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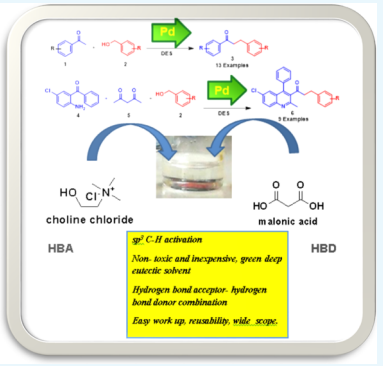
Choline Chloride-Based Deep Eutectic Systems in Sequential Friedländer Reaction and Palladium-Catalyzed sp^3 CH Functionalization of Methyl Ketones

Chitrala Teja and Fazlur Rahman Nawaz Khan*

Organic and Medicinal Chemistry Research Laboratory, School of Advanced Sciences, Vellore Institute of Technology, Vellore 632 014, Tamil Nadu, India

Supporting Information

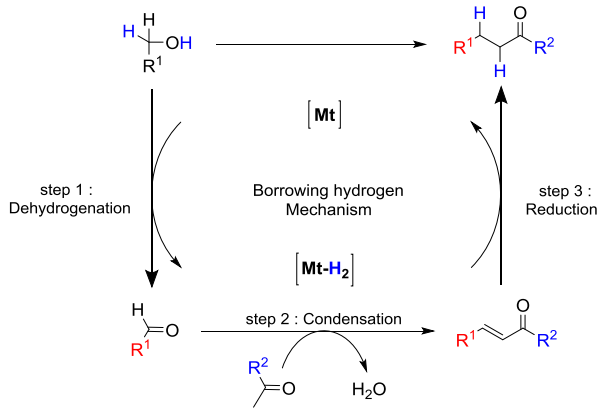
ABSTRACT: A volatile organic solvent-free and choline chloride (ChCl)-based deep eutectic system (DES)-mediated sp^3-CH functionalization of acetophenones **1** with benzyl alcohols **2** to the corresponding α,β-saturated ketones **3** is accounted for. The domino dehydrogenation−aldol condensation (hydrogenation borrowing concept) has been successfully attempted with palladium-tetrakis(triphenylphosphine) $[Pd(PPh_3)_4]$ catalyst−xantphos ligand combination. Furthermore, a sequential Friedländer reaction of 2-aminobenzophenone **4** and palladium-catalyzed α-alkylation of the quinolinyl methyl ketone with benzyl alcohols **2** in ChCl-based DES have been successfully investigated. The C−C bond formation through sp^3-CH functionalization involves a wide scope of the substrates, high atom efficiency, chemoselectivity, and environmentally friendly strategy.



INTRODUCTION

The sp^3-CH functionalization of ketones is an atom-efficient strategy for C−C bond formation.[1−5] The metal (Pd, Ru, Ir, and other transition metals)-catalyzed borrowing hydrogen (BH) strategy has an emerging enthusiasm in ketone alkylation with alcohols.[6−8] The BH concept as presented in Scheme 1 involves temporary oxidation of alcohol into the carbonyl compound through the dehydrogenation strategy. The carbonyl compounds formed have high reactivity owing to their electrophilicity in forming the C−C bond.[9,10] The carbonyl compound at this point through intermediate chalcone (via condensation with the α-CH unit of a ketone) experienced reduction through hydrogen transfer from the transition-metal hydride, resulting in C−C bond formation with water as a byproduct.

Scheme 1. Borrowing Hydrogen Concept in the C−C Bond Formation[6−10]



Recently, Wang, Gülcemal, and co-workers have demonstrated application of iridium complexes in sp^3 C−H functionalization utilizing *t*-amyl alcohol and toluene as a solvent, though at high temperatures[11−13] Likewise, Du and co-workers utilized $RhCl(CO)(PPh_3)_2$ and 1,4-dioxane solvent systems,[14] and other researchers utilized different volatile organic solvents and transition metals such as Fe, Co, and Pd.[15−18] In the above strategy, phosphines (as a P-donor ligand) were fundamental in stabilizing the active low-oxidation states.[19−22] Lang and co-workers reported Ru(*p*-cymene)$Cl_2]_2$, xantphos (P-donor ligand), and NaOH[23] system and demonstrated the vital role of transition metals as well as ligands. Coordinating ligands played an important role in cyclometalation with transition metals as directing groups,[19] thereby facilitating selectivity. By binding to the metal center, a ligand-promoted direct C−H activation[24,25] is realized. The involvement of cyclometalation is the key approach in C−C bond forming reactions.[26−28] However, to avoid toxic solvents, the green chemical approach is essential. Consequently, researchers have reported ILs (ionic liquids) in many organic reactions.[29−33] Notwithstanding their non-biodegradability is a noteworthy concern in the green chemical approach.

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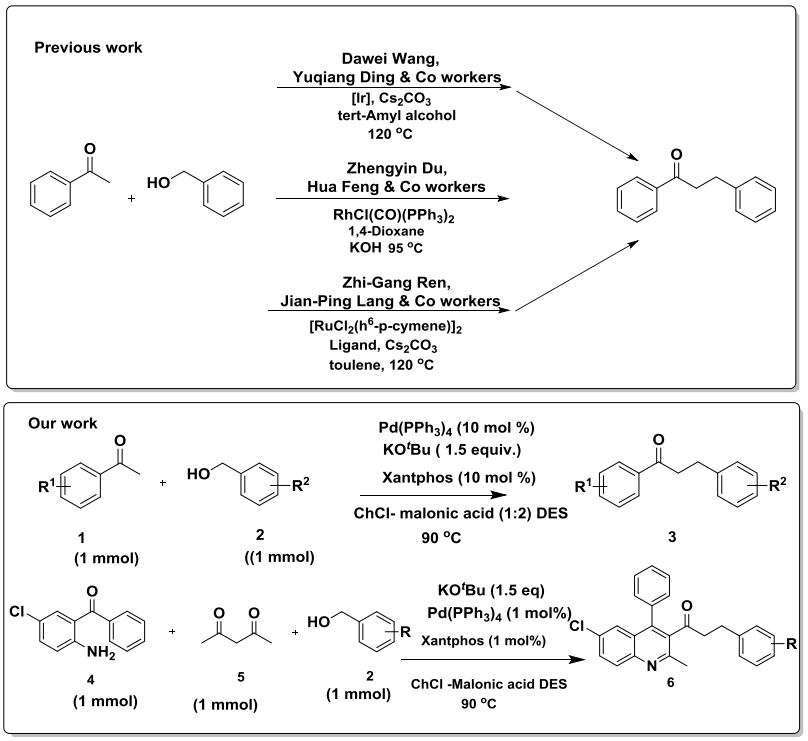
Figure 1. Preparation of various DESs (photograph taken by the first author Chitrala Teja).

