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Graphical Abstract

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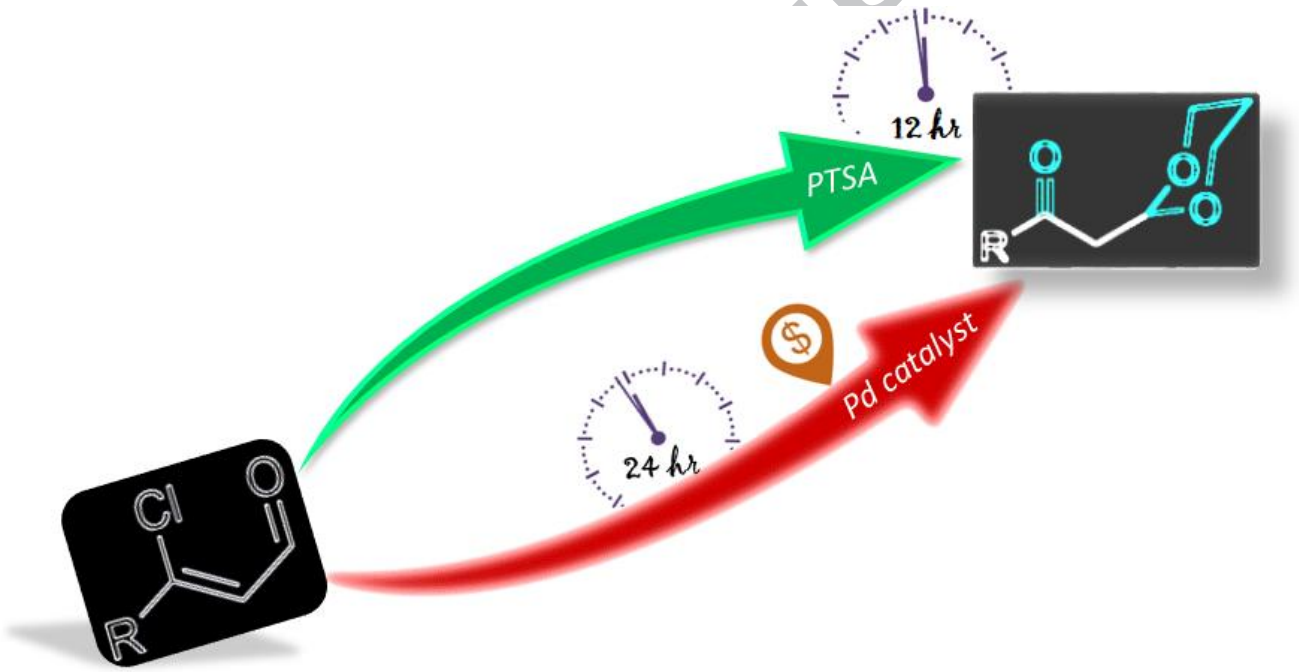
[a]*Department of Chemistry, Malaviya National Institute of Technology Jaipur, JLN Marg, Jaipur 302017, Rajasthan, India*



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Metal-free, PTSA catalyzed facile synthesis of *β*-ketoacetal from *β*-chlorocinnamaldehyde

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ABSTRACT

A toluene solution of β-chlorocinnamaldehyde and dihydroxy alcohols in the catalytic presence of *para*-toluenesulphonic acid (PTSA) yield the β-ketoacetal in good to outstanding amount. The catalyst (PTSA), first selectively protect the aldehydic group to form the β-chloroacetal and the subsequent dechlorination by H_2O result the β-ketoacetal. A significant transformation was achieved with electron donating substituent attached at the β-position of cinnamaldehyde. The selective formation of β-keto-1,3-acetal was also obtained with a mixture of 1, 2- and 1, 3- diol. The present reaction consists a metal-free, economical, robustly feasible, sizeable functional group tolerance and high yield properties. Moreover, the use of different dihydroxy alcohols made this process more benign and valuable towards the metal-free development of ketones. First of its kind, a rare and unusual multitasking nature of PTSA is observed.

