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Citation for the original published paper (version of record):

Vazquez-Romero, A., Bermejo Gómez, A., Martín-Matute, B. (2015)
Acid- and Iridium-Catalyzed Tandem 1,3-Transposition/3,1-Hydrogen Shift/
Chlorination of Allylic Alcohols
ACS Catalysis, 5(2): 708-714
<https://doi.org/10.1021/cs501618h>

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An Acid- and Iridium-Catalyzed Tandem 1,3-Transposition / 3,1-Hydrogen Shift / Chlorination of Allylic Alcohols

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KEYWORDS

Hydrogen Transfer, Chlorination, Allylic Alcohols, Isomerization, Iridium, 1,3-Transposition.

ABSTRACT

A method for the selective synthesis of α -chlorocarbonyls from allylic alcohols is presented. The reaction occurs through an acid- and iridium-catalyzed tandem process that combines a 1,3-transposition, a 3,1-hydrogen shift and a chlorination process, and that can be applied to a wide range of α -aromatic and heteroaromatic allylic alcohols. Saturated non-chlorinated ketones or other side-products derived from overchlorination were not detected.

INTRODUCTION

Molecular rearrangements are important transformations in organic synthesis that give access to structural isomers of the original molecules.¹ An example that has attracted a lot of attention in recent years is the transposition of allylic alcohols, where the positions of the hydroxyl group and the double bond are switched to give isomeric allylic alcohols (Figure 1a).^{2,3} A direct application of this rearrangement would be to use it as a straightforward method for the synthesis of the less accessible isomer: methods to prepare one of the two isomers may be rather challenging, whereas the synthesis of the other isomer may be easy and accomplished in fewer steps from commercially available reagents. Several methods for the transposition of allylic alcohols have been reported.^{2,3a-c} Early examples used very harsh reaction conditions, high temperatures and superstoichiometric quantities of strong acids,^{2a} and gave the rearranged regioisomer in moderate yields. In some instances, the lower yields could be partly explained by the intermediacy of allylic cations, highly reactive species that can lead to the formation of side-products. Additionally, in such reactions, the conversion stops when thermodynamic equilibrium is reached, and thus a mixture of the two regioisomers is usually obtained. The use of transition-

metal catalysts has overcome some of these limitations by promoting the reaction through a [3,3]-sigmatropic rearrangement. For instance, good yields and selectivities were obtained with catalysts based on oxo-vanadium and oxo-molybdenum complexes, as reported by Chabardes^{2b} and Fujita,^{2c} although the reactions required high temperatures (150-160 and 200 °C, respectively). Later, Takai used oxo-metal vanadium and molybdenum complexes that were able to rearrange allylic alcohols at room temperature with good selectivity.^{2d} Although other kinds of catalysts, such as those based on boronic and benzoic acids, have been reported,^{2k-1} one of the most efficient methods is the rhenium-catalyzed rearrangement developed by Osborn^{2f} (Scheme 1a): readily available trioxorhenium complexes $[(\text{ReO}_3(\text{OSiR}_3)]$ and rhenium(VII) oxide catalyze the rearrangement of a wide range of allylic alcohols under mild conditions.^{2g} However, due to the reversibility of the reaction, equilibrium mixtures of constitutional isomers were still formed.

The design of new methods to drive the equilibrium towards a single isomer is still a challenge. A limited number of strategies that result in highly regioselective Re-catalyzed transpositions have been reported.^{2h-j,2m,3a-c} Initial examples by Grubbs and co-workers relied on the use of allylic alcohols that after isomerization gave conjugated alkenes.^{2h} A second method allowed the thermodynamically disfavoured regioisomer, a primary allylic alcohol, to be obtained through a selective silylation.^{2h} Two related approaches by Lee were based on shifting the equilibrium towards the desired direction by introducing certain functionalities within the molecule able to stabilize the resulting transposed allylic alcohol. In one case, the oxophilicity of boron was exploited and a boron-oxygen bond could be formed only in one of the isomeric allylic alcohols.²ⁱ In the second strategy, a ring contraction was used to control the regioselectivity.^{2m} Zakarian and co-workers shifted the equilibrium by using hydroxyl-functionalized allylic alcohols, trapping the transposed compounds as acetals.^{2j} Other recently

reported examples, also catalyzed by rhenium, involve cascade reactions where functional groups such as epoxides, enones or ketals were used to displace this equilibrium.^{3a-c}