Scheme 2. Borrowing Hydrogen Strategy—sp^3 C−H Functionalization of Ketones with Alcohols Using Deep Eutectic Systems



In a similar manner, deep eutectic solvent (DES), a low-melting mixture (Figure 1) has risen as a promising sustainable alternate in organic reaction media and in other fields, attributable to their ready availability. Although DES is closely associated with ILs,[34−38] they are more beneficial owing to the smaller size, transport properties, lower toxicity, high polarity, cost-effectiveness, operational simplicity, and biodegradability of their cations and anions. Moreover, most of the organic reactions required a catalyst to promote reactions. Interestingly, low-melting mixtures can act as reaction medium to facilitate the completion of the organic reactions in a clean and smooth manner without the need of any catalyst or additives. The academic and industrial researchers are developing new methods in decreasing chemical waste. Along these lines, DES-mediated reactions were investigated in sp^3 C−H functionalization of the ketone. Consequently, in the present study, a combination of palladium complexes such as $Pd(PPh_3)_4$ and xantphos was investigated in DES as a green reaction medium or additive to avoid toxic, volatile organic solvents.

Likewise, the quinolines are an important class of heterocyclic compounds,[39−41] owing to their potential pharmacological properties, namely, antimalarial,[42,43] antibacterial,[44,45] antiasthmatic, anti-inflammatory,[46,47] antihypertensive inhibiting properties, and so forth. Despite numerous methods including Friedländer,[48−50] Combes,[51,52] Conrad-Limpach,[53] Doebner von Miller, Skraup and Camps quinoline synthesis, and so forth,[54−57] reported previously, herein, we report the DES-assisted Friedländer quinoline synthesis.

To the best of our knowledge, this is the first case of DES-assisted Pd(0)-catalyzed α-alkylation of ketones with benzyl alcohols to form corresponding α-alkylated enones exclusively. Subsequently, the application of the low-melting mixture ChCl (choline chloride) and L-(+)-malonic acid-melt system in the domino Friedländer and α-alkylation via Friedländer's quinoline synthesis reaction have additionally been successfully attempted (Scheme 2).

RESULTS AND DISCUSSION

At first, screening of reaction conditions utilizing transition-metal catalysts, namely, $NiCl_2$, $CuCl_2$, $FeFl_3$, and $PdCl_2$ with acetophenone **1a** and benzyl alcohol **2a** and K_2CO_3 as a base in toluene at 80 °C was performed. Low yields of 10−15% were obtained (Table 1, entries 1−4); further, by shifting the base to CS_2CO_3 or KO^{t}Bu in $PdCl_2$, 25% yield was obtained (Table 1, entry 5, 6). KO^{t}Bu being a strong base improved the yield in contrast to mild base K_2CO_3 with 20% yield in $Pd(CH_3COO)_2$ (Table 1, entry 7). Consequently, rest of the optimizations was performed with KO^{t}Bu, and a slight improvement in yield was observed with an increased Palladium loading (Table 1, entry 8). Also, the introduction