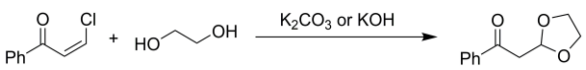
Introduction

Protection and deprotection of the carbonyl functionalities are quite common in multistep organic synthesis[1]. The protection of carbonyls group is usually carried out either in the presence of Lewis acid or protonic acid.[2] Various reagents including the tetrabutylammonium tribromide[1], $ZrCl_4$[2], $PdCl_2Ce(OTf)_3$[3], $PhICl_2$[4], $(EtO)_3CH$ - DDQ[5], $(EtO)_3CH$ - NBS[6], I_2[7] and $Sc(NTf_2)_3$[8] used as common reagents for the protection/deprotection of carbonyls. Literature avident the protection of large numbers of general and functionalized carbonyls groups,[9] but surprisingly the protection of *β*-chlorocinnamaldehydes is still not reported. Hence, it motivate us to investigate the protection of carbonyl functionality present in *β*-chlorocinnamaldehyde and the synthesis of β-chloroacetal was our prime expectation from this reaction. However, quite a few reports are available for synthesis of β-chloroacetals[10,11] but these all consists the multistep process and need quite expensive reagents and catalyst (Di-tert-ButylPeroxide)[10]. Hence, a promising alternative and inexpensive catalyst is highly desire for the chloroacetal formation. PTSA is very cheap and most common catalyst[12] used for the protections of carbonyl groups, moreover, it was not explored for the protection of cinnamaldehyde, hence, use of PTSA as a catalyst become an ideal choice for the desired transformations. But, unlike to our expectations, a different product, a β-ketoacetal was formed in reaction trials. Since, there is no previous report available for the direct synthesis of β-ketoacetal and β-chloroacetal from β-chlorocinnamaldehyde with PTSA or any other catalyst. These observations encouraged us to investigate this particular reaction. The panorama of the methodology developed through this scheme shows that it will be equally beneficial for the synthesis of both the products.

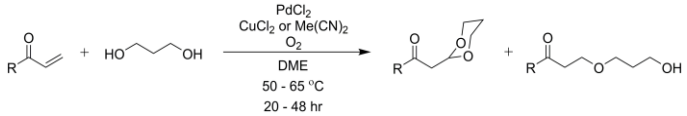
β-ketoacetals are more valuable synthons than β-chloroacetal and have great diversity as a precursor for many natural and biologically active compounds.[13] Nevertheless, as per literature concern, the β-chloroacetals also have sifinificant but limited applications.[11] Moreover, synthesis of β-ketoacetal recorded several patents in last few decades,[14-16] Reported methods mostly use the precious metals, i.e. $PdCl_2$-$CuCl_2$-O_2[17], $PdCl_2$-$(MeCN)_2$-O_2[18], however, quite a few also reported with $SiO_2.H_2SO_4$ - DDQ[19] and K_2CO_3 or KOH[19] catalysts. Moreover, the used reactant already consist of a ketonic functional group which is economically not viable and difficult to synthesise. Literature indicates, the synthesis of *β*-ketoacetal was first reported by Nells et al. in 1937, while, other synthetic methods up to 1960 for the β-ketoacetal are only available in patent forms. The first cyclic β-ketoethyleneacetals was synthesized by Kochetkov et. al.[13] in 1957, by reaction of β-chlorovinylketone and ethandiol in the presence of K_2CO_3 or KOH base. Hosokawa et al.[17] reported $PdCl_2$-$CuCl_2$ catalyzed the synthesis of β-ketoacetal from terminal olefins, the same research group also reported the modified synthesis with $PdCl_2$-$Me(CN)_2$[18] catalyst in the O_2 environment. The most recent method was reported in 1993 by Campi et al.[19], a acid-treated silica gel or DDQ catalyst was used for the transformation of β-aldehyde acetals to β-ketoacetal. In recent, quite similar to β-ketoacetal, the synthesis of β-ketodithiane from the β-chlorodithiane has been reported by Tang et al. with a $FeCl_3$ catalyst and H_2SO_4 (Scheme 1).

