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PAPER

An efficient one pot transfer hydrogenation and N-alkylation of quinolines with alcohols mediated by Pd/C/Zn†

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A Pd/C/Zn mixture with alcohols has been revealed to be an efficient transfer hydrogenation system to quinolines. Furthermore, the metals mixture is able to activate alcohols as N-alkylating agents in a hydrogen autotransfer process. 1,2,3,4-Tetrahydroquinolines and N-alkylated tetrahydroquinolines from quinolines have been obtained with excellent yields in one step.

Introduction

Hydrogenation of organic molecules is one of the processes most used in the synthetic organic chemistry industry. The most common methodology for this process is catalytic hydrogenation, either under homogeneous[1] or heterogeneous[2] catalysis, involving molecular hydrogen and a transition metal. However, despite being a reaction of proven efficiency, it presents a large drawback related with the handling of hydrogen gas (flammable and explosive). For this reason, the scientific community has been working hard in catalytic transfer hydrogenation,[3] which avoids the use of molecular hydrogen in favor of hydrogen donors (alcohols, diimides, amines, hydrocarbons or formic acid). Ruthenium,[3d,e,4] rhodium,[5] iridium,[6] and nickel,[7] are the metals most frequently used as catalysts. Organocatalytic transfer hydrogenation using dihydropyridines as hydride donors and Brønsted acid catalysis has also been intensively investigated.[8]

The transfer hydrogenation field also includes a very interesting approach to the N-alkylation reaction *via* hydrogen autotransfer,[9] or borrowing hydrogen,[10] which allows alkylation of amines using alcohols or amines and a catalyst. This strategy[9–11] avoids the use of alkylating agents, which present large selectivity and toxicity problems, specially at the industrial scale.[12]

There are some examples in which palladium catalyzes hydrogen transfer reactions,[3b,13] a few of them involved in the hydrogen autotransfer process for amine alkylation.[14] On the other hand, the reduction reaction of water with zinc is known to occur at extreme temperatures and pressures,[15] in supercritical fluids,[16] or in special conditions.[17] PdZn alloys are also known to be good catalysts for H_2 generation by methanol steam reforming.[18]

Sasson *et al.* reported in 2000 that the Pd/C/Zn combination in water is capable of generating hydrogen in the absence of an organic substrate, while in the presence of an organic substrate (benzaldehyde, nitrobenzene or 4-nitroanisole) acts as an hydrogen transfer system, giving the hydrogenated product.[19] However, this methodology has not been deeply explored using other hydrogen donors and substrates.

Here we report the use of the Pd/C/Zn combination to the hydrogenation of quinolines. Different alcohols or mixtures of alcohol/water are employed as hydrogen donors and solvents, to obtain 1,2,3,4-tetrahydroquinolines, products of great interest due to their biological activities and their properties as dyes.[20] Furthermore, the Pd/C/Zn mixture has been revealed to be a good system for hydrogen autotransfer alkylation of the secondary amine of tetrahydroquinoline with alcohols yielding N-alkylated tetrahydroquinolines from quinolines in a one pot method under moderate conditions.

Results and discussion

In a typical reaction (Table 1) quinoline, zinc powder, Pd/C and the appropriate solvent (alcohol, water or water/alcohol mixtures) were charged to an autoclave and were maintained at 150 °C during the reaction time. Firstly, we studied the behavior of the reaction towards different hydrogen donors. As it can be observed in Table 1, when the reaction was performed in water, only **2** was obtained, but in low yield. With an increase of temperature to 200 °C (entry 2), the yield of **2** increased slightly but 3,4-dihydroquinolin-2(1*H*)-one was formed as the main product (77%). In the cases of mixtures of H_2O and primary alcohols (MeOH or EtOH) (entries 3–5) both the hydrogenated product **2**, and one pot hydrogenation and N-alkylation product **3** were obtained, except when the reaction with H_2O/EtOH was maintained for 40 h (entry 6), in that case **3b** was the only product, with a high yield.

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†Electronic supplementary information (ESI) available: Evidences and references of known compounds, NMR spectra of all compounds, NMR spectra and GC of acetone detection experiment and NMR spectra of deuterating experiments. See DOI: 10.1039/c1ob05888f

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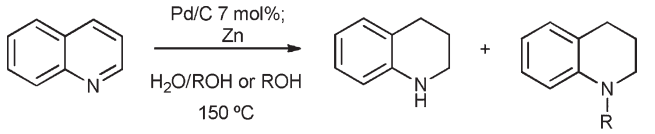
Table 1 Transfer hydrogenation to quinoline with water, alcohol or alcohol/water[a]



Entry	Solvent	*t* (h)	Zn mmol (eq.)	Yield (%)[b]	
				2	**3**
1	H_2O	40	1.14 (1.5)	13	—
2[c]	H_2O	40	1.14 (1.5)	20	—
3	H_2O/MeOH	40	1.14 (1.5)	15	31
4	H_2O/EtOH	15	1.14 (1.5)	33	43
5	H_2O/EtOH	24	1.14 (1.5)	60	24
6	H_2O/EtOH	40	1.14 (1.5)	—	96
7[d]	H_2O/iPrOH	40	1.14 (1.5)	21	—
8[e]	H_2O/t-BuOH	24	1.14 (1.5)	30	—
9[e]	H_2O/t-BuOH	40	1.14 (1.5)	32	—
10	MeOH	40	1.14 (1.5)	—	75
11	EtOH	24	0.038 (0.05)	—	28
12	EtOH	24	0.38 (0.5)	—	50
13	EtOH	15	1.14 (1.5)	—	83
14	EtOH	24	1.14 (1.5)	—	90
15	EtOH	40	1.14 (1.5)	—	96
16	EtOH	24	2.28 (3)	—	95
17	EtOH	40	2.28 (3)	—	89
18	iPrOH	24	1.14 (1.5)	84	12
19	iPrOH	40	1.14 (1.5)	86	9
20	iPrOH	24	2.28 (3)	88	11
21	iPrOH	40	2.28 (3)	80	20
22	t-BuOH	40	1.14 (1.5)	3	—