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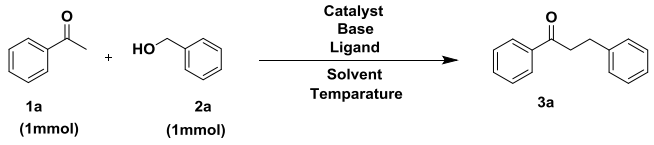
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	base	solvent/additive/reaction medium	temp (°C)	time (h)	yield (%)
1	$NiCl_2$		K_2CO_3	toluene	80	30	10
2	$CuCl_2$		K_2CO_3	toluene	80	30	15
3	$FeCl_3$		K_2CO_3	toluene	80	30	15
4	$PdCl_2$		K_2CO_3	toluene	80	24	10
5	$PdCl_2$		CS_2CO_3	toluene	90	20	20
6	$PdCl_2$		KO^tBu	toluene	90	20	25
7	$Pd(OCOCH_3)_2$		K_2CO_3	toluene	90	21	20
8	$Pd(OCOCH_3)_2$		KO^tBu	toluene	80	15	30
9	$Pd(OCOCH_3)_2$	PPh_3	KO^tBu	toluene	80	10	40
10	$Pd(OCOCH_3)_2$	$P(Cy)_3$	KO^tBu	toluene	80	13	45
11	$Pd(OCOCH_3)_2$	RuPhos	KO^tBu	toluene	80	11	50
12	$Pd(OCOCH_3)_2$	SPhos	KO^tBu	toluene	80	10	53
13	$Pd(OCOCH_3)_2$	xantphos	KO^tBu	toluene	80	9	60
14	Ru(*p*-cymene)$Cl_2]_2$		KO^tBu	toluene	90	30	30
15	$Pd_2(dba)_3$		KO^tBu	toluene	90	20	20
16	$PdCl_2(PPh_3)_2$		KO^tBu	toluene	90	17	40
17	$Pd(PPh_3)_4$		KO^tBu	toluene	90	15	50
18	Ru(*p*-cymene)$Cl_2]_2$	xantphos	KO^tBu	toluene	90	30	50
19	$Pd_2(dba)_3$	xantphos	KO^tBu	toluene	90	11	70
20	$PdCl_2(PPh_3)_2$	xantphos	KO^tBu	toluene	90	3	80
21	$Pd(PPh_3)_4$	xantphos	KO^tBu	Toluene	90	2	85
22	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−oxalic acid (1:1)	90	6	80
23	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−malonic acid (1:1)	90	2	90
24	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−citric acid (2:1)	90	8	60
25	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−tartaric acid (2:1)	90	5	70
26	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−D-glucose (1:2)	90	6	50
27	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−glycol (1:2)	90	6	20
28	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−urea (1:2)	90	6	30
29	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−thiourea (1:2)	90	6	32
30	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−PTSA (2:1)	90	10	65
31	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−$SnCl_2$ (2:1)	90	6	22
32	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl−gallic acid (2:1)	90	6	45
33	$Pd(OCOCH_3)_2$	xantphos	KO^tBu	ChCl−malonic acid (1:1)	90	8	78
34	Ru(*p*-cymene)$Cl_2]_2$	xantphos	KO^tBu	ChCl−malonic acid (1:1)	90	5	75
35	$[PPh_3]_2Ru(CO)_2Cl_2$	xantphos	KO^tBu	ChCl−malonic acid (1:1)	90	6	55
36	$[PPh_3]_3RuCl_2$	xantphos	KO^tBu	ChCl−malonic acid (1:1)	90	6	70
37	$[PPh_3]_4RuCl_2$	xantphos	KO^tBu	ChCl−malonic acid (1:1)	90	5	60
38	$Pd_2(dba)_3$	xantphos	KO^tBu	ChCl−malonic acid (1:1)	90	8	75
39	$PdCl_2(PPh_3)_2$	xantphos	KO^tBu	ChCl−malonic acid (1:1)	90	3	80
40	$Pd(PPh_3)_4$	xantphos	KO^tBu	malonic acid	90	4	trace
41	$Pd(PPh_3)_4$	xantphos	KO^tBu	ChCl	90	4	trace

[a]Reaction conditions: acetophenone, **1a** (1.0 mmol), benzyl alcohol, **2a** (1.0 mmol), Pd or Ru catalysts (10 mol %), ligands (10 mol %), KO^tBu (1.5 equiv) in toluene or DES additive or reaction medium (100 mg) unless otherwise indicated at 90 °C (as indicated).

of the ligand in the reaction brought about an enhancement of yield. It is suggested that the ligands are capable of binding metal ions via multiple sites through their lone pairs of electrons (on more than one atom), that is, cyclometalation resulted in selectivity and enhancement of reaction yield. Thus, the PPh_3 ligand enhanced yield up to 40% in short reaction time (Table 1, entry 9). Among different ligands attempted, a better yield of 60% was accomplished by utilizing Xantphos, a bidentate diphosphine and trans-spanning ligand (Table 1, entry 10−13). The reaction trials with just transition-metal catalysts without the ligand were futile, demonstrating their necessity in the reaction. For instance, with 10 mol % of Ru(*p*-cymene)$Cl_2]_2$, KO^tBu, in toluene an unsatisfying yield of 30% was obtained (Table 1, entry 14) while with $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$ (Table 1, entry 15−17), 20, 40, and 50% of yields, respectively, were obtained . Subsequently, the impact of ligand, base, catalysts, and their loading has been explored. The results revealed that 1.5 equiv of benzyl alcohol and 2 equiv of KO^tBu and 10 mol % of the catalyst brought about quantitative product yield in a shorter time of reaction. Similarly, the xantphos−phosphorous ligand in the presence of Ru(*p*-cymene)$Cl_2]_2$, $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$, and $Pd(PPh_3)_4$

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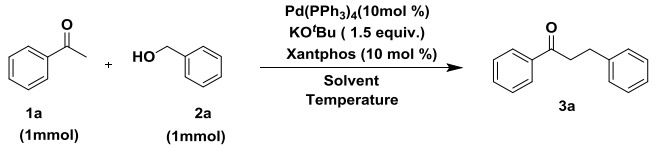
Table 2. DES Preparation, Properties, and Their Application