A related, yet different, rearrangement of allylic alcohols is their irreversible transition-metal-catalyzed isomerization into carbonyl compounds (Scheme 1b).^{4,5,6} Our research has been focused on the development of efficient allylic alcohol isomerizations and their application in organic synthesis.^{6,7} Pioneering works on the isomerization of allylic alcohols in water have been reported by different groups.⁵ Gimeno, Cardieno and co-workers used a very efficient Ru(IV) complex that was able to achieve impressive turnover numbers (TON = 10⁶) at 75 °C.^{5e} In 2010, we reported a rhodium complex that catalyzes the reaction in water and at ambient temperature.^{6b} Interestingly, these isomerizations in water are particularly efficient for allylic alcohols bearing aliphatic substituents on the alcohol carbon. For examples with an aromatic substituent, harsher reaction conditions and considerably higher catalyst loadings had to be used.^{5a,5 d-f,5 i-j}

In the last few years, we have reported the synthesis of α -haloketones from allylic alcohols in aqueous solvents.⁷ The method formally combines an allylic alcohol isomerization (1,3-hydrogen shift) with a fluorination,^{7a} chlorination^{7b} or bromination^{7c} catalyzed by Ir(III) (Figure 1c). The corresponding α -halocarbonyls were obtained as single constitutional isomers in good to excellent yields. Just as for the isomerization of allylic alcohols into ketones in water, substrates bearing aromatic groups at the alcohol carbon required longer reaction times and/or higher catalyst loadings to achieve high conversions than those bearing aliphatic substituents.^{7 a-b}

Steric effects have been considered to explain the lower reactivity of allylic alcohols with α -aryl substituents than those with aliphatic ones in the allylic-alcohol-to-carbonyl isomerizations (Figure 1b) in water.^{5a,5j} However, one must also consider that these two families of substrates are substantially different from an electronic point of view. In this article, we show

that α -aryl allylic alcohols may undergo cleavage of the C–OH bond when subjected to transition-metal-catalyzed isomerization into carbonyl compounds in water. This competing process can account for the lower yields, the longer reaction times, and the higher catalyst loadings needed for this type of substrates. Furthermore, as described above, cleavage of the C–OH bond can result in the formation of a regioisomeric mixture of allylic alcohols. We use the irreversible transition-metal-catalyzed isomerization / chlorination process as a strategy to control the regioselectivity in the 1,3-transposition of allylic alcohols. Thus, we report the first tandem 1,3-transposition / 3,1-hydrogen shift / chlorination of allylic alcohols (Figure 1d). This methodology gives access to certain α -chloroketones from readily available allylic alcohols, avoiding long and tedious synthetic routes.

Figure 1. (a) 1,3-Transposition of allylic alcohols. (b) Transition-metal-catalyzed redox isomerization. (c) Tandem isomerization (1,3-hydrogen shift) / halogenation of allylic alcohols catalyzed by Ir(III) complexes (X = F, Cl or Br). (d) This work.