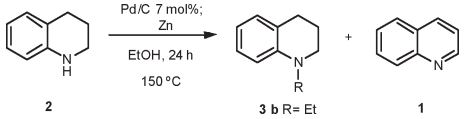
[a] Standard conditions: Quinoline (0.76 mmol), Zn, 10% Pd/C (7 mol%), 150 °C, 3 ml total reaction volume of appropriate solvent (in case of mixtures 1.5 ml ROH/1.5 ml H_2O); [b] Isolated yield. [c] Reaction at 200 °C, 3,4-dihydroquinolin-2(1*H*)-one (77%) was also obtained; [d] 5,6,7,8-tetrahydroquinoline (15%) and 3,4-dihydroquinolin-2(1*H*)-one (17%) were also obtained. [e] 3,4-dihydroquinolin-2(1*H*)-one (5%) was also obtained.

When reactions were carried out with mixtures of H_2O and secondary and tertiary alcohols (*i*PrOH and *t*BuOH) (entries 7, 8, 9), **2** was obtained in moderate yields. In the case of reaction with H_2O/*i*PrOH, 5,6,7,8-tetrahydroquinoline and 3,4-dihydroquinolin-2(1*H*)-one were also obtained, and in the case of reactions with H_2O/*t*BuOH, 3,4-dihydroquinolin-2(1*H*)-one was also obtained.

Performing reactions using only an alcohol as solvent and hydrogen donor, higher selectivity was found in case of primary alcohols (MeOH and EtOH) (entries 10–17), and **3** (**a** or **b**) was the only product. In case of secondary alcohol (*i*PrOH) (entries 18–21), tetrahydroquinoline **2** was the main product, and **3c** was obtained in low yield. With tertiary alcohol (*t*BuOH) (entry 22) only **2** was found in very low yield.

The effect of Zn amount was studied (entries 11–21), performing reactions with EtOH and *i*PrOH, the two hydrogen donors which afforded higher conversions. Little change in yields and conversions were observed using different amounts of Zn higher than 1.14 mmol.

Table 2 Contribution of Zn, Pd/C and metals mixture to the N-alkylation reaction[a]



Entry	Pd/C (mol %)	Zn mmol (eq.)	Yield (%)[b]	
			3b	**1**
1	7	2.28 (3)	93	5
2	7	—	50	47
3	—	2.28 (3)	—	30
4	—	—	—	15

[a] Standard conditions: 1,2,3,4-tetrahydroquinoline (0.76 mmol), Zn, 10% Pd/C (7 mol%), 150 °C, 3 ml EtOH. [b] NMR yield.

Blank experiments using only Pd/C, or Zn, or no metal, were done with EtOH and *i*PrOH as hydrogen donors at 150 °C, and demonstrated that the metal combination is necessary for the hydrogen transfer reaction. In case of the blank experiment done with Pd/C in EtOH, 2,2′-biquinoline (32%) was obtained. Dimerization of pyridine in position 2 is known to occur catalyzed by Pd/C.[21] When the reaction was performed with the whole combination of metals (Pd/C, Zn) at 100 °C, 2,2′-biquinoline was obtained as the only product in higher yield (59%). However, this dimer has never been observed when the mixture (Pd/C, Zn) was heated at 150 °C.

At this stage, we intended to study the N-alkylation process separately. Taking into account the classical mechanism proposed for N-alkylation of amines with alcohols by a hydrogen autotransfer process,[11a] it seemed logical that a secondary alcohol (*i*PrOH) reacted in lower proportion than a primary alcohol (MeOH or EtOH). Since there is one example in the literature of N-alkylation of a primary amine with an alcohol catalyzed by Pd,[14b] it was interesting to clarify whether the Pd/C/Zn mixture was necessary for hydrogen autotransfer N-alkylation in 1,2,3,4-tetrahydroquinoline.

With this aim, we performed the reaction of 1,2,3,4-tetrahydroquinoline in EtOH with Pd/C/Zn and with each metal separately. As can be seen in Table 2, despite Pd/C being able to catalyze this transformation alone, the combination of Pd/C/Zn enhances considerably the activity. This fact suggests that Zn is acting in such a way that makes the borrowing hydrogen process (or hydrogen autotransfer) from the alcohol to Pd more favorable. Formation of **1** can be explained in some measure by the known activity of Pd as a dehydrogenation catalyst of nitrogen containing heterocycles.[22]

The range of hydrogenation and N-alkylation reaction was studied employing the two best hydrogen donors (EtOH and *i*PrOH) with methyl substituted quinolines in the best conditions found for quinoline (Table 3). With EtOH the products of one pot hydrogenation and alkylation **6** were obtained mainly, and with *i*PrOH the hydrogenation product **5** was obtained as the major one. In the case of EtOH, the proportion of N-alkylated compounds diminished due to the steric effect of the methyl group, that hindered N-alkylation (entries 1 and 6), otherwise in