a) Literature precedent

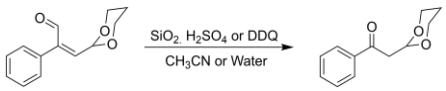
Kochetkov et al., 1961



Hosokawa et al., 1987 and 1989



Campi et al., 1993



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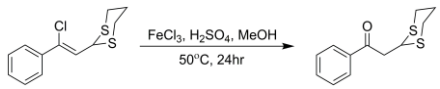
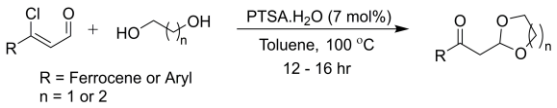
Tang et al., 2015



b) This work



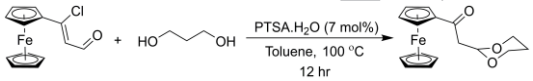
Scheme 1 Synthesis of β-ketoacetal from various reagents

Hydration of alkynes is one of the most common method for the catalytic synthesis of ketones, PTSA catalyzed as well as metal free green methods has also been used for the hydtration of alkynes.[20] Unlike alkynes, alkenes are difficult to hydrate, the Wacker process is extensively used in industries for the production of aryl/alkyl ketones from alkenes/alkynes. This methods, required a Pd-catalyst and Cu salts (co-catalyst) for the significant synthesis of ketones from olefines.[21-25] In the present scheme, wacker type hydration of chlorovinyl is observed.

For to established the missing link found from the literature for the direct synthesis of β-ketoacetal and β-chloroacetal from β-chlorocinnamaldehyde, we decided to add our contribution, and it is the first ever metal-free and direct method for scalable synthesis of β-ketoacetals and β-chloroacetal under different circumstances.

Results and Discussion

Toluene solution of a (2-formyl-1-chlorovinyl)ferrocene and 1,3-propanediol (1:5 ratio) in catalytic presence of PTSA (7 mol%) is thermally heated up to reflux temperature for 12 hr resulted in the formation of β-ketoacetal. Here, the protection of carbonyl followed by the simultaneous dechlorination and hydration of vinyl chloride in the presence of PTSA catalyst yields the β-ketoacetal in 90% **(Scheme 2)**. The reaction with ferrocene substitution selectively produces β-ketoacetal.



Scheme 2 Thermal reaction of a (2-formyl-1-chlorovinyl)ferrocene of and 1,3-propanediol

PTSA is an inexpensive catalyst, it works exceptionally well for the present reaction and brings the desired transformations in 12-16 hr for different functionalities. During the catalyst optimizations, we found, a catalyst-free reaction does not yield the desired β-ketoacetal or β-chloroacetal (Table 1, entry 1). During the optimizations for mol% of PTSA, it was noted that the β-ketoacetal started to form with 4 mol% of PTSA. Moreover, the 7 mol% of PTSA become an ideal for the reaction (Table 1, entries 3-5), and further addition of PTSA does not bring any additional changes in the yield of desired product (Table 1, entry 6). Use of minerals acids (HCl, H_2SO_4, HNO_3, and H_3PO_4) or organic acids (oxalic acid, pivalic acid and acetic acid) as a catalyst for this reaction, fails to mimic the desired transformation of β-ketoacetal (Table 1, entry 7-12 and See SI). Benzoic acid, trifluoroacetic acid and adipic acid were also screened for the reaction, but, the inferior quantity of β-ketoacetal was obtained (see SI). Various alcohols were screened for the reaction and the results are summarized in Table 1, (entry 1 and 13-17). It was observed, that the reaction does not produce any transformation without the alcohol (Table 1, entry 2). Moreover, results were not changed when methanol was introduced as a reagent (Table 1 and entry 13). The trace of the product was obtained with ethanol and propanol, while butanol and pentanol does not form even trace of the desired prodcut (See SI). Furthermore, the secondary and tertiary alcohols were also investigated but could not succeed (Table 1, entry 15 and 16). When dihydroxy alcohols (terminal in nature) were introduced in the reaction, a significant to outstanding transformation of the desired product was obtained (Table 1, entry 5 and 17). It indicates that the diols consisting of terminal hydroxyl groups are highly active reagents for the current transformations. The reaction exhibits a multitasking role of PTSA, the protection of carbonyl group and then facilitates for nucleophilic hydrations to the β-chlorovinyl group. During the reagent optimizations, the continuous addition of 1,3-propanediol (1 to 5 equivalent) significantly improved the yield of β-ketoacetal (Table 1, entry 20-24). Furthermore addition of 1,3-diol de-accelerate the rate of transformation and reduced the formation of β-ketoacetal (Table 1, entry 25). The formation of β-ketoacetal was significantly affected by the solvent used in the reaction. A non-polar benzene solvent yields the 60% desired product while an excellent yield of 91% was obtained in toluene solution. The yield of β-ketoacetal was severely reduced in xylene, tetrahydrofuran and acetonitrile, i.e. 20%, 25%, and 30% of desire products were respectively isolated (See SI). The reaction does not initiate in dimethylformamide solvent. Moreover, we did not find any product when the reaction was investigated in water solvent (Table 1, entry 18). However, a mixture of water and toluene nicely works for the reaction and produces 84% of the desired product with 1,3-propanediol (Table 1, entry 19). The rate of product transformation was also influenced with change in reaction temperature, almost 80-90% yield of the ketoacetal was obtained at 100 °C (see SI), while any negative or positive deviation of the temperature resulted the inconsistent amount of β-ketoacetal.