(a) 1,3-Transposition of allylic alcohols

(b) Redox isomerisation of allylic alcohols (1,3-Hydrogen shift)

(c) 1,3-Hydrogen shift / halogenation in allylic alcohols

(d) This work: tandem 1,3-transposition / 3,1-hydrogen shift / chlorination

RESULTS AND DISCUSSION

We started by comparing the reactivity of aliphatic and aromatic allylic alcohols in their isomerization into carbonyl compounds catalyzed by $[\text{Cp}^*\text{IrCl}_2]_2$, an excellent catalyst for redox isomerization / halogenation tandem reactions,⁷ and the highly active Ru(IV) complex reported by Gimeno (Table 1).^{5e}

The redox isomerization reaction of 1-octen-3-ol (**1a**) into 3-octanone (**2a**) with either $[\text{Cp}^*\text{IrCl}_2]_2$ (1 mol%) or $[\text{Ru}(\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16})\text{Cl}_2]_2$ (0.1 mol%)^{5e} took place with full conversion and complete selectivity in less than 1 h at 75 °C (Table 1, entries 1 and 2). In contrast, the isomerization of α -aryl allylic alcohols required higher catalyst loadings or longer reaction times, and the outcome of the reaction was dependent on the catalyst used. Thus, the isomerization of **1b** was achieved using the procedure described in the literature, in which 2.5 mol% of the Ru(IV) dimer was used^{5e} (Table 1, entry 3 vs entry 1). When we carried out the same reaction using 0.5 mol% of the Ru(IV) catalyst, only a 27% conversion was achieved, and a mixture of transposed allylic alcohol **1'b** and ketone **2b** in a 76 : 24 ratio was obtained after 1 h at 75 °C (Table 1, entry 4). Thus, when lower catalyst loadings are used, cleavage of the C–O bond clearly competes with the allylic-alcohol-to-ketone isomerization reaction. It should be noted that the transposed alcohol **1'b** was not further isomerized into **2'b**. The reaction was also carried out using $[\text{Cp}^*\text{IrCl}_2]_2$ (1 mol%) in a THF / H₂O mixture (1:1) at 75 °C (Table 1, entry 5). After 30 min (time required for the isomerization of **1a**, entry 2 in Table 1), the conversion was low, and ketone **2b** was obtained in 27% yield. However, when the reaction was stirred at 75 °C overnight full conversion into **2b** was achieved (Table 1, entry 6). For the more substituted aromatic allylic alcohol 1-phenylbut-2-en-ol (**1c**), using $[\text{Ru}(\eta^3\text{:}\eta^3\text{-C}_{10}\text{H}_{16})\text{Cl}_2]_2$ (0.5 mol%) in H₂O at 75 °C, afforded **1'c** in quantitative yield after 16 h (Table 1, entry 7). Thus, the transposition of a

secondary allylic alcohol into its isomeric secondary and conjugated allylic alcohol is clearly favored under these conditions. Interestingly, carbonyl products derived from redox isomerization were not detected (neither **2c** nor **2'c**). The reaction of **1c** catalyzed by [Cp*IrCl₂]₂ (1 mol%) in THF / H₂O (1:1) at 75 °C for 16 h promoted the 1,3-transposition, and, surprisingly, and in contrast with the results obtained with the Ru(IV) catalyst, led also to the formation of redox isomerization products from both allylic alcohols **1c** and **1'c** (Table 1, entry 8). When the same reaction was carried out at room temperature, a mixture of redox isomerization products was formed (90% conversion, **2c** : **2'c** = 58 : 42), the remainder being unreacted **1c** (Table 1, entry 9). Thus, the 1,3-transposition also occurred at room temperature when [Cp*IrCl₂]₂ was used as the catalyst, but under these milder reaction conditions, a lower conversion was obtained.

Table 1. Isomerization of allylic alcohols 1a-c by Ru(IV) and Ir(III) catalysts^a