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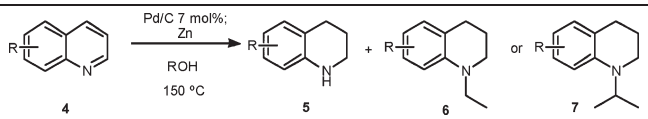
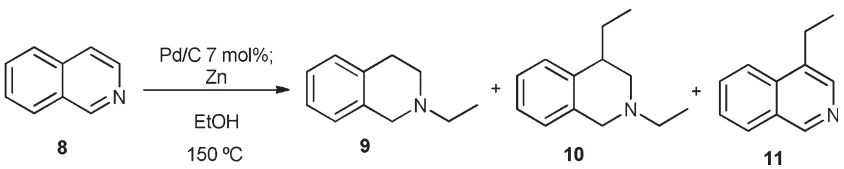
Table 3 Hydrogen transfer reaction of methyl substituted quinolines with EtOH or *i*PrOH[a]



Entry	R	Comp.	Solvent	Yield % (Isolated %)		
				5(a–f)	**6(a–f)**	**7(b–e)**
1	2-Me	**a**	EtOH	13 (12)	76 (71)	—
2	3-Me	**b**	EtOH	—	90 (77)	—
3[b]	4-Me	**c**	EtOH	—	34 (20)	—
4	6-Me	**d**	EtOH	—	88 (74)	—
5	7-Me	**e**	EtOH	—	92 (85)	—
6	8-Me	**f**	EtOH	34 (34)	27 (25)	—
7	2-Me	**a**	*i*PrOH	95 (76)	—	—
8	3-Me	**b**	*i*PrOH	60 (55)	—	35 (33)
9	4-Me	**c**	*i*PrOH	83 (63)	—	6 (4)
10	6-Me	**d**	*i*PrOH	74 (62)	—	25 (22)
11	7-Me	**e**	*i*PrOH	54 (17)	—	23 (20)
12	8-Me	**f**	*i*PrOH	83 (62)	—	—

[a] Conditions for EtOH reactions: Methyl quinoline (0.76 mmol), Zn (1.14 mmol, 1.5 eq), 10% Pd/C (7 mol%), 3 ml EtOH, 150 °C, 40 h. Conditions for *i*PrOH reactions: Methyl quinoline (0.76 mmol), Zn (2.28 mmol, 3 eq), 10% Pd/C (7 mol%), 3 ml *i*PrOH, 150 °C, 24h. [b] A similar result was obtained in reference 6b.



Scheme 1

the case of *i*PrOH, the steric effect prevented alkylation and compounds **5** are the only formed (entries 7 and 12), in other cases (entries 8–11) a small quantity of **7** was also formed.

The reaction was also explored using isoquinoline (Scheme 1) and pyridine as substrates. With pyridine there were no hydrogenation products, however the reaction with isoquinoline gave some interesting results although more complicated than in the case of quinolines. When EtOH was used as hydrogen donor and the reaction was maintained for 40 h, the product of isoquinoline hydrogenation and N-alkylation **9** was obtained as the major one (55%), but also isolated was the product corresponding to tandem C4 alkylation-hydrogenation-N alkylation **10** (25%). Traces of C4 alkylated isoquinoline **11** were also detected, indicating that C4 alkylation of isoquinoline is the first step in the three step tandem process. There is only one example in the literature of tandem N- and C- alkylation of amines catalyzed by ruthenium.[23] Furthermore, C4- alkylation of isoquinoline is almost an unknown process.

We have performed some mechanistic investigations trying to explain these results. The metals mixture was analyzed after typical reactions with quinoline as substrate by X-Ray powder diffraction (XRD) (Fig. 1), finding that almost all the Zn has converted into ZnO.

Reuse tests did not show a complete loss of activity (50% in the first reuse). Changes in the amount of Zn did not affect the reaction considerably. All these data pointed to the certain activity of ZnO, therefore the reaction with quinoline was performed using ZnO, instead of Zn, and optimized conditions for EtOH (Table 1, entry 15), obtaining **3b** in 84% yield. When the

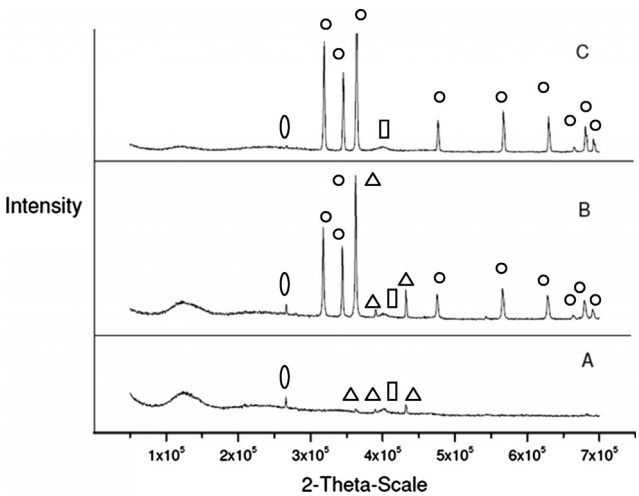


Fig. 1 XRD of: A) Pd/C + Zn mixture before reaction. B) Transformation of metals mixture (Pd/C + Zn) after typical reaction with EtOH in optimized conditions (Table 1, entry 13). C) Pd/C + ZnO mixture after reaction with EtOH in optimized conditions (Table 1, entry 13). □ Pd; ⬯ C (graphite); △ Zn; ○ ZnO.

