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Highly chemoselective transfer hydrogenation of the C═C bonds of α-Keto substituted acrylate compounds catalyzed by an Iridium-TsEN complex in water

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ABSTRACT

Highly chemoselective transfer hydrogenation of the C═C bonds of α-keto substituted acrylate compounds catalyzed by an $[IrCl_2Cp^*]_2$-TsEN Complex ($Cp^* = \eta^5$-C_5Me_5) in water using sodium formate as hydride source has been developed. A variety of α-keto substituted acrylate compounds were reduced smoothly under 0.5 mol% of Iridium catalyst with 1.0 mol% ligand TsEN and 3 equiv. of sodium formate providing the desired product α-alkyl-β-keto esters in high to excellent yields (80–99 %). The procedure presented is simple and makes this method suitable for practical use.

Introduction

β-Keto esters have been proved to be invaluable building blocks and intermediates in organic synthesis due to the ease in converting them into versatile functionalities [1]; which have been widely utilized in the construction of various natural products and biologically active compounds [2]. Therefore, it is not surprising that numerous synthetic strategies through C—C bond-formation process toward such β-keto esters with structural diversity have been explored. These reactions include the Claisen condensation under strong base conditions [3], Lewis acids catalyzed Roskamp reaction of alkyl diazoesters with aldehydes [4], and the Blaise reaction of zinc metal with α-bromoesters and nitriles [5]. Apart from the above feasible methods, the selective reduction of C═C bonds of α-keto substituted acrylate compounds represents another most attractive and efficient approach for the synthesis of β-keto esters with α-alkyl substituents because of the easy access to starting materials from Knoevenagel condensation of β-keto esters with aldehydes. Thus, considerable efforts have been devoted to this area and numerous reduction methodologies have been reported for this purpose. For examples, Park et al reported the reduction of α-keto substituted acrylate to β-keto esters either using Pd/C and H_2 in methanol or using tri-*n*-butyltin hydride in toluene under reflux conditions (Scheme 1a).[1e] However, the 3-bromo moiety was partially removed during the reduction of the unsaturated double bond by Pd/C catalyzed hydrogenation.

Recently, Zhang and co-workers reported the 1,4 conjugate reductions of double bonds using sodium hydride as Michael donor under the catalysis of $PdCl_2$ in DMA (Scheme 1b) [6]. However, when the substrate methyl-3-oxo-2-(phenylmethylene)butanoate (R^1 = Me, R^2 = OEt, Ar = Ph) was employed, the catalyst $PdCl_2$ loading was increased to 50 mol% giving the reduced product in 90 % yield. In 2017, Wang and co-workers described the reduction of α-keto substituted acrylate compounds using Hantzsch ester as reducing agent and 20 mol% of thiourea as catalyst. The reactions performed in water at 100 °C gave the desired α-alkyl-β-keto esters in moderate to high yields (Scheme 1c) [7]. However, these well-established methods frequently suffer from either the use of hazardous hydrogen gas and highly toxic organotin reagent or high catalyst loading (normally 5–20 mol%), which promotes the reactions to be completed in reasonable time scales. Furthermore, the organic solvents, such as toluene, DMA, or MeOH, which are typically used for these reactions, are major problem from a green chemistry perspective. Therefore, the development of highly chemoselective catalysis aimed at lowering catalyst loading and being active in an aqueous media system would be highly desirable.

In this research, we envisioned that the C═C bonds in activated α-keto substituted acrylate compounds could be selectively reduced by Noyori-Ikariya-type catalyst to the corresponding saturated β-keto esters using sodium formate as hydrogen source in aqueous media (Fig. 1d).

Over the past decades, the Noyori-Ikariya-type transition metal complexes catalyzed transfer hydrogenation (TH) represented has