Entry	Allylic alcohol	Catalyst (mol%)	Solvent	T (°C)	Time (h)	Conversion (%)	1' : 2 : 2' ^b
1 ^c	1a	[Ru(η^3 : η^3 -C ₁₀ H ₁₆)Cl ₂] ₂ (0.1)	H ₂ O	75	1	>99	- : >99 : - ^d
2	1a	[Cp*IrCl ₂] ₂ (1.0)	THF : H ₂ O	75	0.5	>99	- : >99 : -
3 ^c	1b	[Ru(η^3 : η^3 -C ₁₀ H ₁₆)Cl ₂] ₂ (2.5)	H ₂ O	75	1	>99	- : >99 : - ^e
4	1b	[Ru(η^3 : η^3 -C ₁₀ H ₁₆)Cl ₂] ₂ (0.5)	H ₂ O	75	1	27	76: 24 : - ^e
5	1b	[Cp*IrCl ₂] ₂ (1.0)	THF : H ₂ O	75	0.5	47	- : >99 : -
6	1b	[Cp*IrCl ₂] ₂ (1.0)	THF :	75	16	>99	- : >99 : -

			H ₂ O				
7	1c	[Ru(η^3 : η^3 -C ₁₀ H ₁₆)Cl ₂) ₂ (0.5)	H ₂ O	75	16	>99	>99 : - : - ^e
8	1c	[Cp*IrCl ₂] ₂ (1.0)	THF : H ₂ O	75	16	>99	8 : 46 : 46
9	1c	[Cp*IrCl ₂] ₂ (1.0)	THF : H ₂ O	r.t.	48	90	- : 58 : 42

^a Reactions were carried out with 0.4 mmol of allylic alcohol **1a-c** (concentration 0.2 M) for 16 h. ^b The ratio **1'** : **2** : **2'** was determined by ¹H NMR spectroscopy. ^c See reference **5e**. ^d Only compound **2a** was observed. ^e Decomposition was observed (*ca.* 10%).

Formation of **1'b-c** could be attributed to the intermediacy of carbocationic species produced upon cleavage of the C–OH bond. Then, the nucleophilic attack of a molecule of water at either end of the allylic cation affords the two isomeric allylic alcohols **1b-c** or **1'b-c**. These could undergo the transition-metal-catalyzed redox isomerization process to form the ketones, **2b-c** and **2'b-c**. In the case of the less substituted α -aryl allylic alcohol **1b**, products derived from this tandem sequence were not obtained (or were only detected in trace amounts). The formation of carbocations may also occur with this substrate (**1b**), but the secondary carbon bears more of the positive charge than does the primary carbon, and the nucleophilic attack by water is faster there. The competing cleavage of the C–OH bond explains the lower yields, higher catalyst loadings and longer reaction times required for α -aryl allylic alcohols compared to those bearing α -aliphatic substituents in the transition-metal-catalyzed redox isomerization in aqueous solvents.

Although α -aryl allylic alcohols with a disubstituted double bond (i.e., **1c**) easily underwent a tandem 1,3-transposition / 3,1-hydrogen shift with the iridium complex, the selectivity obtained was low, which makes this process impractical. We therefore turned our attention to another reaction process that would have a significantly different reaction rate for the transposed allylic

alcohol, and that would thus improve the selectivity. Thus, we attempted to combine the tandem 1,3-hydrogen shift / chlorination^{7b} reaction with the 1,3-transposition of allylic alcohols. This tandem process would give access to α -chlorocarbonyl compounds from allylic alcohols that are commercially available or that may be synthesized through a straightforward synthetic route.