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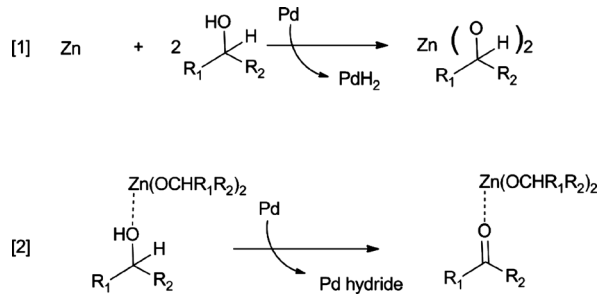


Scheme 2

reaction was carried out using ZnO and H_2O as hydrogen donor, no hydrogenation product **2** or **3b** was observed.

With the aim of studying if the presence of water is necessary for the quinoline reduction to take place, we performed the typical reaction using dry isopropanol as hydrogen donor in anhydrous conditions. In these conditions, quinoline converted at 100%, however the selectivity of the reaction changed, and products **2** and **3** were obtained in the same proportion. This experience informed us that, although traces of water in alcohols employed in the reaction could have a role, they are not a requisite for the oxidation of Zn, in the presence of Pd/C, to a species capable of activating an alcohol to act as a hydrogen transfer compound.

At this point we can propose a mechanism in which alcohols can act as hydrogen donors in the presence of metals mixture Pd/C/Zn (Scheme 2). In this mechanism two sequential paths for the hydrogen transference from alcohols to palladium are proposed. The first step implies a hydrogen transfer from the hydroxyl group with formation of zinc alcoxide, (eq. [1]) which justifies the fact that in anhydrous conditions the reaction takes place, therefore alcohols are able to oxidize Zn performing the hydrogen transfer. Then, zinc alcoxide is generated, which would activate the alcohol for the formation of a palladium hydride in a way that generates a carbonyl function (eq [2]).

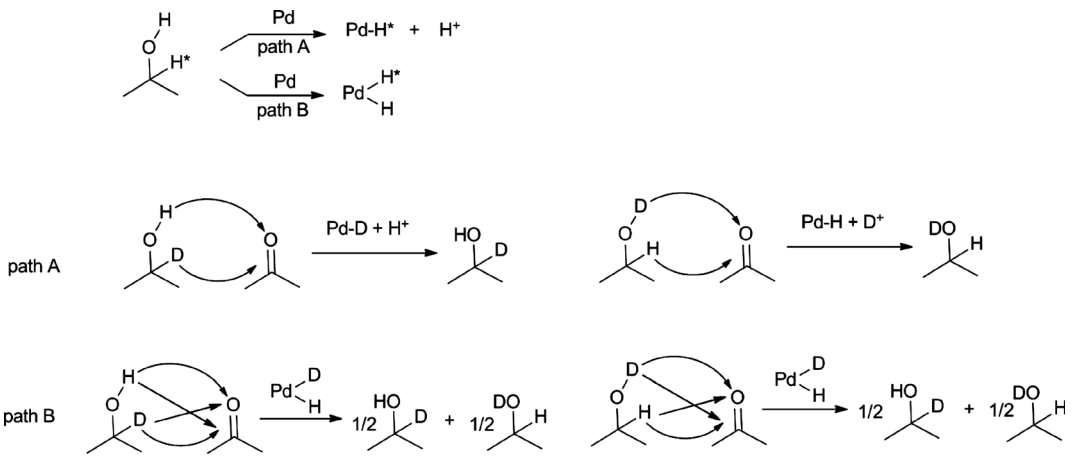
To demonstrate that a carbonyl compound is effectively formed in the process we performed the reaction with isopropanol in standard conditions (Table 1 entry 20) using as catalysts Pd/C/Zn, Pd/C, Zn, Pd/C/ZnO, ZnO and no metal. Also all the reactions were studied in the same conditions but without quinoline. In all experiments the formation of acetone was detected (detected by GC-MS and ^{1}H NMR, see spectra in ESI†). However, acetone amounts detected in experiments performed with Pd/C, Zn and ZnO were of the same magnitude as amounts detected without catalysis; while in the case of metals mixtures (Pd/C/Zn and Pd/C/ZnO) acetone was found in significantly larger amounts. These data support that the metals mixture activity has an important role in the carbonyl formation.

According to the Bäckvall proposal,[3d,h,14d,24] palladium hydride formation described in equation 2 can be carried out by two different pathways: formation of metal monohydride or metal dihydride (Scheme 3). In the case of the monohydride path, hydride should come from the α-CH of the alcohol, while in the case of dihydride path, hydride should come from both the α-CH and OH of the alcohol (Scheme 3). To determine which type of metal hydride is formed in this step, we have carried out several experiments in which we have put 2-propanol-2-d_1 and 2-propan(ol-d) with metal mixtures (Pd/C/Zn and Pd/C/ZnO), at 150 °C in standard conditions and without quinoline. After these experiments, we have analyzed the ^{1}H NMR of the resulting isopropanol/acetone mixture to check if H/D scrambling in alcohol had occurred (see ^{1}H and ^{13}C NMR spectra in ESI†). We have determined the percentage of C-α deuteration, as in the case of OH any exchange with protons in the medium would have altered the results.

