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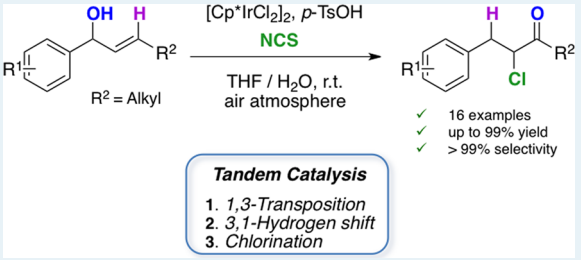
Acid- and Iridium-Catalyzed Tandem 1,3-Transposition/3,1-Hydrogen Shift/Chlorination of Allylic Alcohols

Ana Vázquez-Romero,[†,‡] Antonio Bermejo Gómez,[†,‡] and Belén Martín-Matute*[,†,‡]

[†]Department of Organic Chemistry and [‡]Berzelii Center EXSELENT on Porous Materials, The Arrhenius Laboratory, Stockholm University, Stockholm, 106 91, Sweden

Supporting Information

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 can be applied to a wide range of α-aromatic and heteroaromatic secondary allylic alcohols. Saturated non-chlorinated ketones or other side-products derived from overchlorination were not detected.



KEYWORDS: *hydrogen transfer, chlorination, allylic alcohols, isomerization, iridium, 1,3-transposition*

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. 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,l] one of the most efficient methods is the rhenium-catalyzed rearrangement developed by Osborn:[2f] readily available trioxorhenium complexes [($ReO_3(OSiR_3)$)] 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, mixtures of constitutional isomers were still formed.

The design of new methods to drive this transformation toward 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,m,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 disfavored regioisomer, a primary allylic alcohol, to be obtained through a selective silylation.[2h] Two related approaches by Lee were based on shifting the equilibrium toward 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 (Figure 1b).[4−6] 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, Cadierno, and co-

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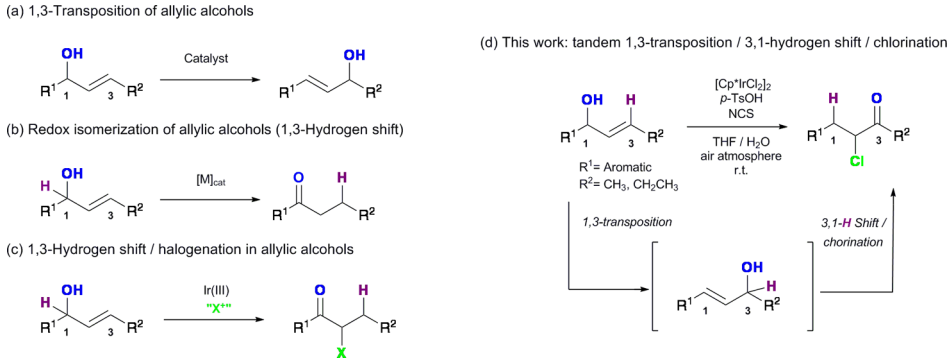
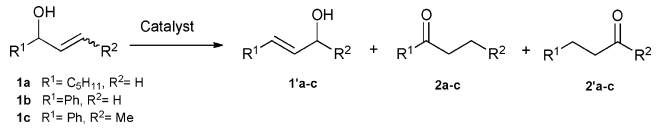


Figure 1. (a) 1,3-Transposition of allylic alcohols. (b) Transition-metal-catalyzed redox isomerization. (c) Tandem isomerization (1,3-hydrogen shift)/halogenation of allylic alcohols catalyzed by Ir(III) complexes (X = F, Cl, or Br). (d) This work: Tandem 1,3-transposition/3,1-hydrogen shift/chlorination.

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**	$[Ru(\eta_3{:}\eta_3\text{-}C_{10}H_{16})Cl_2]_2$ (0.1)	H_2O	75	1	>99	-:>99:-[e]
2	**1a**	$[Cp^*IrCl_2]_2$ (1.0)	THF/H_2O	75	0.5	>99[d]	-:>99:-
3[c]	**1b**	$[Ru(\eta_3{:}\eta_3\text{-}C_{10}H_{16})Cl_2]_2$ (2.5)	H_2O	75	1	>99	-:>99:-[f]
4	**1b**	$[Ru(\eta_3{:}\eta_3\text{-}C_{10}H_{16})Cl_2]_2$ (0.5)	H_2O	75	1	27	76:24:-[f]
5	**1b**	$[Cp^*IrCl_2]_2$ (1.0)	THF/H_2O	75	0.5	47[d]	-:>99:-
6	**1b**	$[Cp^*IrCl_2]_2$ (1.0)	THF/H_2O	75	16	>99[d]	-:>99:-
7	**1c**	$[Ru(\eta_3{:}\eta_3\text{-}C_{10}H_{16})Cl_2]_2$ (0.5)	H_2O	75	16	>99	>99:-:-[f]
8	**1c**	$[Cp^*IrCl_2]_2$ (1.0)	THF/H_2O	75	16	>99[d]	8:46:46
9	**1c**	$[Cp^*IrCl_2]_2$ (1.0)	THF/H_2O	r.t.	48	90[d]	-: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 ^{1}H NMR spectroscopy. [c]See ref 5e. [d]Conversions determined by ^{1}H NMR spectroscopy using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard. [e]Only compound **2a** was observed. [f]Decomposition was observed (ca. 10%).