Table 1 Reaction optimizations with ferrocene substituted β-chlorocinnamaldehyde

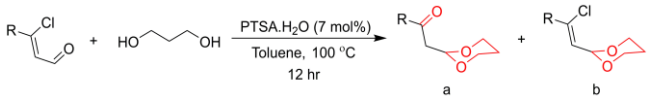
Entry	Catalyst (mol%)	Reagent (Equivalent)	Yield[a] (%)
1.	-	1,3-Propanediol (5)	Nd
2.	PTSA.H_2O (10)	Nil (only solvent)	Nd
3.	PTSA.H_2O (2)	1,3-Propanediol (5)	Nd
4.	PTSA.H_2O (4)	1,3-Propanediol (5)	20
5.	PTSA.H_2O (7)	1,3-Propanediol (5)	91
6.	PTSA.H_2O (10)	1,3-Propanediol (5)	50
7.	HCl (7)	1,3-Propanediol (5)	Nd
8.	H_2SO_4 (7)	1,3-Propanediol (5)	Nd
9.	HNO_3 (7)	1,3-Propanediol (5)	Nd
10.	H_3PO_4 (7)	1,3-Propanediol (5)	Nd
11.	Pivalic acid (7)	1,3-Propanediol (5)	Nd
12.	$(COOH)_2$ (7)	1,3-Propanediol (5)	Nd
13.	PTSA.H_2O (7)	Methanol (5)	Nd
14.	PTSA.H_2O (7)	Ethanol (5)	trace
15.	PTSA.H_2O (7)	2-Propanol (5)	Nd
16.	PTSA.H_2O (7)	*tert*-Butanol	Nd
17.	PTSA.H_2O (7)	1,2-Ethanediol (5)	68
18.	PTSA.H_2O (7)	Water (5)	Nd
19.	PTSA.H_2O (7)	1,3-Propanediol+water	84
20.	PTSA.H_2O (7)	1,3-Propanediol (1)	≈10
21.	PTSA.H_2O (7)	1,3-Propanediol (2)	24
22.	PTSA.H_2O (7)	1,3-Propanediol (3)	51
23.	PTSA.H_2O (7)	1,3-Propanediol (4)	73
24.	PTSA.H_2O (7)	1,3-Propanediol (5)	91
25.	PTSA.H_2O (7)	1,3-Propanediol (6)	70