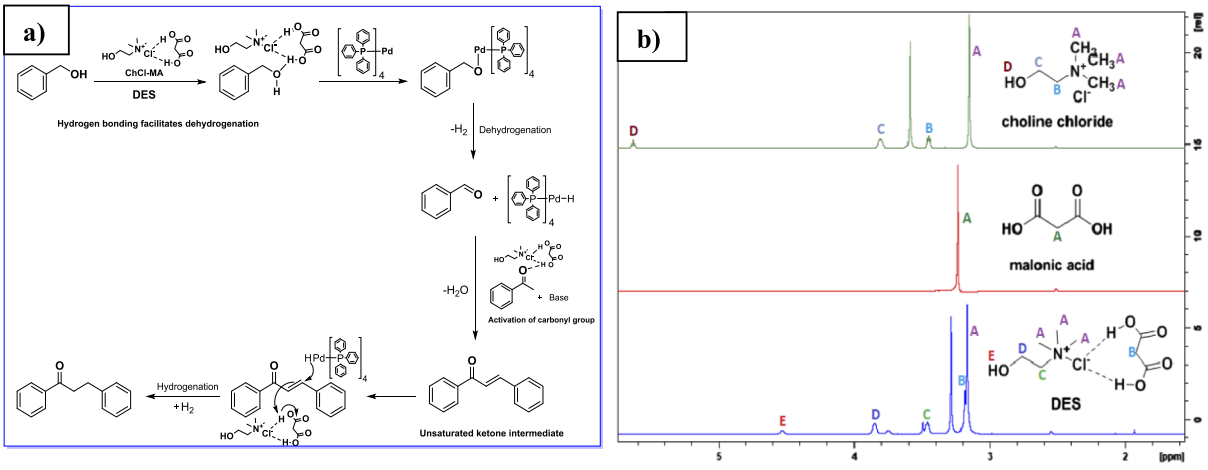
s. no.	DES composition and molar ratio	pH (100 mM/L)	melting point T (°C)	literature mp (°C)	refs
1	ChCl−oxalic acid (1:1)	1.92	liquids at room temperature	Liquids at room temperature	34
2	ChCl−malonic acid (1:1)	2.54	liquids at room temperature	Liquids at room temperature	34
3	ChCl−citric acid (2:1)	3.36	69 ± 2	69	34
4	ChCl−tartaric acid (2:1)	2.73	47 ± 2	47	58
5	ChCl−D-glucose (1:2)	5.56	liquids at room temperature	liquids at room temperature	36
6	ChCl−ethylene glycol (1:2)	7.11	liquids at room temperature	liquids at room temperature	36
7	ChCl−urea (1:2)	8.56	liquids at room temperature	liquids at room temperature	59
8	ChCl−thiourea (1:2)	6.54	69 ± 2	69	59
9	ChCl−PTSA (2:1)	1.22	35 ± 2		
10	ChCl−$SnCl_2$ (2:1)	1.45	110 ± 2		
11	ChCl−gallic acid (2:1)	4.53	77 ± 2	77	36

Table 3. pH Studies in Reaction Medium or DES Additive (Choline Chloride Malonic Acid)



entry	reaction medium or additive	temperature (°C)	time (h)	pH	yield (%)
1	DES (toluene reaction medium)	rt	10 min	5.2 (8)	trace (trace)
2	DES (toluene reaction medium)	rt	1 h	5.5 (8.7)	15 (trace)
3	DES (toluene reaction medium)	60	30 min	6.1 (9)	30 (25)
4	DES (toluene reaction medium)	90	1 h	6.5 (9.3)	45 (35)
5	DES (toluene reaction medium)	90	1.5	6.9 (9.7)	50 (47)
6	DES (toluene reaction medium)	90	2	7.8 (10.1)	75 (70)
7	DES (toluene reaction medium)	90	2.5	7.9 (10.2)	80 (80)
8	DES (toluene reaction medium)	90	3	8 (10.5)	90 (85)

Scheme 3. (a) Plausible Mechanism for the Formation of Alkylated Ketone in ChCl−Malonic Acid DES through the BH Mechanism; (b) ^{1}H NMR Spectra of DES (Demonstrating H Bonding) with HBD and HBA



gave increased product yields of 50, 70, 80, and 85, respectively (Table 1 entry 18−21). Strikingly, $Pd(PPh_3)_4$−xantphos−KO^{t}Bu−toluene combination at 90 °C offered moderate to good yield in shorter reaction time. Having optimized reaction conditions in hand, we explored the application of ChCl-based DES as reaction medium or additive with the intention of eliminating toxic and volatile organic solvents and to accomplish the desired product in high yields. One of the fundamental advantages of DESs is its exceptionally straight forward synthetic process. Further, the present study was attempted to explore C−H alkylation utilizing less expensive DES reaction medium as well as the additive to avoid toxic solvents and expensive catalysts such as Ir, Rh, and Ru. Initially acetophenone **1a** reacted with benzyl alcohol **2a**, utilizing $Pd(PPh_3)_4$, xantphos, and KO^{t}Bu in ChCl−oxalic acid—DES at 80 °C for 6 h, to give 80% yield (Table 1, entry 22). It is evident that in the earlier reports,[11,12,23,58−60] a volatile and toxic solvent has been utilized, including toluene, 1,4-dioxane, *t*-amyl alcohol, tetrahydrofuran, *N*-methyl-2-pyrrolidone, and so forth. However, in the present work to avoid toxic organic solvents, the DES made from cheap and biodegradable choline chloride has been utilized (Table 2). The DES presented several advantages, namely, green reaction medium, additive and catalyst, high conversion, easy workup, low cost, and