In the experiment of 2-propanol-2-d_1 (Scheme 3, path A) with Pd/C/Zn or Pd/C/ZnO, if the reaction follows the monohydride pathway, no changes of labeling in α-C should be found, and the deuteration percentage of α-C must be near to 100%. On the other hand, in the dihydride pathway (Scheme 3, path B) the expected result would be a change in the deuteration percentage of α-C to 50%.

In the experiment with 2-propan(ol-d) with Pd/C/Zn or Pd/C/ZnO, in the case of the monohydride pathway (Scheme 3, path A), the expected percentage of deuteration in α-C should be near to 0%, while in the dihydride pathway (Scheme 3, path B) it should be also near to 50%.

As can be observed in Table 4, deuteration percentages obtained in α-C in the case of the 2-propanol-2-d_1 experiment were high, while in the case of 2-propan(ol-d) they were near to 0%. These results are consistent with a mechanism of palladium



Scheme 3

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Table 4 Deuteration percentage of α-C after reaction of deuterated alcohols with metals mixture

Entry	Deuterated Isopropanol	Conditions[a]	%Deuteration in α-C[b]
1	2-propanol-2-d_1	Pd/C/Zn	88
2	2-propanol-2-d_1	Pd/C/ZnO	92
3	2-propan(ol-d)	Pd/C/Zn	8
4	2-propan(ol-d)	Pd/C/ZnO	9

[a] 150 °C, 24h, sealed ampoule. [b] Percentage determined by NMR.

monohydride. The fact that the percentage of deuteration in the α-C in 2-propanol-2-d_1 Pd/C/Zn experiment was lower than in the case of the experiment with the same alcohol but with Pd/C/ZnO mixture can be explained by the existence of the two steps postulated in Scheme 2. In the experiment with the Pd/C/ZnO mixture, the process described in Scheme 2 equation 1 is avoided, PdH_2 is not formed, and as a consequence, the addition of a hydride to the α-C does not take place.

Palladium hydride intermediates are able to hydrogenate quinoline to 1,2,3,4-tetrahydroquinoline (eq [3]), which can react with a zinc alcoxide activated carbonyl compound forming an iminium salt or an enamine. This species can be hydrogenated by palladium hydrides to give the N-alkylated tetrahydroquinoline (eq [4]). Finally ZnO formation could be explained by equation [5] (Scheme 4).

The process expressed in Scheme 5, studied previously by Sasson,[19] should be considered as another possible way of hydrogen transfer and zinc oxide formation, as water is generated in the N-alkylation (Scheme 4, equation [4]) and non dry alcohols are used to perform the reactions.

The roles of ZnO and zinc alcoxide in the mechanism could be associated with their acid/base properties. Since these species have amphoteric character, they can act both as Lewis acids, activating alcohols or carbonyls, and as bases, promoting the formation of the alcoxide in the monohydride mechanism.

In the mechanism proposal there are three different routes of hydrogen transfer implicated[25] and none of them can be discarded, although the monohydride pathway seems the one of major relevance due to the results obtained in the deuteration experiment.

Finally, a new reaction was performed, using as hydrogen donor and solvent ethylene glycol, and ethylene glycol/H_2O combinations, obtaining different proportions of the corresponding tetrahydroquinoline **2** and the interesting indol **12**, of which the skeleton has properties as a 5-HT_3 receptor antagonist.[26,27] The upper yield for indol **12** (50%) was found when the reaction was performed in a total volume of 15 ml with 33% of H_2O during 70 h (entry 9 Table 5), however tetrahydroquinoline **2** was also found (45%). When the reaction was carried out in a volume of 3 mL and 17% of H_2O only indol **12** was obtained although in moderate yield (30%) (entry 4 Table 5).

Hydrogen transfer to quinolines using diols mediated by Pd/C/Zn (Table 5) opens an interesting strategy for the synthesis of different complex heterocycles with tetrahydroquinoline substructure. We are currently working in the application of this strategy.

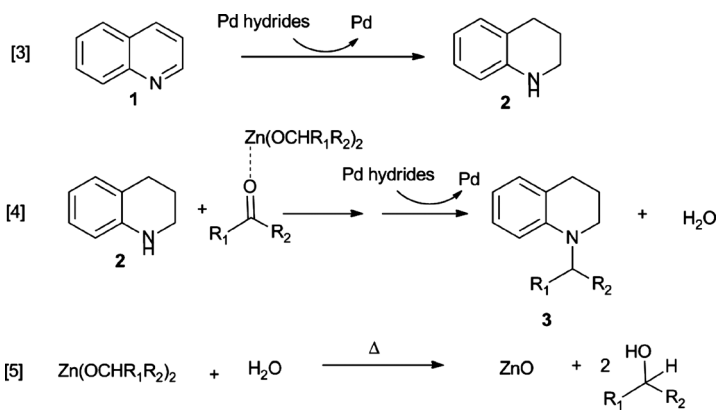
Conclusions

In conclusion, the Pd/C/Zn mixture has been demonstrated to be efficient for alcohol activation in transfer hydrogenation. We have proposed a mechanism in which three different pathways of hydride transfer are involved, the palladium monohydride path being the most important one. From the synthetic point of view, a simple methodology to obtain tetrahydroquinolines and/or N-alkylated tetrahydroquinolines from quinolines in a one pot reaction has been developed. In addition, we have evidenced cases of C-alkylation using this methodology, which make us think that this strategy can offer great synthetic potential. The use of non dry alcohols as hydrogen donors and alkylating agents simultaneously, offers a green alternative to the classical approaches with great industrial applications.[12]