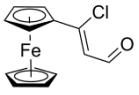
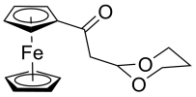
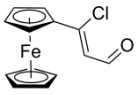
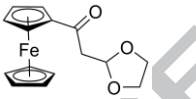
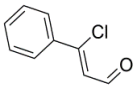
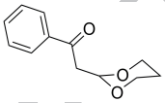
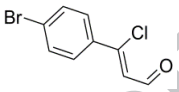
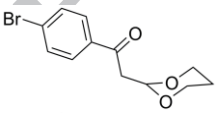
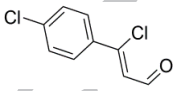
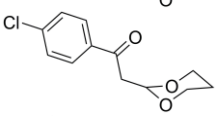
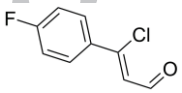
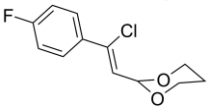
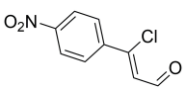
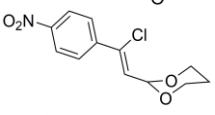
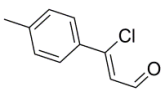
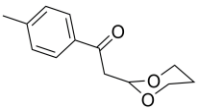
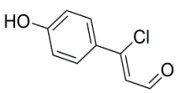
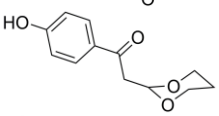
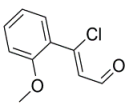
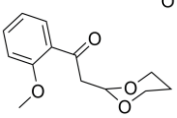
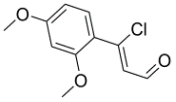
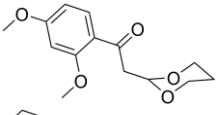
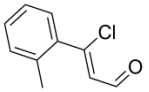
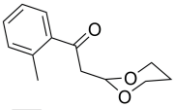
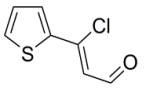
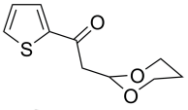
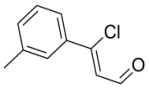
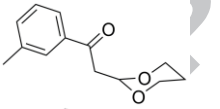
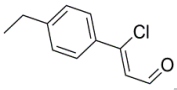
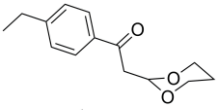
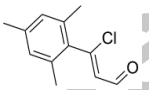
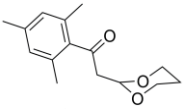
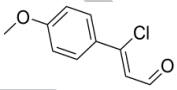
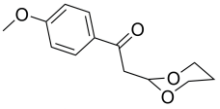
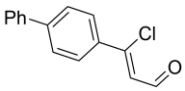
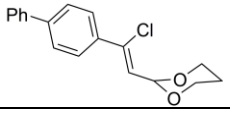
[a]Isolated yields, reaction conditions, Toluene (solvent, 20 ml), Temp. 100˚ C, 12hr, nd = not detected

After successful optimizations, the forthcoming task is to explore the substrate scope for the reaction. Hence, the reaction was generalised with various aryl derivatives of β-chlorocinnamaldehydes (Table 2). Aryl substitutions dramatically affect the course of reaction which includes the slow transformations (12 to 16 hrs), no product formation and the selective formation of β-chloroacetal. The presence of different functionalities (electron

donating and electron withdrawing) on the benzene ring strongly affects the yield of products, moreover, the bulkier groups present on aryl group bring some steric hindrance and reduced yield of desired product. It was observed that, all the electron donating functionalities present at the para position of benzene ring, strongly favours the formation of β-ketoacetal, except 4-methoxy, for which we are unable to perceive the reason. While on the other hand, the electron withdrawing functionalities present on the para position, selectively produced the β-chloroacetal. We assumed that a an intermediate (**I in scheme 4**) a carbocation formed during the nucleophilic substitution (SN^1) of Cl to OH.[26a] This vinylic carbocation is relatively stable with electron donating groups and vice versa, hence, it decides the fate of the product. Unlike to the para position, electron donating group at ortho- position decreases the yield of desired product and also form multiple insignificant bands on TLC. Meta-substituted benzene was found much active than the ortho- substitution. Multiple substitutions on aryl like 1,3,5-trimethyl drastically reduce the yield of β-ketoacetal, perhaps, steric hindrance may be the reason for this. The 2,4-dimethoxy substitution produces an average yield of β-ketoacetal. Chloro and bromo derivative at the para- positions of benzene produce a mixture of β-ketoacetal and β-chloroacetal, while fluoro and nitro substitutions result only β-chloroacetal due to the decreased stability of vinylic carbocation.

