table 3**, entries 1-3). Formation of the saturated ketone reached a maximum within 36 h (45%, entry 2); at this time, the saturated imine formation is low (17%, entry 2). At 48 h, the conversion of **1a** was complete, but the yield of **4** was significantly reduced (14%, entry 3), while the yield of saturated imine **7** was increased to 80% (entry 3). Therefore, we propose that **1a** was reduced first to produce **4** by benzylamine acting as hydrogen source, and subsequently the condensation of **4** was carried out to yield the saturated imine **7**.

Table 3. Monitoring Saturated Products Formation: Effect of the Time Reaction [a]

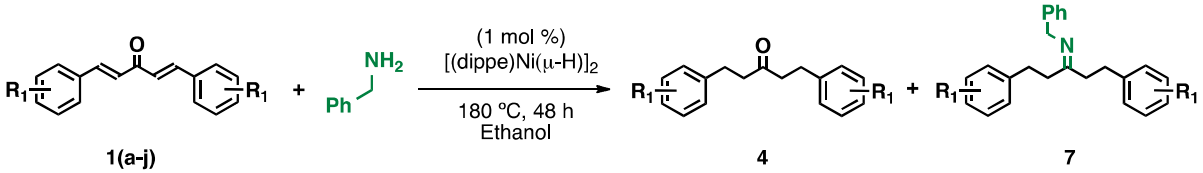


Entry	Time (h)	Conv 1a (%)	Yield (%) [b]				
			3	4	5	6	7
1	24	97	15	37	19	5	21
2	36	100	-	45	26	12	17
3[c]	48	100	-	14	-	6	80

[a] Reaction Conditions: **1a** (0.15 mmol), Benzylamine (0.77 mmol), **2** (1 mg, $1.55*10^{-3}$ mmol), ethanol (3 mL), 180 ºC. [b] All yields were measured by GC-MS. [c] Mercury-drop test using the same reaction conditions resulted in no inhibition.

With the optimized conditions at hand, we next assessed the use of other substituted α,β-enones having a variety of different substituents. α,β–Enones were prepared by the reported procedures[1a-1e] and selected NMR and GC-MS for each substrate are available in the SI Section. The reactivity shown by these substrates in the transfer hydrogenation is summarized in **Table 4**. All of them achieve total conversion but with different selectivity. For instance, *o*-substituted derivatives exhibit a better yield in the transfer hydrogenation and condensation tandem processes to yield the saturated imine **7** with moderate to good yields (62 % - 91 %) (entries 1, 3, 5-8, **Table 4**). The products derived only from a transfer hydrogenation process to yield the saturated ketones were particularly favored having enones bearing the electro-donating group (**1i** and **1j**) CH_3 and OCH_3 at the *para* position (Entries 9-10). Note that the reaction of DBA (**1h**) with benzylamine and catalytic amounts of $[(dippe)Ni(\mu\text{-}H)]_2$ yield the corresponding saturated imine **7** in high yield 91 %.

Table 4. Substrate Scope for the Transfer Hydrogenation and Condensation of Enones [a]



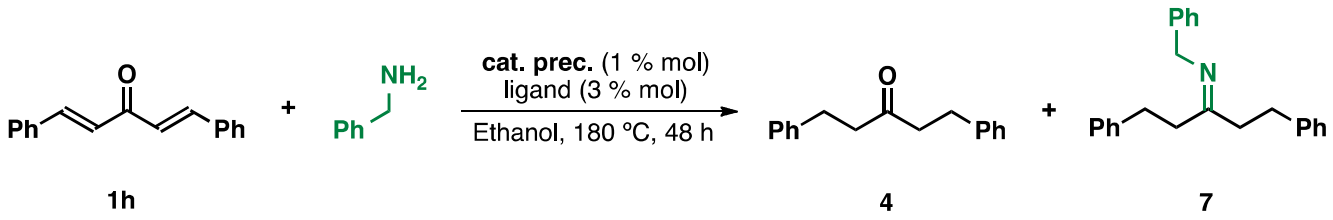
Entry	Substrate	R_1	Conv 1 [c] (%)	Yield (%) [b]	
				4	7
1	**1a**	*o*-CF_3	100	14	80
2	**1b**	*p*-F	100	36	40
3	**1c**	*o*-F	100	32	68