Experimental section

General methods

NMR spectra were recorded on a Bruker AC300 MHz in $CDCl_3$ as solvent. COSY experiments were done for all compounds. HRMS Electron Impact (EI) or ElectroSpray (ES) determinations were made using a VG Autospec Trio 1000 (Fisons). For acetone detection GC-MS was used (Agilent Technologies 6890 N gas chromatograph equipped with a capillary column, supra-wax-280 Teknokroma 30 m × 250 μm × 0.25 μm). DRX powder spectra were done on a BRUKER AXS D5005 powder



Scheme 4

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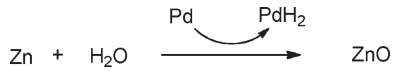

Scheme 5

diffractometer (Cu radiation, 40 kV, 30 mA, 0.05 step, 6 s). All quinolones and deuterated *i*PrOH used are from commercial sources (Aldrich). IR spectra were recorded using a Thermoscientific Nicolet FT IR iS10 ATR. Rf were calculated using TLC silicagel 60 F_{254} Merck.

General procedures

To a solution of the corresponding quinoline (0.76 mmol, 100 mg) in the appropriate solvent, Pd/C (7 mol%) and variable amounts of Zn (1.14 or 2.28 mmol) were added. The mixture was charged in an autoclave and was maintained at 150 °C during the reaction time. After cooling to room temperature, the reaction mixture was filtered and washed with dichloromethane. Then, water was added and was extracted with dichloromethane. The organic solvent was evaporated and dried giving a residue which was purified by chromatotron, eluting firstly with hexane and then with mixtures of ethyl acetate/hexane at increasing polarity.

1,2,3,4-Tetrahydroquinoline **2**,[28] 1-methyl-1,2,3,4-tetrahydroquinoline **3a**,[29] 1-ethyl-1,2,3,4-tetrahydroquinoline **3b**,[28] 5,6,7,8-tetrahydroquinoline,[30] 3,4-dihydroquinolin-2(1H)-one,[31] 2,2′-biquinoline,[32] 2-methyl-1,2,3,4-tetrahydroquinoline **5a**,[33] 3-methyl-1,2,3,4-tetrahydroquinoline **5b**,[33] 4-methyl-1,2,3,4-tetrahydroquinoline **5c**,[34] 6-methyl-1,2,3,4-tetrahydroquinoline **5d**,[34] 8-methyl-1,2,3,4-tetrahydroquinoline **5f**,[34] 2-ethyl-1,2,3,4-tetrahydroisoquinoline **9**,[35] 4-ethyl-isoquinoline **11**,[36] 5,6-dihydro-4*H*-pyrrolo[3,2,1-ij]quinoline **12**,[27] are known compounds.

1-Isopropyl-1,2,3,4-tetrahydroquinoline 3c. Yellow oil. R_f 0.73 (hexane-ethyl acetate, 1:1). IR (neat) 2923, 2853,1464, 1386, 1032, 802 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (1H, ddd, J = 8.3, 7.3, 1.8 Hz), 6.95 (1H, dd, J = 7.3, 1.6 Hz), 6.70 (1H, d, J = 8.3 Hz), 6.55 (1H, ddd, J = 7.3, 7.3, 1.0 Hz), 4.12 (1H, sept, J = 6.6 Hz), 3.17 (2H, t, J = 5.7 Hz), 2.74 (2 H, t, J = 6.4 Hz), 1.91 (2H, m), 1.19 (6H, d, J = 6.6 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 129.2, 127.0, 123.1, 115.1, 110.6, 46.8, 40.2, 28.5, 22.4, 18.9. HRMS found for $[M+H]^+$ 176.1439; $C_{12}H_{18}N$ requires 176.1439.

7-Methyl-1,2,3,4-tetrahydroquinoline 5e. Yellow oil. R_f 0.73 (hexane-ethyl acetate, 1:1). IR (neat) 3405, 2921, 2850, 1510, 1459, 1371, 1264, 804 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (1H, d, J = 7.6 Hz), 6.46 (1H, d, J = 7.7 Hz), 6.35 (1H, s), 3.29 (2H, t, J = 5.5 Hz), 2.72 (2H, t, J = 6.4 Hz), 2.21 (3H, s), 1.93 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 129.4, 119.1, 118.7, 115.3, 100.0, 42.1, 26.4, 22.2, 21.2. HRMS found for $[M+H]^+$ 148.1129; $C_{10}H_{14}N$ requires 148.1126.

1-Ethyl-2-methyl-1,2,3,4-tetrahydroquinoline 6a. Yellow oil. R_f 0.93 (hexane-ethyl acetate, 1:1). IR (neat) 2961, 2924, 2853, 1607, 1500, 1382, 1262, 799 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (1H, dd, J = 8.0, 8.0), 6.94 (1H, d, J = 7.3), 6.53 (m, 2H), 3.48 (m, 1H), 3.31 (m, 2H), 2.81 (m, 2H), 1.79 (m, 2H), 1.14 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.1, 128.9, 127.0, 126.7, 114.6, 110.2, 51.8, 43.4, 29.7, 28.1, 24.0, 19.6, 12.5. HRMS found for $[M+H]^+$ 176.1441; $C_{12}H_{18}N$ requires 176.1439.