In our initial experiments, we investigated the 1,3-transposition / 3,1-hydrogen shift / chlorination of 1-phenylbut-2-en-ol (**1c**). When allylic alcohol **1c** was treated with 1 mol% of [Cp*IrCl₂]₂ in the presence of a slight excess of NCS (1.2 equiv) at room temperature, a mixture of chloroketones **3c** and **3'c** (1:4) was obtained in 96% yield (Scheme 1). To improve the selectivity towards **3'c**, we first tried to identify the reactant responsible for the 1,3-transposition (Table 2). Stirring **1c** overnight in the presence of a catalytic amount of [Cp*IrCl₂]₂ (1 mol%) at r.t. gave only traces of the transposed allylic alcohol **1'c** (Table 2, entry 1). Additional control experiments were carried out in the presence of succinimide (1.1 equiv., Table 2, entry 2), a by-product formed during the chlorination step, and also in the presence of NCS (1.2 equiv.), the latter without the iridium catalyst (Table 2, entry 3). We found that succinimide did not promote the 1,3-transposition. In contrast, the reaction did occur with NCS, although the results were highly dependent on the batch of NCS used. Since the reaction can be catalyzed by acid,^{8,9} we concluded that traces of hydrochloric acid⁹ in the NCS reagent were responsible for the observed reactivity. When the reaction was carried out using a mixture of THF and HCl (aq., 0.1 M) instead of THF / H₂O, complete conversion of **1c** into **1'c** was achieved (Table 2, entry 4). We also evaluated the effect of other acidic additives such as *p*-TsOH,^{2c} BF₃·Et₂O and salicylic acid.²¹ In the presence of a stoichiometric amount of *p*-TsOH, after 16 h at r.t., **1'c** was obtained as a single isomer (Table 2, entry 5). BF₃·Et₂O afforded only

19% of **1'c** after 16 h, and it also gave decomposition side-products (Table 2, entry 6). Salicylic acid did not improve the outcome of the reaction, and afforded a 1 : 1 mixture of **1c** and **1'c** (Table 2, entry 7).

Scheme 1. Formation of two α -chloroketones from 1-phenylbut-2-en-ol (1c**).^a**

Table 2. 1,3-Transposition of **1c.^a**

Entry	Reagents	1c : 1'c ^b
1	$[\text{Cp}^*\text{IrCl}_2]_2$ ^c	> 99 : < 1
2	$[\text{Cp}^*\text{IrCl}_2]_2$ / succinimide ^d	> 99 : < 1
3	NCS ^e	1 : 1.4 – 1 : 10
4	0.1 M HCl ^f	<1 : >99
5	<i>p</i> -TsOH ^g	<1 : >99
6	BF ₃ ·Et ₂ O ^{g,h}	<1 : 99
7	Salicylic acid ^g	46 : 54

^a Unless otherwise noted, the reactions were carried out with 0.15 mmol of allylic alcohol **1c** for 16 h r.t. in a mixture THF / H₂O (1:1, 0.2 M). ^b Ratio **1c** : **1'c** determined by ¹H NMR spectroscopy. ^c 1mol% of $[\text{Cp}^*\text{IrCl}_2]_2$ was used. ^d 1.1 equiv. of succinimide was used. ^e Different batches of NCS (1.2 equiv.) were used. ^f In a mixture THF / HCl (aq., 0.1 M). ^g 1 equiv. of acid was used. ^h 19% yield of compound **1'c** and 72% of unidentified compounds determined by ¹H NMR spectroscopy using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard.

To obtain further insight into the kinetics of the acid-catalyzed 1,3-transposition, we studied the reactions by ^1H NMR spectroscopy. A set of electronically different α -aryl allylic alcohols [**1c** (*p*-H), **1d** (*p*-OMe) and **1e** (*p*-Cl)] was subjected to the reaction conditions (1 or 0.5 equiv. of *p*-TsOH in D_2O / $\text{THF-}d_8$), and the reactions were monitored by ^1H NMR spectroscopy (Figure 2). The 1,3-transposition of allylic alcohol **1c** using 1 equiv. of *p*-TsOH was complete after 52 min, whereas a conversion of only 66% was achieved with 0.5 equiv. of *p*-TsOH after the same reaction time. For the more electron-rich aryl substrate **1d**, full conversion into **1'd** was achieved in less than 2 min using either 1 equiv. or 0.5 equiv. of *p*-TsOH. On the other hand, the transposition rate was much lower for the *p*-chloro-substituted alcohol **1e**: after 60 min, only 41 or 28% of **1'e** was observed using 1 or 0.5 equiv. of *p*-TsOH, respectively. Therefore, the 1,3-transposition of α -aryl allylic alcohols promoted by *p*-TsOH in aqueous media is favored by the presence of electron-rich substituents on the aromatic moiety.