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emerged as one of the most powerful tools for the reduction of C═O groups with highly chemoselective for the C═O function and tolerant of alkenes [8]. However, when the α,β-unsaturated keto compounds are used as substrates, the TH leads to a rather more complex pattern of selectivities with 1,2- and 1,4-reduction products. For examples, Deng et al. reported the reductions of α,β-unsaturated methyl ketones to allylic alcohols with $[RuCl_2(cymene)]_2$-TsEN and $[RuCl_2(cymene)]_2$-TsDPEN catalysts, using the azeotrope of formic acid and trimethylamine as hydrogen source (Fig. 2a) [9]. When the chalcone was used as the substrate under the same reaction conditions, the reaction resulted in a mixture (3:1) product of saturated ketone and saturated alcohol. He also found that under the same reaction conditions, the reduction of C═C bonds can be promoted by incorporating electron withdrawing groups into substrate. Interestingly, when the trifluoromethyl group was introduced into β position of α,β-unsaturated ketones, the reaction only yielded 1,2-reduction products under the catalytic system of $[RuCl_2(cymene)]_2$-TsDPEN with formic acid/trimethylamine as both hydrogen source and solvent (Fig. 2b) [10]. Recently, Costa and co-workers reported the asymmetric 1,4 reduction of arylidene-substituted chromanones and tetralones, which are catalyzed by 5 mol% of $[RuCl_2(cymene)]_2$-TsDPEN and HCO_2Na (5 equiv.) in a mixture solvent of DCE/H_2O, resulting in the saturated benzylic alcohols as the major products along with the corresponding minor products saturated ketones and allylic alcohols. In addition, 20 mol% of phase-transfer catalyst is required to promote the reactions (Fig. 2c) [11]. Vidal et al also reported the same asymmetric TH of arylidene-substituted chromanones catalyzed by tethered Rh-diamine complex and a mixture of HCO_2H/DABCO (2:1) in CH_3CN, affording the saturated benzylic alcohols [12].

As part of our continuous research interest in the development of water-compatible catalysts that are effective in aqueous media [13], herein, we wish to report a new method with high specific chemoselectivity for the TH of the C═C double bonds of α-keto substituted acrylate compounds catalyzed by iridium-diamine complex using sodium formate as hydride source in water [14].

Results and discussion

Initially, the transfer hydrogenation of α-keto substituted acrylate compound **3a** was selected as a model reaction for screening the transition metal precursors, ligands, hydride source, and solvents, and the results were summarized in Table 1. As shown in Table 1, with 1 mol% of $[RhCl_2Cp^*]_2$ as catalyst and 2 mol% of (R,R)-TsDPEN **1** as ligand, a mixture of formic acid and trimethylamine as hydride source, the reaction proceeded smoothly in CH_2Cl_2 for 3 h to give the reduced product **4a** in 89 % yield. However, the enantioselectivity is low with only 5 % ee (entry 1). When we changed the solvents and hydride sources, the reactions gave the excellent yields with comparable low enantioselectivities (entries 2–3). The low enantioselectivity was observed due to partial and complete enolization of resulted ketone **4a** [9]. Therefore, asymmetric TH of α-keto substituted acrylate compound **3** was not further investigated.

Next, we examined the model reaction using the achiral TsEN **2** as ligand, 4 equiv. of HCO_2Na as the hydride source and 1 mol% of metal precursors as catalysts in water, all reactions could work smoothly to give excellent yields 90–98 % (entries 4–6) with long reaction time for Ru metal precursor catalyst (entry 5). The influence of hydride donor HCO_2Na loading was also investigated. When the amount of HCO_2Na was decreased from 4 equiv. to 3 equiv. and 2 equiv., respectively, the reactions gave the reduced products in comparable high yields (entries 7–8). When 2 equiv. of HCO_2Na was used under 0.5 mol% catalyst, the reaction took 24 h to give the product in 99 % yield (entry 9). However, further decrease of the catalyst loading to 0.25 mol% resulted in 50 %