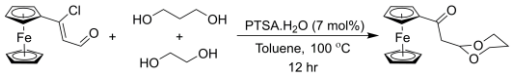
Table 2 PTSA catalysed the formation of various *β*-ketoacetal.



Entry	Reactant	Product	Yield % [a]	
			a	b
1.			91	nd
2.			68	nd
3.			67	22
4.			63	27
5.			58	38
6.			nd	72
7.			nd	69
8.			71	nd
9.			55	nd
10.			50	nd
11.			44	nd
12.			67	nd
13.			86	nd
14.			63	nd
15.			59	nd
16.			14	nd
17.			09	nd
18.			nd	58

Reaction conditions, PTSA (7 mol %), 1,3-Propanediol (5 mmol)), *β*-chlorocinnamaldehydes (1 mmol), Toluene (20 ml), 100° C, 12-16 hr. [a]isolated yield, nd=not detected.

In the reaction of the model substrate with a mixture of 1, 2 and 1, 3-diol (1:1 equimolar ratio, **5** equivalent of each) under the optimised reaction conditions, the selective formation of β-ketoacetal with 1, 3-propanediol was obtained (Scheme 3). This indicates the reaction shows complete chemo-selectivity for the formation of β-ketoacetal with 1,3-diol. Previous reports also state the selective acetal formation from aldehydes and showed the higher affinity towards the formation of 1,3-dioxanes(six-membered) than the 1,2-dioxolanes (five-membered).[1]



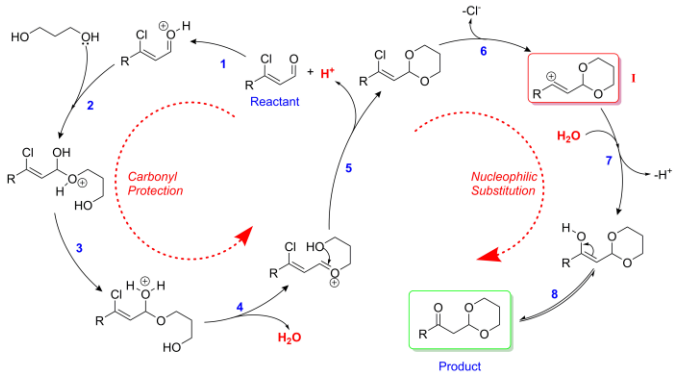
Scheme 3 Chemo-selective formation of ferrocene-substituted β-keto-1,3-acetal

Structural features of all obtained products were spotted by systematic characterisation using FTIR, ^{1}H and ^{13}C NMR, mass spectrometry and single crystal X-ray diffraction (SCXRD) analysis. C=O bond stretching frequencies in FTIR of various *β*-ketoacetals were recorded in the range of 1666 to 1685 cm^{-1}. In ^{1}H NMR, the characteristic doublet of the 2H present at α-carbon (concerning ketone group towards dioxane ring) appeared in a range of 2.98 to 3.20 ppm, while a triplet of 1H, present at β-carbon recorded in the range of 4.42 to 5.20 ppm. In ^{13}C spectra, a characteristic signal of the carbonyl group was found in the range of 195 to 200 ppm. The detailed spectral data is separately provided in supporting information. Suitable quality single crystals of ferrocene-substituted β-ketoacetal were grown and the x-ray diffraction data were collected at low temperature; data were resolved and the molecular structure of compound was established (fig 1. SI).

The present transformation consists of concomitant acetal formation followed by the dechlorination and oxygenation of β-chloroacetal. The formation of β-ketoacetal is evident from two simultaneous concomitant reactions after one another. There are several reports

available which show the use of PTSA for protection of carbonyl group, which result in the acetal and water (by-product).[9] The water formed as a by-product of the acetal formation facilitates the formation of the desired product. Literature evidence suggests, water is a recognised nucleophile, and in particular conditions, it can work as nucleophilic reagent.[28]

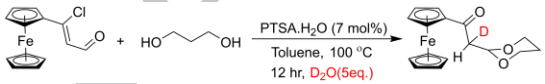
Since no intermediate was trapped during the reaction, however, a tentative mechanism has been proposed and depicted in scheme 4. The reaction was initiated by brønsted acid (PTSA.H_2O) and undergoes a conventional carbonyl protection reaction with the diol (step 1-5).[29] Formation of dioxane ring produces water as a by-product (step 4).