Figure 2. 1,3-Transposition of allylic alcohols **1a-c** promoted by *p*-TsOH.

Next, we attempted the tandem chlorination process by using iridium catalysis under acidic conditions. In the presence of HCl (aq. 0.1 M) (Table 3, entry 1), **1c** was consumed to give chloroketone **3'c** as the sole product, however, the yields were only moderate (41-56%) (see ESI). The same reaction was also carried out at higher temperature under microwave irradiation: after 1 min at 100 °C, chloroketone **3'c** was obtained with excellent selectivity, but in a moderate yield (54%) (Table 3, entry 2).¹⁰ Excellent yields of chloroketones and good selectivities (**3c** : **3'c** = 16 : 84 – 10 : 90) were obtained using 0.1-0.2 equiv. of either salicylic acid,²¹ *p*-toluenesulfonic acid^{2e} (*p*-TsOH) or BF₃·Et₂O (Table 3, entries 3-8). Further screening revealed that increasing the number of equivalents of *p*-TsOH to 0.5 or 1 considerably improved the selectivity (Table 3, entries 9-10). Decreasing or increasing the iridium loading, did not improve the outcome (Table 3, entries 11 and 12). To minimize the formation of unwanted chloroketone **3c**, we allowed **1c** to react with *p*-TsOH for a given time (*t*₁) (Table 2, entries 13-18) before adding the remaining reagents (NCS and the iridium catalyst). The best results were obtained

when $t_1 = 30$ or 60 min, and under these conditions **3'c** was formed in excellent yields (95%) and with excellent selectivities (>99%) (Table 3, entries 17 and 18). Good to excellent selectivities and yields were also obtained using catalytic amounts of *p*-TsOH (0.1-0.5 equiv.) (Table 3, entries 19-21).

Table 3. Optimization of tandem 1,3-transposition / 3,1-hydrogen shift / chlorination of 1c.^a

Entry	Acid (equiv.)	t_1 (min) ^b	Yield (%) ^c	1'c : 3c : 3'c ^d
1	HCl ^e	-	41-56	7-25: - : 56-75 ^f
2 ^g	HCl ^e	-	54	14 : - : 86
3	BF ₃ ·Et ₂ O (0.1)	-	96	- : 16 : 84
4	BF ₃ ·Et ₂ O (0.2)	-	94	- : 10 : 90
5 ^h	BF ₃ ·Et ₂ O (0.1)	-	98	- : 14 : 86
6	Salicylic acid (0.1)	-	96	1 : 13 : 86
7	<i>p</i> -TsOH (0.1)	-	92	- : 13 : 87
8	<i>p</i> -TsOH (0.2)	-	93	- : 12 : 88
9	<i>p</i> -TsOH (0.5)	-	96	- : 9 : 91
10	<i>p</i> -TsOH (1)	-	96	- : 3 : 97
11 ⁱ	<i>p</i> -TsOH (1)	-	90	- : 2 : 98
12 ^j	<i>p</i> -TsOH (1)	-	88	- : 3 : 97
13	<i>p</i> -TsOH (1)	1	95	- : 3 : 97
14	<i>p</i> -TsOH (1)	5	96	- : 3 : 97

15	<i>p</i> -TsOH (1)	10	93	- : 2 : 98
16	<i>p</i> -TsOH (1)	20	97	- : 1 : 99
17	<i>p</i> -TsOH (1)	30	95	- : - : >99
18	<i>p</i> -TsOH (1)	60	95	- : - : >99
19	<i>p</i> -TsOH (0.1)	60	96	- : 9 : 91
20	<i>p</i> -TsOH (0.2)	60	97	- : 5 : 95
21	<i>p</i> -TsOH (0.5)	60	>99	- : 1 : 99