4	**1d**	*p*-CF_3	100	25	36
5	**1e**	*o*-CH_3	100	38	62
6	**1f**	*o*-OCH_3	100	36	64
7	**1g**	*o*-Br	100	21	78
8	**1h**	H	100	8	91
9	**1i**	*p*-CH_3	100	51	48
10	**1j**	*p*-OCH_3	100	90	10

[a] Reaction Conditions: **1a** (0.15 mmol), Benzylamine (0.77 mmol), **2** (1 mg, $1.55*10^{-3}$ mmol), ethanol (3 mL), 180 ºC, 48 h. [b] All yields were measured by GC-MS. [c] Complete conversion of **1(a-j)** is calculated by summing **4, 7** and additional product **5** (α,β-unsaturated imine).

The effect of the ancillary ligand in the activity and selectivity of this tandem process was assessed (see **Table 5**). In general, the use of bidentated σ-donor ligands allowed to selectively producing **7** (entries 1-4); however, the steric hindrance of the terbutyl and cyclohexyl groups does not compete in terms of selectivity with isopropyl groups. Interestingly, when the reaction was carried out without a catalytic precursor, the product **7** was produced in very poor yield and with low conversion of the starting material (entry 7). Thus, a tandem hydrogenation and condensation of α,β-enone **1h** with benzylamine was successfully achieved with $[(dippe)Ni(\mu\text{-}H)]_2$.

Table 5. Ancillary Ligand Screening [a]



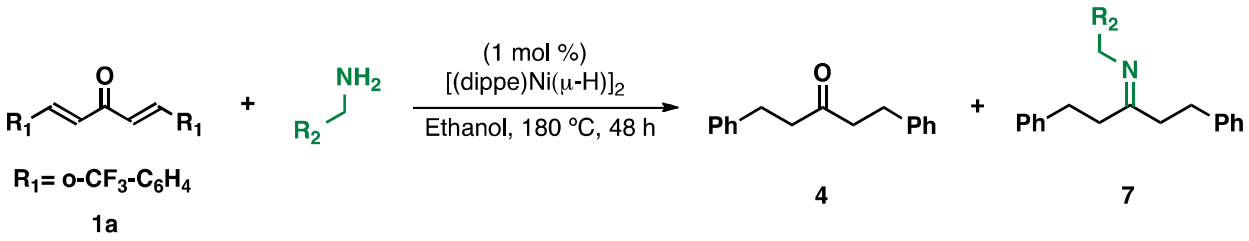
Entry	Catalytic Precursor	Ligand (P-P)	Conv 1h [c] (%)	Yield (%) [b] 4	7
1	$[(dippe)Ni(\mu\text{-}H)]_2$	None	100	9	91
2	$[(dcype)Ni(\mu\text{-}H)]_2$	None	100	45	55
3	$[(dtbpe)Ni(\mu\text{-}H)]_2$	None	100	27	63
4	$[(dippe)NiCl_2]$	None	100	35	65
5	$Ni(COD)_2$	dppe	100	34	51
6	$Ni(COD)_2$	dippe	100	19	11
7	None	None	51	-	20

[a] Reaction Conditions: **1a** (0.15 mmol) , Benzylamine (0.77 mmol), **Cat. Prec.** (1 mol %), **Ligand** (3 mol %), ethanol (3 mL), 180 ºC, 48 h. [b] All yields were measured by GC-MS. [c] Complete conversion of **1h** is calculated by summing **4**, **7** and additional product **5** (α,β-unsaturated imine).

Since benzylamines turned out to be the useful reagents in the transfer hydrogenation (**Table 1**), we decided to use a variety of mono-substituted benzylamines including electron-donating and

electron-withdrawing groups using the optimized reaction conditions (500 equiv of amine, 100 equiv of **1a**, 1 mol % of **2** in ethanol at 180 ºC). The main results are summarized on **Table 6**. As expected, benzylamine produced **7** in good yield (80 %, entry 1). Using *ortho*-substituted benzylamines (entries 2-5), the reaction afforded the desired products **4** and **7** with high yields (54 % to 86 %). Unfortunately, the use of *para*-substituted benzylamines (entries 6-8) gave poor product selectivity. A mechanistic proposal for this process is presented in the SI section.