1-Ethyl-3-methyl-1,2,3,4-tetrahydroquinoline 6b. Yellow oil. R_f 0.90 (hexane-ethyl acetate, 1:1). IR (neat) 2357, 1652, 1590, 1370, 1096, 1047, 756 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (1H, dd, J = 8.2, 7.3 Hz), 6.99 (1H, d, J = 7.3 Hz), 6.62 (2H, m), 3.50 (1H, m), 3.30 (1H, m), 3.23 (1H, m), 2.98 (1H,

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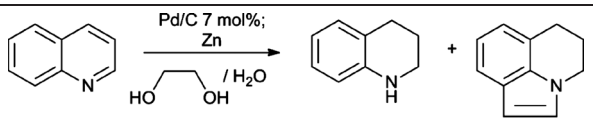
Table 5 Hydrogen transfer reaction of quinoline with ethylene glycol or ethylene glycol/water[a]



Entry	V (ml) ($OHCH_2CH_2OH/H_2O$)	t (h)	% H_2O	Yield (%)[b]	
				2	**12**
1	3 (3/0)	24	0	—	5
2	3 (3/0)	40	0	—	6
3	3 (2.95/0.05)	24	2	—	12
4	3 (2.5/0.5)	24	17	—	30
5	3 (2.5/0.5)	40	17	33	33
6[c]	3 (1.5/1.5)	24	50	37[c]	16[c]
7	15 (12.5/2.5)	40	17	30	40
8	15 (10/5)	40	33	33	33
9	15 (10/5)	70	33	45	50
10	15 (7.5/7.5)	24	50	74	20
11	15 (7.5/7.5)	40	50	62	33

[a] Standard conditions: Quinoline (0.76 mmol), Zn (2.28 mmol), 10% Pd/C (7 mol%), 150 °C. [b] NMR yield. [c] Isolated yield.

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m), 2.81 (1H, m), 2.52 (1H, m), 2.15 (1H, m), 1.19 (3H, t, J = 7.0 Hz), 1.10 (3H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 129.2, 126.9, 121.9, 115.3, 110.1, 55.4, 45.1, 36.4, 27.0, 19.0, 10.7. HRMS found for $[M+H]^+$ 176.1444; $C_{12}H_{18}N$ requires 176.1439.

1-Ethyl-4-methyl-1,2,3,4-tetrahydroquinoline 6c. Yellow oil. R_f 0.90 (hexane-ethyl acetate, 1:1). IR (neat) 2918, 2847, 1600, 1502, 1458, 1373, 1283, 1112, 761 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (2H, m), 6.59 (2H, m), 3.31 (4H, m), 2.88 (1H, dd, J = 12.5, 6.7 Hz), 2.00 (1H, m), 1.69 (1H, m), 1.27 (3H, d, J = 7.0 Hz), 1.14 (3H, t, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 128.1, 127.5, 127.0, 115.3, 110.5, 100.0, 45.3, 45.0, 31.0, 29.7, 29.6, 22.5, 10.7. HRMS found for $[M+H]^+$ 176.1442; $C_{12}H_{18}N$ requires 176.1439.

1-Ethyl-6-methyl-1,2,3,4-tetrahydroquinoline 6d. Yellow oil. R_f 0.90 (hexane-ethyl acetate, 1:1). IR (neat) 2972, 2920, 2848, 1673, 1510, 1373, 1262, 1200, 802 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (1H, d, J = 8.3 Hz), 6.80 (1H, s), 6.55 (1H, d, J = 8.3 Hz), 3.34 (2H, q, J = 7.1 Hz), 3.23 (2H, t, J = 5.6 Hz), 2.74 (2H, t, J = 6.4 Hz), 2.22 (3H, s), 1.97 (2H, m), 1.14 (3H, t, J = 7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 129.9, 127.4, 124.5, 122.6, 110.9, 48.3, 45.4, 28.1, 22.4, 20.1, 10.6. HRMS found for $[M+H]^+$ 176.1443; $C_{12}H_{18}N$ requires 176.1439.

1-Ethyl-7-methyl-1,2,3,4-tetrahydroquinoline 6e. Yellow oil. R_f 0.92 (hexane-ethyl acetate, 1:1). IR (neat) 2952, 2898, 1515, 1468, 1325, 1119, 858 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (1H, d, J = 7.4 Hz), 6.42 (1H, s), 6.38 (1H, d, J = 7.5 Hz), 3.33 (2H, q, J = 7.1 Hz), 3.24 (2H, t, J = 5.6 Hz), 2.71 (2H, t, J = 6.4 Hz), 1.93 (2H, m), 1.26 (3H, s), 1.14 (3H, t, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 136.5, 129.0, 119.5, 116.1, 111.2, 48.4, 45.3, 27.8, 22.4, 21.7, 10.9. HRMS found for $[M+H]^+$ 176.1443; $C_{12}H_{18}N$ requires 176.1439.