^a Unless otherwise noted, **1c** (0.54 mmol) and the acid additive were dissolved in THF / H₂O (1:1, total volume 2.7 mL). NCS (0.65 mmol) and [Cp*IrCl₂]₂ (1 mol%) were added, and the mixture was stirred for 12 h (full conversion) at r.t. ^b A solution of **1c** (0.54 mmol) and *p*-TsOH (0.1, 0.2, 0.5, 1 equiv.) in THF / H₂O (1:1, total volume 2.7 mL) was stirred at r.t. for *t*₁. Then, NCS (0.65 mmol) and [Cp*IrCl₂]₂ (1 mol%) were added and the mixture was stirred for 12 h (full conversion) at r.t. ^c Yield of **3c** + **3'c**. Determined by ¹H NMR spectroscopy using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard). ^d Determined by ¹H NMR spectroscopy. ^e Reactions were carried out on a 0.14 mmol scale in a 1:1 THF / HCl (0.1 M) mixture (total volume 680 μL). ^f **3'c** was formed together with polymeric material. ^g Microwave irradiation, 100 °C for 1 min. ^h 40 °C. ⁱ 0.5 mol% of [Cp*IrCl₂]₂. ^j 2 mol% of [Cp*IrCl₂]₂.

The scope of the tandem reaction was evaluated (Scheme 2) under the optimized reaction conditions (Table 2, entry 18) using *p*-TsOH (1 equiv.) and [Cp*IrCl₂]₂ (1 mol%) at ambient temperature. Since the 1,3-transposition is highly dependent on the electronic properties of the aryl substituent (*vide supra*, Figure 2), a *t*₁ of 1 h was used for all the allylic alcohols (Scheme 2). A variety of functional groups on the aromatic rings, including *p*-OMe, *p*-Cl, *p*-Br and *m*-OMe were well tolerated (Scheme 2, **1c-g**). Alkyl groups and disubstituted aromatic substrates also gave the corresponding α-chloroketones **3'** in good to excellent yields (Scheme 2, **1h-j**). Substrates containing 2-naphthyl (**1k**) and 2-thiophenyl (**1l**) moieties gave moderate yields. For **1k**, decomposition reactions were observed, and **3'k** was obtained in a moderate 44% isolated yield. The reaction of the α-heteroaromatic allylic alcohol **1l** proved to be strongly dependent on

the solvent mixtures used (see ESI). In a 2:1 THF / H₂O mixture, the heteroaromatic α -chloroketone **3'1** was isolated in 63% yield (Scheme 2).

Substrates **1m** and **1n** were synthesized with acetal protecting groups, in order to avoid undesired reactions on the ketone or aldehyde functional groups (see ESI). As the deprotection of acetals is usually accomplished in aqueous acidic media, we tried to combine it with the tandem chlorination reaction. These two substrates did not give good results under the optimized reaction conditions, and variable amounts of the corresponding α,β -unsaturated ketones were detected. Different reaction conditions were therefore tested, including higher loadings of *p*-TsOH, different acidic additives and THF / H₂O mixtures (see ESI). The best result for **1m** was obtained using 3 equiv. of BF₃·Et₂O, which gave **3'm** as a single regioisomer in 68% isolated yield (Scheme 2). For the protected aldehyde **1n**, the best result was obtained using 3 equiv. of *p*-TsOH (Scheme 2), which gave **3'n** in 45% isolated yield. Substrate **1o**, which contains two types of allylic alcohols in the aromatic core was transformed selectively into **3'o** in high yield (Scheme 2) as a result of a 1,3-transposition / 3,1-hydrogen shift / chlorination on the more substituted allylic alcohol and a 1,3-hydrogen shift / chlorination on the less substituted one. Substrate **1p**, symmetrically substituted with two identical allylic alcohol moieties, underwent a clean double tandem chlorination involving two 1,3-transpositions on the allylic alcohol moieties using 2 equiv. of *p*-TsOH to give bis(α -chloroketone) **3'p** in high yield (Scheme 2). For substrates with longer-chain alkyl substituents on the double bond of the allylic alcohol (**1q-r**), very good results were obtained, and the corresponding chloroketones **3'q** and **3'r** were both isolated in 88% yield. Importantly, saturated ketones or other side-products derived from overchlorination (i.e., chlorination at the benzylic or aromatic positions) were not detected for any of the substrates, and neither were chlorinated products derived from the direct redox

isomerization / chlorination pathway for the allylic alcohols moieties (**3**) having a disubstituted double bond.