Table 6. Scope of Amines in Transfer Hydrogenation and Condensation of 1a [a]



Entry	R_2	Conv 1a [c] (%)	Yield (%) [b]	
			4	7
1	C_6H_5	100	14	80
2	*o*-OCH_3-C_6H_4	100	24	76
3	*o*-CH_3-C_6H_4	100	45	54
4	*o*-CF_3-C_6H_4	100	13	86
5	*o*-F-C_6H_4	100	43	57

6	*p*-CH_3-C_6H_4	100	13	14
7	*p*-F-C_6H_4	100	55	19
8	*p*-CF_3-C_6H_4	100	10	7

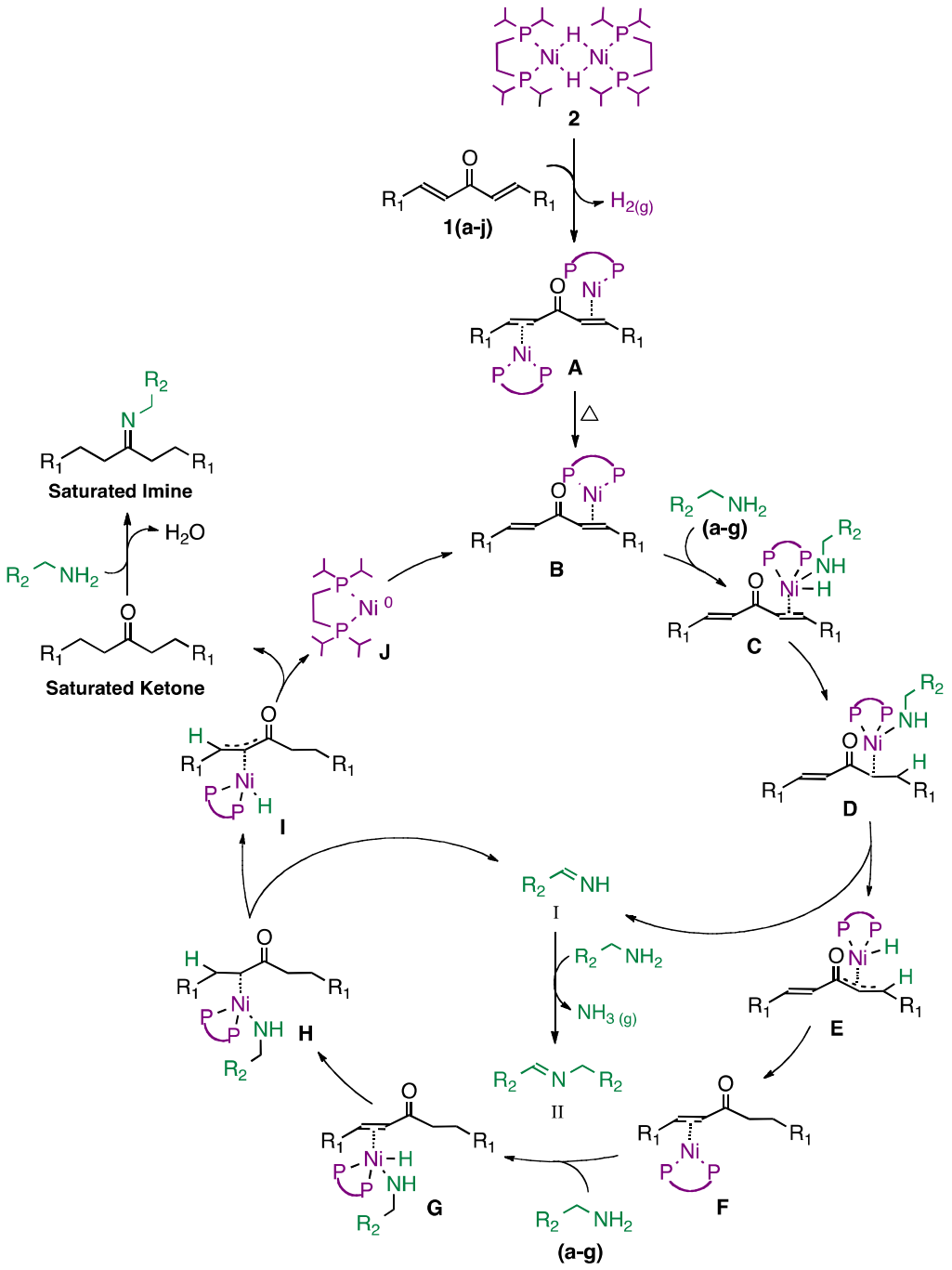
[a] Reaction Conditions: **1a** (0.15 mmol), Benzylamines (0.77 mmol), **2** (1 mg, $1.55*10^{-3}$ mmol), ethanol (3 mL), 180 ºC, 48 h. [b] All yields were measured by GC-MS. [c] Complete conversion of **1a** is calculated by summing **4, 7** and additional product **5** (the corresponding α,β-unsaturated imine).