1-Ethyl-8-methyl-1,2,3,4-tetrahydroquinoline 6f. Yellow oil. R_f 0.94 (hexane-ethyl acetate, 1:1). IR (neat) 2925, 2863, 1456, 1388, 1267, 1122 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, d, J = 7.2 Hz), 6.88 (1H, d, J = 7.1 Hz), 6.81 (1H, dd, J = 7.3, 7.3 Hz), 3.08 (2H, m), 2.81 (4H, m), 2.26 (3H, s), 1.79 (2H, m), 1.22 (3H, t, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 131.4, 128.8, 128.7, 127.1, 121.0, 48.6, 46.5, 28.0, 18.8, 17.3, 14.1. HRMS found for $[M+H]^+$ 176.1441; $C_{12}H_{18}N$ requires 176.1439.

1-Isopropyl-3-methyl-1,2,3,4-tetrahydroquinoline 7b. Yellow oil. R_f 0.93 (hexane-ethyl acetate, 1:1). IR (neat) 2964, 2848, 1262, 1092, 1019, 792 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (1H, ddd, J = 8.3, 7.3, 1.5 Hz), 6.97 (1H, dd, J = 7.3, 1.6 Hz), 6.69 (1H, d, J = 8.3 Hz), 6.56 (1H, dd, J = 7.3, 7.3 Hz), 4.12 (1H, sept, J = 6.6 Hz), 3.21 (1H, m), 2.77 (1H, m), 2.68 (1H, m), 2.42 (1H, m), 1.98 (1H, m), 1.20 (3H, d, J = 6.6 Hz), 1.17 (3H, d, J = 6.6 Hz), 1.05 (3H, d, J = 6.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 129.3, 127.0, 122.6, 115.1, 110.2, 47.0, 46.9, 36.7, 36.4, 27.1, 19.2, 18.6. HRMS found for $[M+H]^+$ 190.1595; $C_{13}H_{20}N$ requires 190.1596.

1-Isopropyl-4-methyl-1,2,3,4-tetrahydroquinoline 7c. Yellow oil. R_f 0.93 (hexane-ethyl acetate, 1:1). IR (neat) 2962, 2921, 2852, 1597, 1528, 1379, 1264, 1087, 796 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (2H, m), 6.62 (2H, m), 4.10 (1H, m), 3.17 (2H, m), 2.86 (1H, m), 1.97 (1H, m), 1.61 (1H, m), 1.19 (6H, m), 1.12 (3H, m). HRMS found for $[M+H]^+$ 190.1596; $C_{13}H_{20}N$ requires 190.1596.

1-Isopropyl-6-methyl-1,2,3,4-tetrahydroquinoline 7d. Yellow oil. R_f 0.94 (hexane-ethyl acetate, 1:1). IR (neat) 2974, 2922, 1670, 1587, 1494, 1367, 1189, 810 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.88 (1H, d, J = 8.3 Hz), 6.80 (1H, s), 6.62 (1H, d, J = 8.3 Hz), 4.09 (1H, sept, J = 6.6 Hz), 3.13 (2H, t, J = 5.6 Hz), 2.72 (2H, t, J = 6.4 Hz), 2.21 (3H, s), 1.90 (2H, m), 1.17 (6H, d, J = 6.6 Hz).^{13}C NMR (75 MHz, $CDCl_3$) δ 143.3, 130.0, 127.4, 124.2, 123.2, 110.8, 46.8, 40.1, 28.4, 22.6, 20.1, 18.8. HRMS found for $[M+H]^+$ 190.1593; $C_{13}H_{20}N$ requires 190.1596.

1-Isopropyl-7-methyl-1,2,3,4-tetrahydroquinoline 7e. Yellow oil. R_f 0.93 (hexane-ethyl acetate, 1:1). IR (neat) 2924, 2849, 1666, 1451, 1060, 984 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (1H, d, J = 7.3 Hz), 6.52 (1H, s), 6.38 (1H, d, J = 6.7 Hz), 4.09 (1H, sept, J = 6.6 Hz), 3.14 (2H, t, J = 5.8 Hz), 2.69 (2H, t, J = 6.3 Hz), 2.26 (3H, s), 1.88 (2H, m), 1.18 (6H, d, J = 6.6 Hz). HRMS found for $[M+H]^+$ 190.1599; $C_{13}H_{20}N$ requires 190.1596.

2,4-Diethyl-1,2,3,4-tetrahydroisoquinoline 10. Yellow oil. R_f 0.89 (hexane-ethyl acetate, 1:1). IR (neat) 2974, 2917, 2845, 1380, 1270, 1094, 1047, 880, 800 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (1H, dd, J = 7.5, 6.4 Hz), 7.11 (2H, m), 7.02 (1H, d, J = 7.0 Hz), 3.59 (2H, m), 2.79 (1H, m), 2.72 (1H, m), 2.54 (3H, m), 1.83 (1H, m), 1.68 (1H, m), 1.18 (3H, t, J = 7.2), 0.99 (3H, t, J = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ138.9, 129.5, 127.9, 126.4, 126.1, 125.4, 56.6, 54.5, 52.2, 39.6, 28.1, 12.3, 11.9. HRMS found for $[M+H]^+$ 190.1595; $C_{13}H_{20}N$ requires 190.1590.

Anhydrous experiment

All material was dried, quinoline was distilled and Pd/C and Zn were maintained overnight at 80 °C in vacuum. Isopropanol anhydrous 99.5% was purchased from Aldrich, refluxed with CaH_2 under Argon and distilled. The reaction was made using conditions described in the general procedure (with 2.28 mmol of Zn) under argon atmosphere in a sealed ampoule that was maintained for 24 h at 150 °C in an autoclave. Reaction work up and purification were done as described in the general procedure.

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