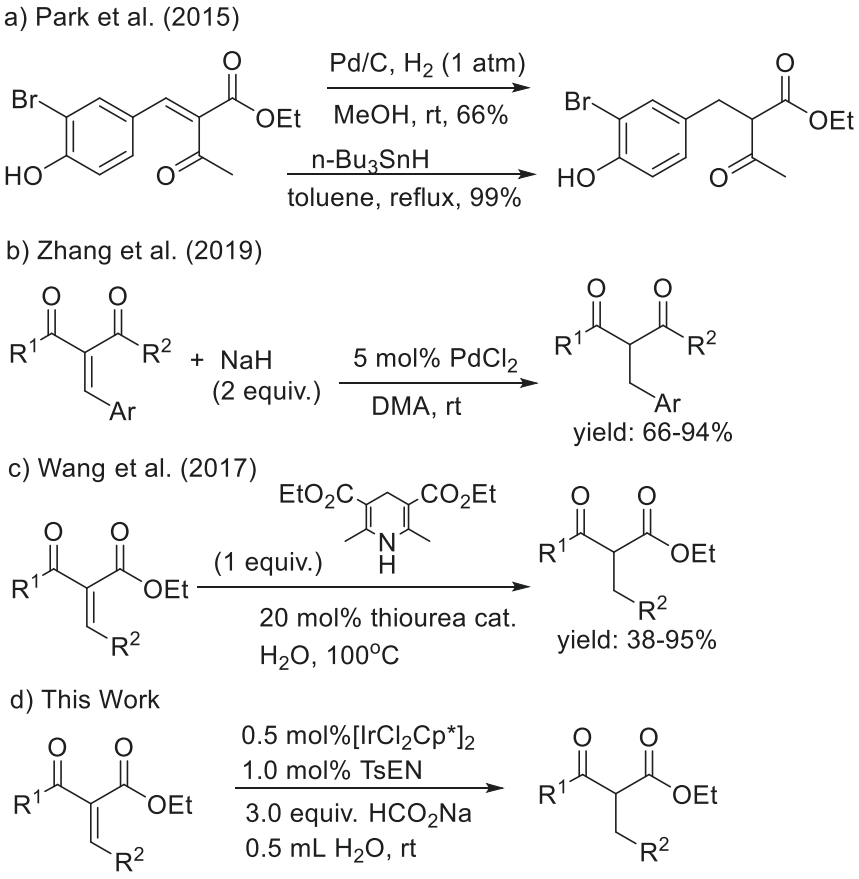


Fig. 1. Representative approaches for α-alkyl-β-keto esters from reduction of C═C bonds.

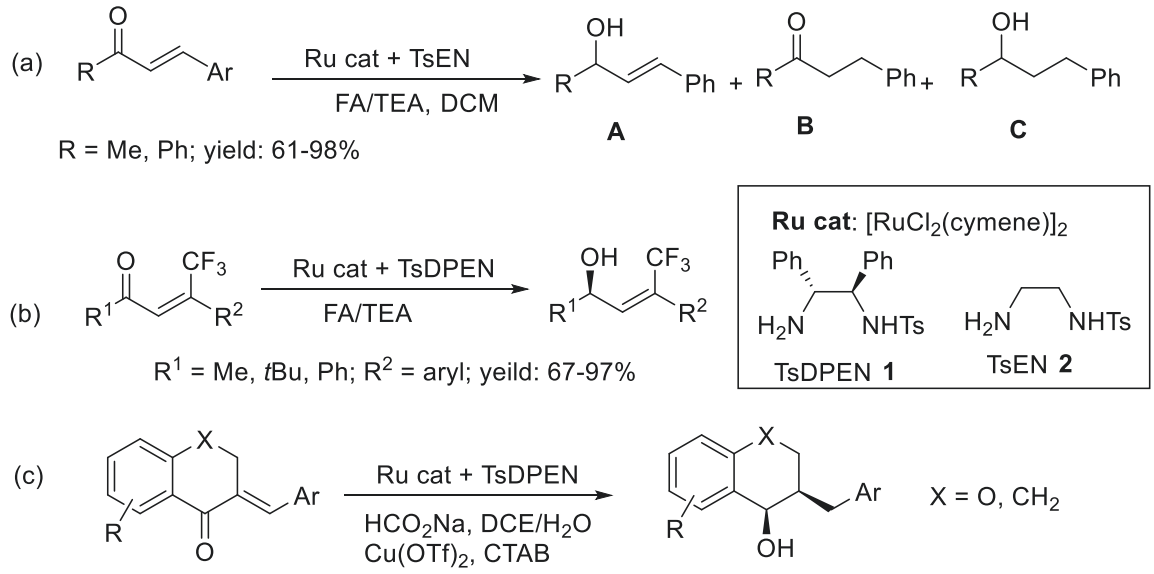
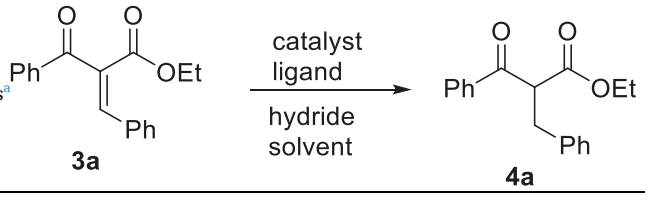


Fig. 2. Transfer hydrogenation of α,β-unsaturated ketones.