2.3. Catalytic Proposal.

A mechanistic proposal for this tandem process is illustrated in **Scheme 3**, to explain the initial transfer hydrogenation of α,β-Enones to the corresponding saturated ketones and subsequent condensation with primary benzylamines we propose an initial step reacting the corresponding dienones **1(a-j)** with **2** to yield the complex **A**. Dinuclear complex **A** can be converted to active catalyst **B** by heating *via* the sequence showed in **Scheme 2**, followed by the oxidative addition of benzylamines **(a-g)** and hydride transfer to nickel complex **B** to give intermediate **C**. Then a hydride addition to the β-position produce species **D**. □□□□nickel □□□□□□□ **D** undergo β-hydride elimination to produce imine formation (**I**) and enolization to produce **E**. It is known that, an amine, once oxidized to the imine by hydrogen transfer, reacts with another equivalent of the substrate amine obtaining a transamination product with liberation of ammonia.[34] In the mechanism, one equivalent imine **I** or **II**. The resulting Ni-enolate **E** underwent hydride addition to α-position in α,β-unsaturated ketones and followed by a reductive elimination to give the

corresponding nickel-enone complex **F**. The secondary transfer hydrogenation occurs in the same way to initial steps **C** to **E** followed by a reductive elimination to give saturated ketone. The 1,2-addition of benzylamines to saturated ketones gave the corresponding saturated imines.

Scheme 3. Proposed Catalytic Cycle



3. CONCLUSION

We have demonstrated that [(dippe)Ni(μ-H)]$_2$ (**2**) was an effective catalytic precursor for the transfer hydrogenation of α,β-unsaturated ketones using benzyl- amines as hydrogen donors to afford saturated ketones in low to moderate yields. Furthermore, the 1,2-addition of benzylamines to the produced saturated ketones allowed the formation of saturated imines in good to excellent yields in a tandem process. These features, along with the tolerance to a variety of *ortho* and *para* substituents in aromatic enones and benzylamines, extends the scope of the current method to the synthesis of saturated imines.

4. EXPERIMENTAL SECTION

Unless otherwise noted, all manipulations were performed using standard Schlenk techniques in an inert-gas/vacuum double manifold or under an argon atmosphere (Praxair 99.998) in an MBraun glovebox (<1 ppm H_2O and O_2). All liquid reagents were purchased as reagent grade and were degassed before use. The α,β-Unsaturated ketones **1h-1j** were purchased from Aldrich and were stored in a glovebox for their further use. Compounds **1a-1g** were prepared by an aldol condensation, following the method of Masuda *et al*.[1a] The nickel (I) complexes, [(P-P)Ni(μ-H)]$_2$ (P-P = chelating phosphine ligand), were prepared from a *n*-hexane slurry of [(P-P)NiCl$_2$][36a] using Super-Hydride (LiHBEt$_3$), according to the reported procedure. [36b] The solvents were dried using standard techniques and stored in the glovebox before use. Deuterated solvents were purchased from Cambridge Isotope Laboratories and were stored under 4 Å molecular sieves for 24 h before use. NMR spectra were recorded at room temperature on a 300 MHz Varian Unity spectrometer unless otherwise noted. ^{1}H NMR spectra (δ parts per million) are reported relative