workers used a very efficient Ru(IV) complex that was able to achieve impressive turnover numbers (TON = 10^6) 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,d−f,i,j]

In the past 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) complexes (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.[7a,b]

Steric effects have been considered to explain the lower reactivity of α-aryl allylic alcohols compared to that of α-alkyl ones in the allylic-alcohol-to-carbonyl isomerizations (Figure 1b) in water.[5a,j] 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.

RESULTS AND DISCUSSION

We started by comparing the reactivity of aliphatic and aromatic allylic alcohols in their isomerization into carbonyl compounds catalyzed by $[Cp^*IrCl_2]_2$, 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 $[Cp^*IrCl_2]_2$ (1 mol %) or $[Ru(\eta_3{:}\eta_3\text{-}C_{10}H_{16})Cl_2]_2$ (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

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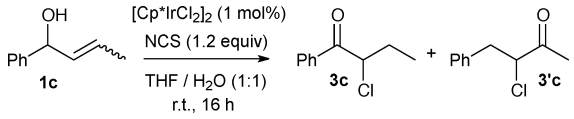
required higher catalyst loadings or longer reaction times, and the outcome of the reaction was dependent on the catalyst used. Thus, the isomerization of **1b** was achieved using the procedure described in the literature, in which 2.5 mol % of the Ru(IV) dimer was used[5e] (Table 1, entry 3 vs entry 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 $[Cp^*IrCl_2]_2$ (1 mol %) in a THF/H_2O 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-1-ol (**1c**), using $[Ru(\eta_3{:}\eta_3\text{-}C_{10}H_{16})Cl_2]_2$ (0.5 mol %) in H_2O 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 $[Cp^*IrCl_2]_2$ (1 mol %) in THF/H_2O (1:1) at 75 °C for 16 h promoted the 1,3-transposition. 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 $[Cp^*IrCl_2]_2$ was used as the catalyst, but under these milder reaction conditions, a lower conversion was obtained.

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 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.

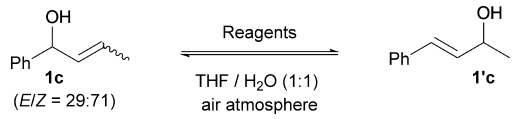
In our initial experiments, we investigated the 1,3-transposition/3,1-hydrogen shift/chlorination of 1-phenylbut-2-en-1-ol (**1c**). When allylic alcohol **1c** was treated with 1 mol % of $[Cp^*IrCl_2]_2$ in the presence of a slight excess of NCS (1.2 equiv) at room temperature, a mixture of chloroketones **3c** and **3′c** (1:4) was obtained in 96% yield (Scheme 1). To improve the selectivity toward **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 $[Cp^*IrCl_2]_2$ (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 acid[9] 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/H_2O, 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*-toluenesulfonic acid (*p*-TsOH),[2e] $BF_3{\cdot}Et_2O$, and salicylic acid.[2f] In the presence of a stoichiometric amount of *p*-TsOH, after 16 h at r.t., **1′c** was obtained as a single

Scheme 1. Formation of Two α-Chloroketones from 1-Phenylbut-2-en-1-ol (1c)



96% (**3c** : **3′c** = 1 : 4)

Table 2. 1,3-Transposition of 1c[a]



entry	catalyst (mol %)	reagent (equiv)	**1c**:**1′c**[b]
1	$[Cp^*IrCl_2]_2$ (1)	--	>99:<1
2	$[Cp^*IrCl_2]_2$ (1)	Succinimide (1.1)	>99:<1
3	--	NCS (1.2)[c]	1:1.4−10
4	--	0.1 M HCl[d]	<1:>99
5	--	*p*-TsOH (1)	<1:>99
6	--	$BF_3{\cdot}Et_2O$ (1)[e]	<1:99
7	--	Salicylic acid (1)	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/H_2O (1:1, 0.2 M). [b]Ratio determined by ^1H NMR spectroscopy. [c]Different batches of NCS (1.2 equiv) were used. [d]Using a mixture THF/HCl (aq., 0.1 M). [e]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.

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isomer (Table 2, entry 5). $BF_3{\cdot}Et_2O$ 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).