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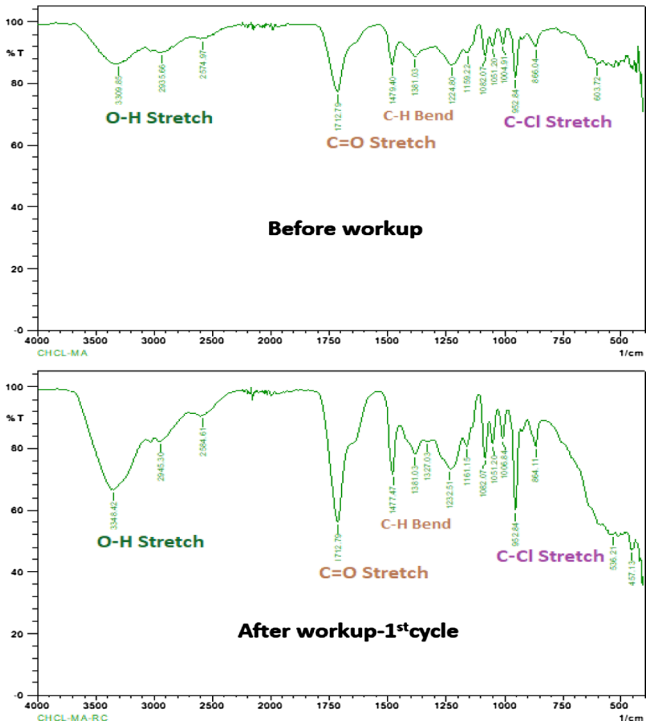
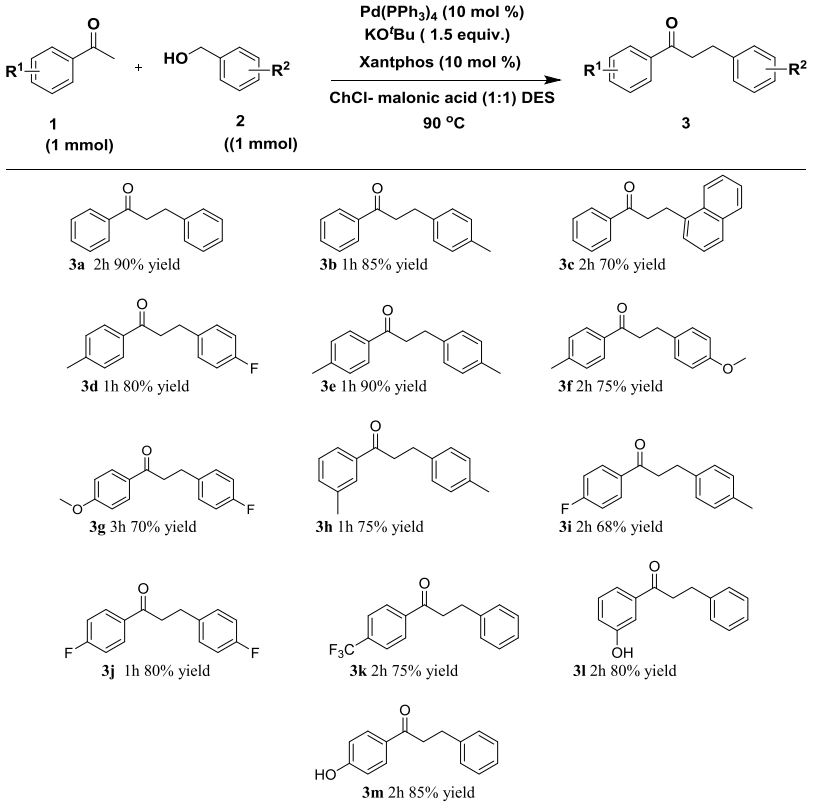


Figure 2. IR spectrum comparison of choline chloride–malonic acid (ChCl–MA) DES before and after the workup indicates no loss in H bonding and hence no loss in activity.

environment friendliness. The streamlining of different DES in the palladium-catalyzed α-alkylation of benzyl alcohols was tabulated (Table 1, entry 23–32). The efficiency of the reaction was strongly dependent on the nature of the DES. The employment of deep eutectic ChCl–malonic acid has brought a moderate-to-high yield, whereas the relatively weak hydrogen bonding interaction containing DES-like (ChCl–urea) resulted in trace conversion of the product. By optimizing different DESs, best results were obtained in the formation of the α-alkylated product. The results also depended on the loading of the DES, that is, lowering the amount of DES to 1.0 equiv was feasible. However, further reduction of DES gave lower efficiency. According to optimization studies, ChCl–malonic acid (Table 1, entry 23) emerged out as an efficient DES for the reaction medium. Further, it is evident that only ChCl or malonic acid alone provided a trace amount of the product (entry 40, 41 Table 1), while the combination of ChCl–malonic acid (DES) provided a quantitative yield of the desired product formation. The hydrogen bonding in the DES (as an additive and catalyst) is fundamental for the selectivity of the products, that is, minimizing side products, replacing toxic solvents as well as expensive transition-metal catalysts. Accordingly, ChCl–malonic acid DES emerged out as the best DES additive or reaction medium for different transition-metal catalysts as tabulated (Table 1, entry 33–39). ChCl–malonic acid DES, $Pd(PPh_3)_4$, xantphos, and KO^{t}Bu combination at 90 °C in 2 h (Table 1, entry 23) gave quantitative yield in short time in comparison to the solvent-based optimization (Table 1).

Table 4. Scope of α-Alkylation of Acetophenones, 1 with Benzyl Alcohols, 2[a]



[a]Reaction conditions: acetophenone, **1** (1.0 mmol), benzyl alcohol, **2** (1.0 mmol), $Pd(PPh_3)_4$ (10 mol %), xantphos (10 mol %), KO^{t}Bu (1.5 equiv), in ChCl–malonic acid (1:1) DES (100 mg) at 90 °C for 1–3 h.

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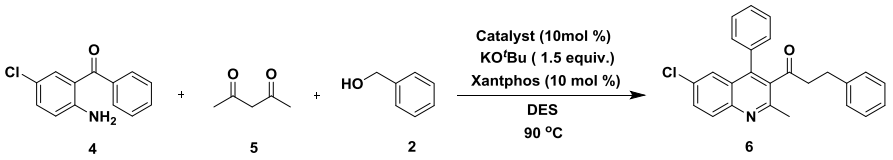
Table 5. Optimization of Sequential Friedländer Reaction sp^3−CH Activation (α-Alkylation of Ketones)[a]



entry	DES	catalyst	time (h)	yield (%)
1	ChCl−oxalic acid (1:1)	$Pd(PPh_3)_4$	6	65
2	ChCl−malonic acid (1:1)	$Pd(PPh_3)_4$	3	80
3	ChCl−citric acid (1:1)	$Pd(PPh_3)_4$	8	55
4	ChCl−tartaric acid (2:1)	$Pd(PPh_3)_4$	5	70
5	ChCl−D-glucose (1:1)	$Pd(PPh_3)_4$	6	45
6	ChCl−glycol (1:1)	$Pd(PPh_3)_4$	6	20
7	ChCl−urea (1:2)	$Pd(PPh_3)_4$	6	25
8	ChCl−thiourea (1:2)	$Pd(PPh_3)_4$	6	20
9	ChCl−PTSA (1:1)	$Pd(PPh_3)_4$	10	60
10	ChCl−$SnCl_2$ (1:2)	$Pd(PPh_3)_4$	6	30
11	ChCl−gallic acid (1:0.5)	$Pd(PPh_3)_4$	6	50
12	ChCl−malonic acid (1:1)	$Pd(OCOCH_3)_2$	12	50
13	ChCl−malonic acid (1:1)	$[Ru(p\text{-cymene})Cl_2]_2$	5	70
14	ChCl−malonic acid (1:1)	$[PPh_3]_2Ru(CO)_2Cl_2$	6	45
15	ChCl−malonic acid (1:1)	$[PPh_3]_3RuCl_2$	10	60
16	ChCl−malonic acid (1:1)	$[PPh_3]_4RuCl_2$	8	50
17	ChCl−malonic acid (1:1)	$Pd_2(dba)_3$	10	65
18	ChCl−malonic acid (1:1)	$PdCl_2(PPh_3)_2$	4	70
19	malonic acid	$Pd(PPh_3)_4$	2	trace
20	ChCl	$Pd(PPh_3)_4$	2	trace