to the residual protio-solvent. $^{13}C\{^1H\}$ spectra give the characteristic carbon signal of each solvent. $^{31}P\{^1H\}$ NMR chemical shifts (δ parts per million) are reported relatively to external 85% H_3PO_4. ^{19}F NMR chemical shifts (δ parts per million) are reported relatively to external trifluoroacetic acid. Coupling constants (*J* values) are given in Hz. GC-MS determinations were performed using an Agilent Technologies G3171A equipped with a column: 5 % phenylmethylsilicone, 30 m * .25 mm * .25 μm. ^1H and $^{13}C\{^1H\}$ NMR spectra of the reduction products were obtained in $CDCl_3$. An Oxford Diffraction Gemini "A" diffractometer with CCD area detector ($\lambda_{Mo\ K\alpha}$ = 0.71073 Å) was used for X-ray structure determinations. Catalytic experiments were carried out in a 100 mL stainless steel Parr, T315SS reactor. Elemental analyses (EAs) were also performed by USAI-UNAM using a PerkinElmer microanalizer 2400. EAs of pure compounds showed variable inconsistencies due to their high oxygen sensitivity and were not reported; however, all of them display satisfactory MS-EI^+. Mass spectrometry determinations (MS-EI^+) of pure compounds were performed by USAI-UNAM using a Thermo-Electron DFS.

4.1. Preparation [{(dippe)Ni}$_2$(η^2-Cα,Cβ-$C_{19}H_{12}F_6O$)] (2a): The reaction of $C_{19}H_{12}F_6O$ = 1,5-bis(2-(trifluoromethyl)phenyl)penta-1,4-dien-3-one **1a** (0.081 mmol, 0.030 g) with [(dippe)Ni(μ-H)]$_2$ **2** (0.081 mmol, 0.0521 g) in THF-d_8 (1mL) yielded dinuclear Ni(0) complex [{(dippe)Ni}$_2$(η^2-Cα,Cβ-$C_{19}H_{12}F_6O$)] (**2a**). Immediate effervescence due to reductive elimination of H_2 was observed during mixing. The resulting solution was analyzed by NMR spectroscopy: ^1H NMR (300 MHz, THF-d_8, r.t.): δ = 7.36 (d, J_{H-H} = 9 Hz, H(**f**), H(**f'**), aromatic), 7.22 (d, J_{H-H} = 9 Hz, H(**c**), H(**c'**), aromatic), 7.12 (t, J_{H-H} = 9 Hz, H(**d**), H(**d'**), aromatic), 6.87 (t, J_{H-H} = 9 Hz, H(**e**), H(**e'**), aromatic), 4.44 (m, J_{H-P} = 6 Hz, H(**b**), H(**b'**), CH-olefinic), 4.31 (m, J_{H-P} = 6 Hz, H(**a**), H(**a'**), CH-olefinic), 2.5-0.5 (m, *i*Pr CH, CH_2, CH_3). $^{31}P\{^1H\}$ NMR (121.32 MHz, THF-d_8,

r.t.): δ = 74.0 (dd, J_{P-P} = 51 Hz, J_{C-P} = 7.27 Hz), 69.0 (dd, J_{P-P} = 51 Hz, J_{C-P} = 7.27 Hz). $^{13}C\{^1H\}$ NMR (75.36 MHz, THF-d_8, r.t.): δ = 193.4 (s, C(**a**), C=O), 150.4 (s, C(**d**), C(**d'**), C-aromatic), 132.5 (s, C(**f**), C(**f'**), CH-aromatic), 132.2 (s, C(**g**), C(**g'**), CH-aromatic), 131.3 (s, C(**e**), C(**e'**), CH-aromatic), 120.8 (t, J_{C-F} = 30.89 Hz, C(**i**), C(**i'**), C-aromatic), 150.4 (quadruplet, J_{C-F} = 5.27 Hz, C(**h**), C(**h'**), CH-aromatic), 115.76 (t, J_{C-F} = 274.3 Hz, C(**j**), C(**j'**), CF_3-aromatic), 62.4 (d, J_{C-P} = 15 Hz, C(**c**), C(**c'**), CH-olefinic), 44.6 (d, J_{C-P} = 15 Hz, C(**b**), C(**b'**), CH-olefinic), 30.0 – 17.0 (m, iPr, CH, CH_2, CH_3). ^{19}F NMR (282 MHz, THF-d_8, r.t.): δ = -60.2 (s, F(**a**), CF_3-aromatic) [MS-EI$^+$, *m/z* (%) 1011 (15%)]. Suitable crystals for single-crystal X-ray studies for compound **2a** were grown from a concentrate solution in THF-d_8 at -30 ºC.