The selective tandem reaction could also be achieved using only a catalytic amount of *p*-TsOH, but the reactivity was strongly influenced by the electronic properties of the α -aryl group of the allylic alcohol, as noted above (Scheme 2, **1c-e**). Using 0.1 equiv. of *p*-TsOH and the iridium catalyst, allylic alcohol **1e**, containing a Cl substituent at the *para* position of the aromatic ring, reacted slowly (Scheme 2, **1e**), and after 16 h, a small amount of the desired α -chloroketone **3'e** was observed (13%) along with the corresponding transposed allylic alcohol **1'e** in 35% yield. In contrast, when an electron-donating group (*p*-OMe) was present in the aromatic ring (Scheme 2, **1d**), the corresponding α -chloroketone **3'd** was obtained in quantitative yield (99%) after 16 h using 0.1 equiv. of *p*-TsOH. For the substrate with an unsubstituted phenyl ring (Scheme 2, **1c**), α -chloroketone **3'c** was obtained in high yield (91%).

Scheme 2. Scope: 1,3-Transposition / redox isomerization / chlorination of α -(hetero)aromatic allylic alcohols.^a

^a Unless otherwise noted: reactions were carried out with 1 mmol of allylic alcohol in THF / H₂O, 1:1 (concentration 0.2 M) with p -TsOH (1 equiv.) at r.t. After 60 min, NCS (1.2 equiv.) and

[Cp*IrCl₂]₂ (1 mol%) were added at r.t. Yields of isolated products are shown (in parentheses yields determined by ¹H NMR spectroscopy using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard). ^a Reactions carried out with 10 mol% of *p*-TsOH. ^b 35% of transposed allylic alcohol **1e'** was remaining and decomposition was observed. ^c A mixture THF / H₂O (2:1) was used. ^d 3 equiv. of BF₃•Et₂O was used. ^e 3 equiv. of *p*-TsOH was used. ^f 2 equiv. of *p*-TsOH was used.

CONCLUSIONS

A mild and efficient methodology based on a tandem 1,3-transposition / 3,1-hydrogen shift / chlorination of α -aryl allylic alcohols to synthesize a wide range of α -chloroketones has been reported. The reactions are run under an atmosphere of air, using low loadings of iridium(III), at room temperature and in a THF / H₂O mixture (1:1). α -Chloroketones with different aryl substituents have been isolated in high yields as single constitutional isomers without any evidence of the formation of saturated ketones derived either from redox isomerization of the starting allylic alcohols or from a 1,3-transposition / redox isomerization process without chlorination. Although the general procedure requires a stoichiometric amount of inexpensive and readily available *p*-TsOH, catalytic amounts of this acid are able to promote the selective transformation for several substrates. Diverse electron-donating and electron-withdrawing groups as well as reactive functionalities have been shown to be compatible with the reaction conditions. This simple and practical method appears to be an attractive and powerful way to synthesize a very important and common type of synthetic intermediates widely used in organic synthesis.

ASSOCIATED CONTENT

Supporting Information. Experimental details, characterization data and NMR spectra of organic compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This project was supported by the Knut and Alice Wallenberg Foundation, the Swedish Research Council (VR) and the Swedish Governmental Agency for Innovation Systems (VINNOVA) through the Berzelii Center EXSELENT. B.M.-M. was supported by VINNOVA through a VINNMER grant. A.V.-R. thanks the Wenner-Gren Foundation for a postdoctoral grant.

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