[a]Reaction conditions: 2-aminobenzophenone, **4** (1.0 mmol), acetyl acetone, **5** (1.0 mmol), DES (100 mg at 90 °C for 30 min): benzyl alcohol, **2** (1.0 mmol), Pd or Ru catalyst (10 mol %), xantphos (10 mol %), KO^{t}Bu (1.5 equiv), at 90 °C (for overall time as indicated).

The pH values of the prepared DES were close to the pK_a of carboxylic acids utilized (Table 2). Further, a pH-based study has been explored to avoid the side product formation from the desired products. The highly basic pH [as seen in toluene conditions (Table 3)], should be avoided to reduce the side products (further reduction of the ketones to alcohols). The DES system provided slightly basic medium under the reaction conditions, thereby reducing side product formation (see Table 3). It is known that the several reaction intermediates are involved in the desired product formation through dehydrogenation and hydrogenation steps through ligand and base utilization, consequently resulting in the increment of the basicity in the reaction medium in toluene as well as DES; however, in the latter case, it was neutralized to some extent because of acidic DES.

Coming to the mechanism, DES has the ability of hydrogen bonding with the reactants, thereby facilitating reaction progress as seen in the plausible mechanism. Initially, benzyl alcohol is activated by the DES, subsequently, which undergoes dehydrogenation as facilitated by the palladium complex resulting in palladium hydride and benzaldehyde. DES being an ionic medium involves H bonds with the oxygen atom of the ketone group (activates), thereby increasing electrophilicity. This facilitates the nucleophilic attack (Scheme 3) at aldehyde to offer the α,β-unsaturated carbonyl compound as an intermediate (chalcone) by removal of water. At this point, the transfer of a proton from the palladium hydride complex takes place resulting in α-alkylated saturated ketone accompanied by regeneration of the active palladium complex. DES assumes a dual role of solvent as well as a catalyst. Likewise, DES through H bonding facilitates the formation of the palladium hydride complex $[PdH_2]$. The aldol condensation product chalcone and hydrogenation by $[PdH_2]$ then provided the desired product in short reaction time.

The reusability of the DES was demonstrated by recovering the same from the reaction mixture using aqueous workup after completion of the reaction as ascertained by thin layer chromatography. In other words, the reaction mixture was diluted with water to precipitate and filter the desired products. Then, the filtrate was evaporated to yield the DES−catalyst mixture which was reused for several runs without significant loss in catalytic properties. The DES alone was recycled utilizing CH_2Cl_2 or ether extraction from the water (after water workup filtration of reaction products), functional groups unaffected as evident from FT-IR signals (Figure 2) and tested successfully in five subsequent runs in comparable product yields without loss in their activity.

Having streamlined the reaction conditions in the ChCl−malonic-based DES, the scope of the reaction was explored utilizing electron-rich and electron-deficient acetophenones, such as 3-methyl, 4-methyl, 4-methoxy, 4-trifluoro, 3-hydroxy, 4-hydroxy, and 4-fluoro acetophenones, and corresponding benzyl alcohols. The sp^3 C−H functionalization underwent smoothly to provide α-alkylated enones **3a**−**m** in high yields as tabulated in (Table 4). Moreover, 2-amino-5-chlorobenzophenone, **4** reacted sequentially with acetyl acetone **5** and benzyl alcohol **2a** in the presence of $Pd(PPh_3)_4$, xantphos, KO^{t}Bu, and different DESs. The optimization revealed that ChCl−oxalic acid gave the 65% Friedländer reaction—α-alkylation product, **6a** (Table 5, entry 1) while ChCl−tartaric acid and ChCl−malonic acid melt resulted in 70 and 80% yield, respectively (Table 5 entry 4, 2).