Table 1

Optimization of the TH reaction conditions[a]



entry	catalyst (loading)	ligand	solvent	hydride source	time (h)	yield[b] (%)	ee[c] (%)
1	$[RhCl_2Cp^*]_2$ (1 mol%)	TsDPEN	CH_2Cl_2	FA:TEA (3:2)	3	89	5
2	$[RhCl_2Cp^*]_2$ (1 mol%)	TsDPEN	EA-H_2O	HCO_2Na (4 eq.)	3	93	5
3	$[RhCl_2Cp^*]_2$ (1 mol%)	TsDPEN	H_2O	HCO_2Na (4 eq.)	3	97	5
4	$[RhCl_2Cp^*]_2$ (1 mol%)	TsEN	H_2O	HCO_2Na (4 eq.)	5	90	–
5	$[RuCl_2Cp^*]_2$ (1 mol%)	TsEN	H_2O	HCO_2Na (4 eq.)	24	98	–
6	$[IrCl_2Cp^*]_2$ (1 mol%)	TsEN	H_2O	HCO_2Na (4 eq.)	5	98	–
7	$[IrCl_2Cp^*]_2$ (1 mol%)	TsEN	H_2O	HCO_2Na (3 eq.)	5	99	–
8	$[IrCl_2Cp^*]_2$ (1 mol%)	TsEN	H_2O	HCO_2Na (2 eq.)	5	94	–
9	$[IrCl_2Cp^*]_2$ (0.5 mol%)	TsEN	H_2O	HCO_2Na (2 eq.)	24	99	–
10	$[IrCl_2Cp^*]_2$ (0.25 mol%)	TsEN	H_2O	HCO_2Na (3 eq.)	24	50	–
11	$[IrCl_2Cp^*]_2$ (0.5 mol%)	TsEN	H_2O	HCO_2Na (3 eq.)	5	99	–

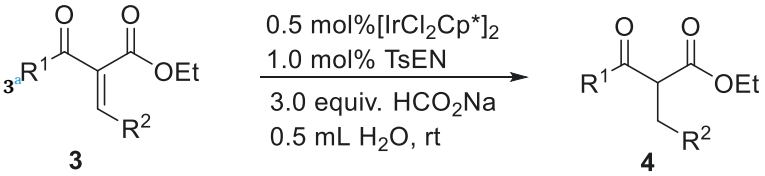
[a] Reactions performed on a 0.2 mmol scale at room temperature in 0.5 mL of solvent. [b] isolated yield. [c] Determined by chiral HPLC using Chiralcel OD column.

yield for 22 h (entry 10). We found that the reaction under 0.5 mol% of catalyst and 3 equiv. of HCO_2Na in water at room temperature gave the best result with 99 % yield of product **4a** in 5 h (entry 11). It was also worth noting that the substrate was reduced cleanly under the optimized reaction conditions, providing the pure product by simple purification by a short chromatography column.

With the optimized reaction conditions in hand, the substrate scope of the transfer hydrogenation of a series of α-keto arylate compounds **3a-o** using 0.5 mol% $[IrCl_2Cp^*]_2$-TsEN complex as catalyst, 3.0 equiv. of sodium formate as hydride source in water was investigated, and the results were summarized in Table 2. As shown in Table 2, all the α-keto substituted acrylate compounds bearing electro-deficient and electron-rich aromatic substituents of R^2 groups were good substrates for the TH and the reactions gave the desired products **4a-r** in good to excellent yields. When the R^2 in **3** were 4-substituted phenyl, all the tested substrates could be reduced to the corresponding products with 89–99 % yields (entries 1–7). The substrates with an electron-deficient group on the 4-position of the phenyl rings were easier to be reduced and a shorter reaction time could be required comparing with the substrates with an electron-rich groups (entries 2–3 vs 4–7). When the R^2 in **3 h-m** were 2-/3-substituted phenyls, the substrates were reduced to give the desire products **4 h-m** in comparable high yields (entries 8–10, 11–13) except