4.2. Preparation [{(dippe)Ni}$_2$(η^2-Cα,Cβ-$C_{17}H_{12}F_2O$)] (2b): Similar to the preparation of compound **2a** (vide supra), the reaction between $C_{17}H_{12}F_2O$ = 1,5-bis(4-fluorophenyl)penta-1,4-dien-3-one **1b** (0.199 mmol, 0.054 g) and [(dippe)Ni(μ-H)]$_2$ **2** (0.199 mmol, 0.0128 g) in THF-d_8 (1mL) yielded dinuclear Ni(0) complex [{(dippe)Ni}$_2$(η^2-Cα,Cβ-$C_{17}H_{12}F_2O$)] (**2b**). Immediate effervescence due to reductive elimination of H_2 was observed during mixing. The resulting solution was analyzed by NMR spectroscopy: (300 MHz, THF-d_8, r.t.): δ = 7.10 (t, J_{H-H} = 6 Hz, H(**c**), H(**c'**), aromatic), 6.75 (t, J_{H-H} = 9 Hz, H(**d**), H(**d'**), aromatic), 4.41 (d, J_{H-P} = 12 Hz, H(**b**), H(**b'**), CH-olefinic), 4.30 (d, J_{H-P} = 15 Hz, H(**a**), H(**a'**), CH-olefinic), 2.4-0.1 (m, *i*Pr CH, CH_2, CH_3). $^{31}P\{^1H\}$ NMR (121.32 MHz, THF-d_8, r.t.): δ = 72.6 (dd, J_{P-P} = 57 Hz, J_{C-P} = 8.49 Hz), 71.2 (dd, J_{P-P} = 57 Hz, J_{C-P} = 8.49 Hz). $^{13}C\{^1H\}$ NMR (75.36 MHz, THF-d_8, r.t.): δ = 190.56 (s, C(**a**), ^{13}C=O), 146.46 (s, C(**g**), C-aromatic), 130.88 (s, C(**d**), C(**d'**), CH-aromatic), 126.22 (s, C(**e**), C(**e'**), CH-aromatic), 115.53 (s, C(**f**), C(**f'**), CH-aromatic), 60.66 (d, J_{C-P} = 12.8 Hz, C(**c**), C(**c'**), CH-olefinic), 49.18 (d, J_{C-P} = 20.34 Hz, C(**b**), C(**b'**), CH-olefinic), 30.0 – 15.0 (m, iPr,

CH, CH_2, CH_3). ^{19}F NMR (282 MHz, THF-d_8, r.t.): δ = -124.28 (s, F(**a**), F-aromatic) [MS-EI$^+$, *m/z* (%) 911 (10%)]. Slow evaporation of THF-d_8 at -26 ºC in the drybox allowed the crystallization of the pure product.

4.3. Preparation [(dippe)Ni(η^2-Cα,Cβ-$C_{19}H_{12}F_6O$)] (3a): The reaction of $C_{19}H_{12}F_6O$ = 1,5-bis(2-(trifluoromethyl)phenyl)penta-1,4-dien-3-one **1a** (0.081 mmol, 0.030 g) with [(dippe)Ni(μ-H)]$_2$ **2** (0.0405 mmol, 0.0261 g) in THF-d_8 (1mL) yielded mononuclear Ni(0) complex [{(dippe)Ni}(η^2-Cα,Cβ-$C_{19}H_{12}F_6O$)] (**2b**). Immediate effervescence due to reductive elimination of H_2 was observed during mixing. The resulting solution was analyzed by NMR spectroscopy: (300 MHz, THF-d_8, r.t.): δ = 7.65 (d, J_{H-H} = 6 Hz, H(**f**), H(**f'**), aromatic), 7.57 (d, J_{H-H} = 6 Hz, H(**c**), H(**c'**), aromatic), 7.42 (t, J_{H-H} = 9 Hz, H(**d**), H(**d'**), aromatic), 7.26 (t, J_{H-H} = 9 Hz, H(**e**), H(**e'**), aromatic), 6.13 (d, J_{H-P} = 15 Hz, H(**b**), H(**b'**), CH-olefinic), 5.71 (d, J_{H-P} = 12 Hz, H(**a**), H(**a'**), CH-olefinic), 2.5-0.1 (m, *i*Pr CH, CH_2, CH_3). $^{31}P\{^1H\}$ NMR (121.32 MHz, Tol-d_8, r.t.): δ = 75.0 (d, J_{P-P} = 39 Hz), 73.5 (d, J_{P-P} = 39 Hz). [MS-EI$^+$, *m/z* (%) 690 (10%)]. Crystals of **3a** were obtained from Tol-d_8 at -26 ºC in the drybox and allowed the crystallization of the pure product.