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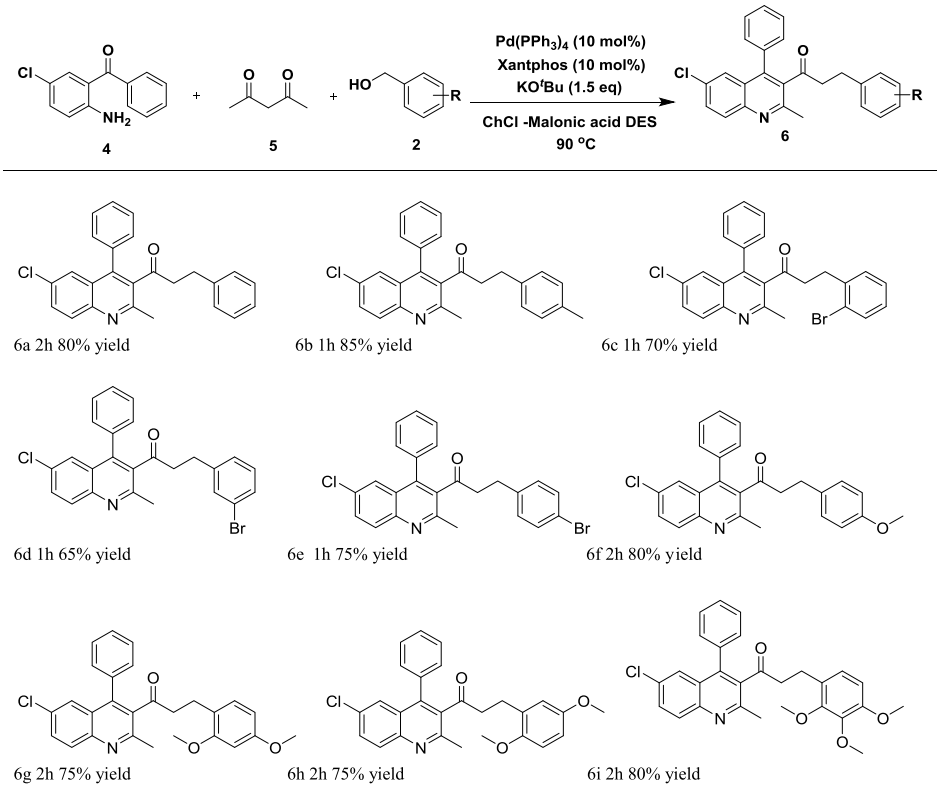
ACS Omega 2019, 4, 8046−8055

Table 6. Scope of Sequential Friedländer Reaction of 4-α-Alkylation of N-Heterocyclic Ketone 7 with Benzyl Alcohols 2[a]



[a]Reaction conditions: 2-aminobenzophenone, **4** (1.0 mmol), acetyl acetone, **5**, ChCl−malonic acid DES (100 mg) at 90 °C for 30 min: benzyl alcohol, **2** (1.0 mmol), $Pd(PPh_3)_4$ (10 mol %), xantphos (10 mol %), KO^{t}Bu (1.5 equiv), at 90 °C (for overall time as indicated).

Table 7. α-Alkylation of Benzyl Alcohol and Ketones, Comparison with Previous Reports

entry	catalyst	solvent	time (h)	temp (°C)	yield (%)	refs
1	[Cp*Ir(2,2′-bpyO)(H_2O)]	*t*-amyl alcohol	6	110	92	13
2	Ir(III)−CNP complexes	*t*-amyl alcohol	24	120	92	11
3	Ir^I−NHC complexes	toluene	2	130	97	12
4	$RhCl(CO)(PPh_3)_2$	dioxane	9	95	91	14
5	$RuHCl(CO)(PPh_3)$	toluene	20	14	86	18
6	$[RuCl^2(h^6\text{-}p\text{-cyene})]_2$/P,N ligand complexes	toluene	18	120	87	23
7	Pd/AlO(OH)	toluene	8	80	97	15
8	Fe-complexes	toluene	16	90	89	16
9	cobalt(II) complexes	toluene	24	120	93	17
10	**$Pd(PPh_3)_4$**	**DES**	**2**	**90**	**90**	**this work**

Generally, Friedländer quinoline reaction undergoes in the presence of acid or base, given literature reports in the introduction part. There is no such literature from the DES method; herein, DES facilitated the Friedländer reaction as well as α-alkylation among the tested DES (Table 5, entry 1−11). Further, among the tested transition-metal catalyst, $Pd(PPh_3)_4$, ChCl−malonic acid DES, xantphos, and KO^{t}Bu combination at 90 °C in 3 h gave a quantitative yield of **6a** (Table 5, entry 2, 12−18). The scope of the sequential Friedländer reaction and the α-alkylation reaction has been investigated by changing the substitutions on N-heterocyclic ketone and the influence on the yield of the desired product, **6** is tabulated in (Table 6). It is noteworthy to emphasize that, in all cases, byproduct-reductive products, ketals, and hemiketals formation were not observed. The reaction outcomes are identical comparing to earlier reports using iridium and[11,12,60,61] ruthenium,[23,62] in organic solvents (Table 7).

Control Experiments. To support the role of DES in the sequential Friedländer-α-alkylation reaction between ketone **4** acetylacetone **5** and benzyl alcohol **2** control reactions were performed in the presence or absence of the Pd catalyst. The reaction outcome revealed the chalcone intermediate formation **8** [as evidenced from gas chromatography−mass spectroscopy (GC−MS) analysis] in the presence of the Pd catalyst similar to the mechanism established so far[7] (see the Supporting Information). Anyway in the absence of the Pd catalyst, the quinoline methyl ketone formation was observed **7** (see, Scheme 4).

α-Alkylation of acetophenone with benzyl alcohol without the presence of catalyst-methyl ketone, **4** (1.0 mmol), benzyl alcohol **2** (1.0 mmol), KO^{t}Bu (1.5 mmol), ChCl−malonic acid

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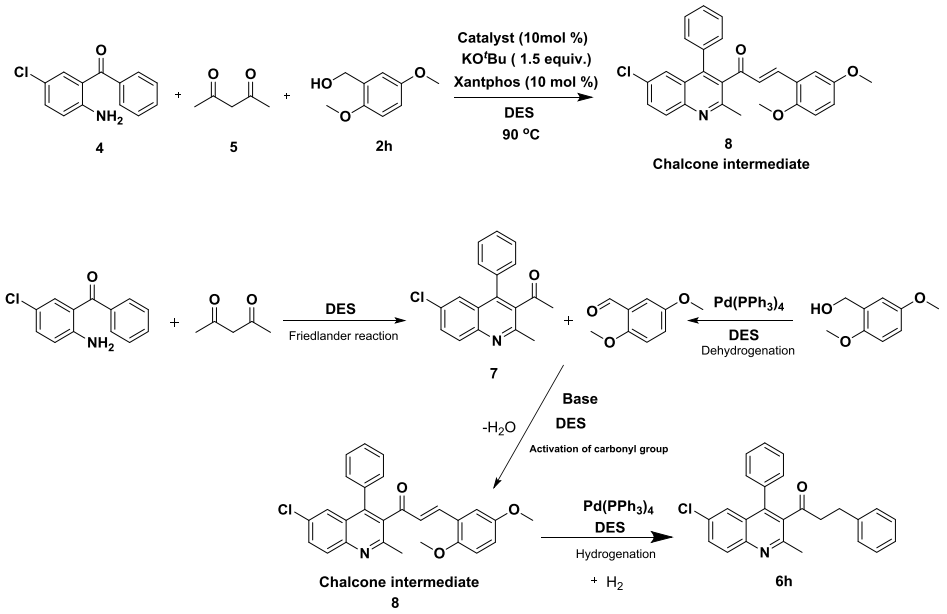
Scheme 4. Control Experiment