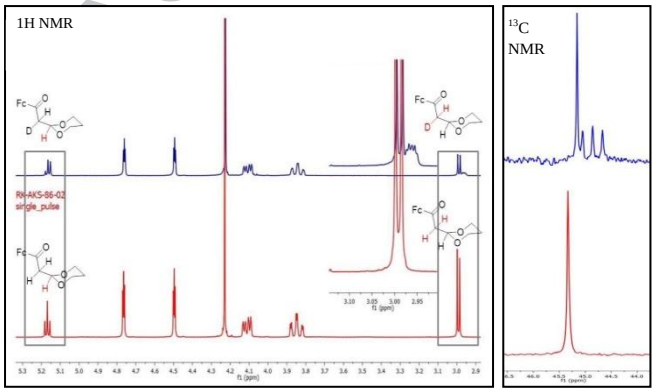


Scheme 4 Plausible mechanism of the formation of β-ketoacetal

This water works as a nucleophile (step 6), and the nucleophilic substitution reaction (via SN^1) of H_2O yielded β-hydroxy-1,3-dioxane (step 7).[28] Finally the keto-enol tautomerism produces the desired product. Vinyl carbocations (VC's) are the interesting intermediates; an excellent literature[26] is abundant that shows nucleophilic substitutions at halo substituted vinyl carbon favoured the SN^1 pathway. Here, in this scheme vinyl carbocation is the crucial step that controls the formation of β-ketoacetal and β-chloroacetal. As the presence of electron withdrawing groups at aryl severely discourages the stability of vinyl carbocation. While on the other hand, electron donating groups proceeds to form β-ketoacetal.

To confirm the proposed hypothesis, reaction of the model substrate along with the reagents and deuterated water (D_2O) was conducted in optimized reaction conditions (Scheme 5). After 12 hour, the reaction was terminated and the product was isolated in yield of 63%. The spectral analysis (^1H and ^{13}C NMR) of the obtained product was recorded and depicted in scheme 5, it was noted that the spectral data strongly supports the plausible mechanism.





Scheme 5 ^1H and ^{13}C NMR data of 2-(1,3-dioxan-2-y1)-1-ferrocenylethanone in comparison to ^2D labelled 2-(1,3-dioxan-2-y1)-1-ferrocenylethanone

Since, the ^1H NMR of the isolated β-ketoacetal shows the signals of deuterium at β-position of ketoacetal. We assume incorporation of deuterium is either may be due to the direct attack of D_2O which facilitated by PTSA to chlorine bonded carbon in the second step (nucleophilic substitution) of the mechanism. The other may be the cause of D_2O undergo hydrogen exchange equilibrium with the H_2O formed (as a by-product) during the first step (carbonyl protection) of the reaction to form HDO. This HDO acts as a nucleophile and performs the nucleophilic substitution.

In conclusion, the aryl derivatives of β-chlorocinnamaldehyde and diols in the presence of PTSA significantly results in the β-ketoacetal in good to the excellent yield. First in kind, rare and unusual multitasking PTSA catalyst produces the selective protection of formyl group followed by a concomitant formation of β-ketoacetal. Considerable to sizeable transformations observed with ortho-, para- and meta-substituted benzene derivatives, but para- substitution seems to be more selective and provide a commercially scalable yield in most of the cases. We conclude the present reaction offers an economical, high yielding, metal free, robustly feasible, aqueous biphasic, broad functional group tolerance and chemo-selective synthesis of ketoacetal. Moreover, the product can be achieved with different alcohols and made the process more facile and highly valuable for the metal-free development of ketones.

Acknowledgements

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Highlights

- First, metal free PTSA catalyzed wacker type oxidation of β-chlorocinnamaldehyde.
- Outstanding yield with chemo-selective transformation of β-ketoacetal.
- Excellent functional group compatibility with electron donating functional groups.
- A novel, economical, robustly feasible, aqueous biphasic and high yielding method.
- One pot synthesis method of β-ketoacetal via concomitant acetal and ketone formation.