4.4. Preparation [(dippe)Ni(η^2-Cα,Cβ-$C_{17}H_{12}F_2O$)] (3b). Similar to the preparation of compound **2b** (vide supra), the reaction between $C_{17}H_{12}F_2O$ = 1,5-bis(4-fluorophenyl)penta-1,4-dien-3-one **1b** (0.199 mmol, 0.054 g) and [(dippe)Ni(μ-H)]$_2$ **2** (0.199 mmol, 0.0128 g) in THF-d_8 (1mL) yielded mononuclear Ni(0) complex [(dippe)Ni(η^2-Cα,Cβ-$C_{17}H_{12}F_2O$)] (**3b**). Immediate effervescence due to reductive elimination of H_2 was observed during mixing. The resulting solution was analyzed by NMR spectroscopy: (300 MHz, THF-d_8, r.t.): δ = 7.41 (t, J_{H-H} = 6 Hz, H(**c**), H(**c'**), aromatic), 6.96 (t, J_{H-H} = 9 Hz, H(**d**), H(**d'**), aromatic), 5.91 (d, J_{H-P} = 12 Hz, H(**b**),

H(**b'**), CH-olefinic), 5.70 (d, J $_{H-P}$ = 15 Hz, H(**a**), H(**a'**), CH-olefinic), 2.3-0.1 (m, *i*Pr CH, CH_2, CH_3). $^{31}P\{^1H\}$ NMR (121.32 MHz, THF-d_8, r.t.): δ = 76.2 (d, J $_{P-P}$ = 41 Hz), 73.5 (d, J $_{P-P}$ = 41 Hz). [MS-EI$^+$, *m/z* (%) 591 (40%)].

4.5. Preparation 1,5-bis(2-(trifluoromethyl)pentan-3-one. The reaction of $C_{19}H_{12}F_6O$ = 1,5-bis(2-(trifluoromethyl)phenyl)penta-1,4-dien-3-one **1a** (0.15 mmol, 0.057 g), C_7H_9N = benzylamine (0.77 mmol, 0.0 g) and [(dippe)Ni(μ-H)]$_2$ (0.0015 mmol, 0.001 g) in ethanol, (0.3 mL), was prepared in the drybox. The resulting mixture (yellow solution) was stirred at 180 ºC for 2 days (Entry 5, Table 2). The product (yellow oil) was purified in silica gel TLC (10% Hexane in THF) to give 1,5-bis(2-(trifluoromethyl)pentan-3-one **4**. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.51 (d, *J* $_{H-H}$ = 9 Hz, H(**f**), H(**f'**), aromatics), 7.36 (t, *J* $_{H-H}$ = 9 Hz, H(**d**), H(**d'**), aromatic), 7.20 - 7.14 (m, J $_{H-H}$ = 9 Hz, H(**c**), H(**c'**), H(**e**), H(**e'**), aromatic), 2.99 (t, J $_{H-H}$ = 9 Hz, H(**b**), H(**b'**), CH-olefinic), 2.62 (t, J $_{H-H}$ = 9 Hz, H(**a**), H(**a'**), CH-olefinic). $^{13}C\{^1H\}$ NMR (75.36 MHz, THF-d_8, r.t.): δ = 208.1 (s, C(**a**), ^{13}C=O), 139.98 (s, C(**d**), C-aromatic), 132.19 (s, C(**f**), C(**f'**), CH-aromatic), 131.42 (s, C(**e**), C(**e'**), CH-aromatic), 128.54 (t, J $_{C-F}$ = 29.4 Hz C(**i**), C(**i'**), CH-aromatic), 126.60 (s, C(**g**), C(**g'**), CH-aromatic), 126.40 (quadruplet, J $_{C-F}$ = 5.27 Hz C(**h**), C(**h'**), CH-aromatic), 122.98 (t, J $_{C-F}$ = 273.5 Hz C(**j**), C(**j'**), CF_3-aromatic), 44.66 (s, C(**b**), C(**b'**), CH-pentan-3-one), 26.91 (s, C(**a**), C(**a'**), CH-pentan-3-one). ^{19}F NMR (282 MHz, THF-d_8, r.t.): δ = -59.7 (s, F(**a**), CF_3-aromatic).