(1:1) (100 mg) DES, and xantphos (10 mol %), at 90 °C were charged into a screw-capped glass vial and heated at 90 °C. After 3 h, the crude reaction mixture was analyzed by using GC−MS, and there was no chalcone intermediate **8** observed. However in the presence of $Pd(PPh_3)_4$ (10 mol %), GC−MS analysis revealed chalcone intermediate **8** formation.

CONCLUSIONS

Overall, an efficient C−C bond formation through α-alkylation (BH strategy) of ketones with benzyl alcohols in DES was established. This method proved to be a broad functional group tolerant with wide substrate scope. At the same time, we developed an efficient, catalyst-free, sequential Friedländer reaction-α alkylation using DES as an environmental friendly reaction medium without further addition of toxic solvents such as toluene, dioxane, *t*-amyl alcohol, and so forth. This is the first time this method is adapted to produce such kind of C−C bond formation with DES. This method also provided mild reaction conditions, simple workup, and high product yields. The synthesized products are highly useful synthetic blocks in further functionalization which are in progress in our laboratory and will be communicated soon separately elsewhere.

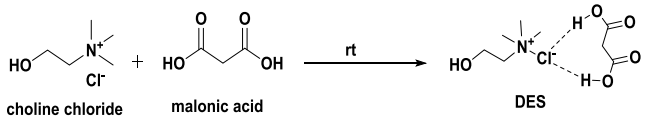
EXPERIMENTAL SECTION

Materials and Methods. All chemicals and reagents were purchased from Sigma-Aldrich Chemicals Ltd and used without further purification. The reactions were performed by using screw-capped glass vials in Apptec Lab Mate Manual Parallel Synthesizer. TLC was performed by using precoated aluminum TLC sheets (silica gel 60 F254, Merck). After the reaction, the reaction mixture was passed through, manual column chromatography was performed by silica gel (100−200 mesh, Merck and Co.) to give the pure product on petroleum ether and the ethyl acetate solvent system. FTIR spectra were recorded by using the Shimadzu IRTracer-100 FTIR Spectrometer. Wave numbers (ν_{max}) are reported in cm^{-1}. NMR spectra were recorded by using Bruker AVANCE-III (400 MHz) in $CDCl_3$, and chemical shift delta values (d) are reported in ppm (δ).

All our reactions are carried out in the LabMate Personal Manual Parallel Synthesizer, (see the Supporting Information) in closed vessels to exclude byproducts.

Scheme 5. ChCl−Malonic Acid Deep Eutectic Solvent Preparation[34]

Preparation of Choline-chloride based deep eutectic solvents (Ch-Cl DES):



Preparation of Choline Chloride-Based Deep Eutectic Solvents (ChCl DES). DES is a binary mixture of a salt and hydrogen bond donor (HBD), here tried with salt and HBD (organic acid composition). Choline chloride-based deep eutectic solvents were prepared according to the literature (Scheme 5);[34,36] choline chloride and the second component (HBD) were mixed on the basis of different amount ratios reported in Table 2, and reactants were heated until a clear liquid solution appeared, Abbott, et al. (2004).[34] Obtained DES was used directly without any further purification (Figure 1).

α-Alkylation of Methyl Ketones. Acetophenone **1** (1.0 mmol), benzyl alcohol **2** (1.0 mmol), $Pd(PPh_3)_4$ (10 mol %), xantphos (10 mol %), and KO^{t}Bu (1.5 mmol) were stirred in ChCl−malonic acid (1:1) DES at 90 °C after reaction completion was monitored by using TLC and the reaction mixture was diluted with water and extracted CH_2Cl_2 solvent. The crude reaction mixture after solvent removal was passed through manual column chromatography on silica gel to provide the pure product, **3a**.

Sequential Friedländer Reaction-α Alkylation. A mixture of 2-amino5-chlorobenzophenone **4** (1.0 mmol) and acetyl acetone **5** (1.0 mmol) in DES was heated at 90 °C for 30 min to offer Friedländer product, **6**. Then, benzyl alcohol **2** (1.0 mmol), $Pd(PPh_3)_4$ (10 mol %), xantphos (10 mol %), and

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KO^{t}Bu (1.5 equiv) was added and continued stirring at 90 °C till reaction completion as monitored by TLC. Then, the reaction mixture was diluted by using water and extracted with CH_2Cl_2 solvent. The reaction mixture after evaporation of the solvent was passed through column chromatography on silica gel to give the pure product, **6a**.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b00310.

Copies of ^{1}H, ^{13}C NMR, HRMS, and IR spectra of the synthesized products, control experiment GC−MS data, additional data, and figures and tables (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nawaz_f@yahoo.co.in. Phone: +91-9444234609.

ORCID

Fazlur Rahman Nawaz Khan: 0000-0001-7828-526X

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

DES, deep eutectic solvent; BH, borrowing hydrogen; ILs, ionic liquids; ChCl, choline chloride; Pd, palladium; Ru, ruthenium; Ir, iridium; Rh, rhodium; TLC, thin-layer chromatography

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