Table 2

Substrate scope of TH reactions of **3**[a]



entry	R^1	R^2	product	time (h)	yield (%)[b]
1	Ph	Ph	**4a**	5	99
2	Ph	4-MeC_6H_4	**4b**	22	90
3	Ph	4-$MeOC_6H_4$	**4c**	48	98
4	Ph	4-FC_6H_4	**4d**	5	97
5	Ph	4-ClC_6H_4	**4e**	6	96
6	Ph	4-$CF_3C_6H_4$	**4f**	6	89
7	Ph	4-$NO_2C_6H_4$	**4 g**	6	98
8	Ph	3-$MeOC_6H_4$	**4 h**	6	98
9	Ph	3-ClC_6H_4	**4i**	6	95
10	Ph	3-BrC_6H_4	**4j**	24	95
11	Ph	2-MeC_6H_4	**4k**	6	98
12	Ph	2-ClC_6H_4	**4l**	6	98
13	Ph	2-$NO_2C_6H_4$	**4m**	4	97
14	Ph	naphthyl	**4n**	9	98
15	4-MeC_6H_4	Ph	**4o**	6	97
16	4-$MeOC_6H_4$	Ph	**4p**	6	97
17	4-ClC_6H_4	Ph	**4q**	7	96
18	3-ClC_6H_4	Ph	**4r**	10	98
19	2-furyl	Ph	**4 s**	6	95
20	methyl	Ph	**4 t**	24	90
21	Ph	*i*-Pr	**4u**	20	80

[a] Reactions performed on a 0.2 mmol scale at room temperature in 0.5 mL of solvent. [b] isolated yield.

the longer reaction time (24 h) required for 3-bromo substituted group (entry 10). The relatively bulky ring naphthyl group could be also a suitable substrate and gave the reduced product **4n** in 98 % yield with slightly longer reaction time (entry 14). Next, the TH of the R^1 substituents on substrate α-keto substituted acrylate compound, bearing electron-donating and electron-withdrawing on phenyl ring, that influences the yields and chemoselectivities was also examined. All the reactions proceeded smoothly affording the selective products **4o-r** in quantitative yields (entries 15–18). This result indicated that the nature and position of the substituents on the aromatic rings have little effect on this TH reactions. The catalytic system was also highly effective for the substrate **3 s** with a 2-furyl substituent under standard reaction conditions, providing the product **4 s** in 95 % yield (entry 19). Furthermore, the alkyl group of R^1 in **3 t** was also compatible for TH reaction under standard reaction conditions, providing the C═C bond reduced product **4 t** in 90 % for 24 h (entry 20). When R^2 was alkyl group, the reaction also proceeded smoothly and afforded the desired product **4u** in 80 % (entry 21). Based on the results summarized in Table 2, a possible mechanism should be similar to the transfer hydrogenation of activated C═C bonds catalyzed Ru complexes, in which the formic acid as hydride source [9].

Conclusion

In conclusion, we have developed a new method for the transfer hydrogenation of α-keto arylate compounds by $[IrCl_2Cp^*]_2$-TsEN complex as catalyst and sodium formate as hydride source in water. There are several advantages in the present reactions: (a) the reaction provided the desired products in high chemoselectivity with high to excellent yields; (b) a wide range of substrates are accessible with a broad tolerance of substituted groups; (c) the reaction can be conducted under mild conditions using low catalyst loading (0.5 mol%); (d) no phase transfer reagent is required; (e) the substrates are reduced cleanly to afford the products by simple extraction without further purification by chromatography column. These remarkable advantages make this simple and green approach very suitable for practical use.

CRediT authorship contribution statement

Ala' Ahmad: . **Crystal Wong:** Data curation. **Jordan Chapin:** Investigation. **Bukuo Ni:** Writing – original draft, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2023.154904.

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[14] **Typical experimental procedure for the transfer hydrogenation of α-keto substituted acrylate compound 3 to α-alkyl-β-ketoester 4.** To a solution of TsEN ligand (0.002 mmol) and $[IrCl_2Cp^*]_2$ (0.001 mmol) in water (0.5 mL) was added α-keto substituted acrylate compound **3** (0.2 mmol) and sodium formate (0.6 mmol). The reaction reaction was stirred at room temperature for the corresponding time. After completion, the reaction mixture was extracted with EtOAc (5 mL x 2). The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography (ethyl acetate: hexane = 1:5) to give 56 mg (99% yield) of the product **4**.