4.6. Catalytic Transfer Hydrogenation. All reactions were made in a 150 mL Schlenk flask fitted with a Rotaflo valve, typically charged with [(dippe)Ni(μ-H)]$_2$ (1 mg, 1.55*10^{-3} mmol), and the corresponding α,β-unsaturated ketone: $C_{19}H_{12}F_6O$ = 1,5-bis(2-(trifluoromethyl)phenyl)-penta-1,4-dien-3-one **1a** (57.35 mg, 0.155 mmol), Benzylamine **(a)** (82.5 mg, 0.77 mmol),

dissolved in ethanol (3 mL). The resulting mixtures were heated with vigorous stirring at 180 ºC and durations indicated in the Table 3. After that duration, the Schlenk flask was opened in a well-vented hood prior to workup. Orange or yellow colored solutions were formed. These were filtered over Celite and then analyzed by CG-MS.

4.7. Mercury Drop Test. Following the procedure described in section 2.2, **Table 3**, entry 3, the same reaction was prepared, and one drop of elemental Hg was added to the reaction mixture. At the end of each run, the corresponding solution was filtered over Celite and analyzed by CG-MS.

4.8. X-ray Structure Determination. The crystals for compounds **2a-2b** and **3a** were first cryoprotected using Paratone-N and mounted on glass fibers; then, the crystals were immediately cooled at 130 K using Cryojet cryostream (Oxford Cryosystems device). Diffraction data were collected on an Oxford Diffraction Gemini diffractometer with a CCD-Atlas area detector using a radiation source graphite monochromator, $\lambda_{Mo\ K\alpha}$ = 0.71073 Å. CrysAlisPro and CrysAlis RED software packages[37a] were used for data collection and data integration. The double pass method of scanning was used to exclude any noise. The collected frames were integrated by using an orientation matrix determined by using analytical numeric absorption correction[37b] using a multifaceted crystal model based on expressions upon the Laue symmetry using equivalent reflections.

Structure solution and refinement were carried out with the program(s) SHELXS-2013 and SHELXL-2013[37c]; for molecular graphics, the program ORTEP-3 for Windows[37d] was used, and to prepare material for publication, the software WinGX was used. [35e] Full-matrix least-squares refinement was carried out by minimizing $(F_o^2 - F_c^2)^2$. All non-hydrogen atoms were refined anisotropically. H positions were refined as riding on their parent atoms with C-H = 0.95-1.00 Å

and U_{iso} (H) = 1.2Ueq (C) for aromatic, methylene and methyne groups, and 1.5Ueq (C) for methyl group. Crystal data and experimental details of the structure determination are listed in the Supporting Information (see Table S1 to Table S9 at SI section).

The crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1407778-1407780. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223-336-033, e-mail: deposit@ccdc.cam.ac.uk).

ASSOCIATED CONTENT

Supporting Information available. Includes complete experimental procedures, ORTEP drawings, NMR spectra, GC-MS determinations of all products and a mechanistic proposal.

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ACKNOWLEDGMENTS

We thank CONACyT (0178265) and PAPIIT-DGAPA-UNAM (IN-201010) for their financial support to this work. N.C.-B. thanks CONACyT for a graduate studies grant. Also, we thank Dr. Alma Arévalo for her technical support.

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TOC entry

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