To obtain further insight into the kinetics of the acid-catalyzed 1,3-transposition, we studied the reactions by ^{1}H 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/THF-d_8), and the reactions were monitored by ^{1}H NMR spectroscopy (Figure 2). The 1,3-transposition of allylic alcohol

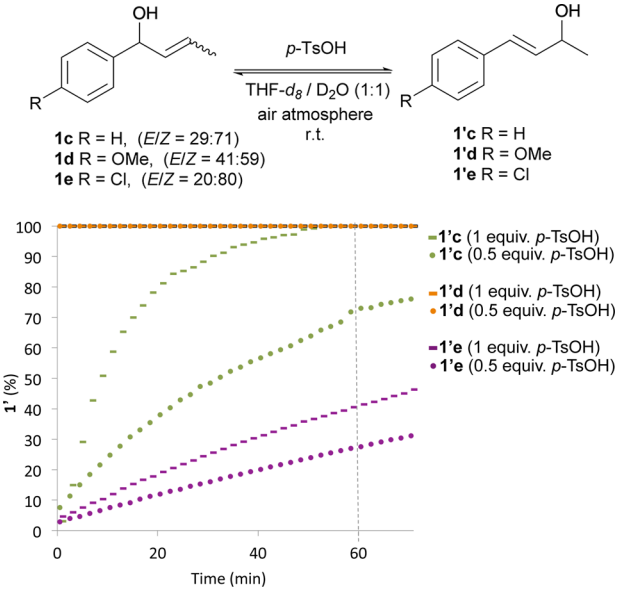
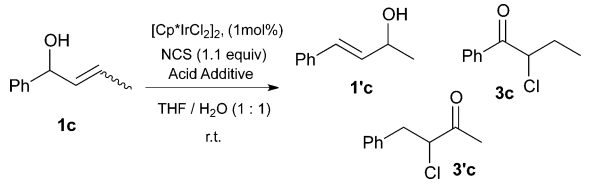


Figure 2. 1,3-Transposition of allylic alcohols **1c–e** promoted by *p*-TsOH.

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 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.

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 Supporting Information).[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,[2l] *p*-TsOH,[2e] or $BF_3{\cdot}Et_2O$ (Table 3, entries 2–5 and Supporting Information Table S2). Further screening revealed that increasing the number of equivalents of *p*-TsOH to 0.5 or 1 considerably improved the selectivity (Table 3, entries 6 and 7). Decreasing or increasing the iridium loading did not improve the outcome (Supporting Information Table S2). 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 8–11 and

Table 3. Optimization of the Tandem 1,3-Transposition/3,1-Hydrogen Shift/Chlorination of 1c[a]



entry	acid (equiv)	t_1 (min)[b]	**3c** + **3′c** (%)[c]	ratio of **1′c**:**3c**:**3′c**[d]
1	HCl[e]	-	41–56	7–25:-:56–75[f]
2	$BF_3{\cdot}Et_2O$ (0.1)	-	96	-:16:84
3	Salicylic acid (0.1)	-	96	1:13:86
4	*p*-TsOH (0.1)	-	92	-:13:87
5	*p*-TsOH (0.2)		93	-:12:88
6	*p*-TsOH (0.5)	-	96	-:9:91
7	*p*-TsOH (1)	-	96	-:3:97
8	*p*-TsOH (1)	1	95	-:3:97
9	*p*-TsOH (1)	10	93	-:2:98
10	*p*-TsOH (1)	30	95	-:-:>99
11	*p*-TsOH (1)	60	95	-:-:>99
12	*p*-TsOH (0.1)	60	96	-:9:91
13	*p*-TsOH (0.2)	60	97	-:5:95
14	*p*-TsOH (0.5)	60	>99	-:1:99

[a]Unless otherwise noted, **1c** (0.54 mmol) and the acid additive were dissolved in THF/H_2O (1:1, total volume 2.7 mL). NCS (0.65 mmol) and $[Cp^*IrCl_2]_2$ (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/H_2O (1:1, total volume 2.7 mL) was stirred at r.t. for t_1. Then, NCS (0.65 mmol) and $[Cp^*IrCl_2]_2$ (1 mol %) were added and the mixture was stirred for 12 h (full conversion) at r.t. [c]Determined by ^{1}H NMR spectroscopy using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard. [d]Determined by ^{1}H 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.

Supporting Information Table S2) 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 10 and 11). Good to excellent selectivities and yields were also obtained using catalytic amounts of *p*-TsOH (0.1–0.5 equiv) (Table3, entries 12–14).

The scope of the tandem reaction was evaluated (Scheme 2) under the optimized reaction conditions (Table 3, entry 11) using *p*-TsOH (1 equiv) and $[Cp^*IrCl_2]_2$ (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 (Supporting Information Table S3). In a 2:1 THF/H_2O mixture, the heteroaromatic α-chloroketone **3′l** was isolated in 63% yield (Scheme 2).

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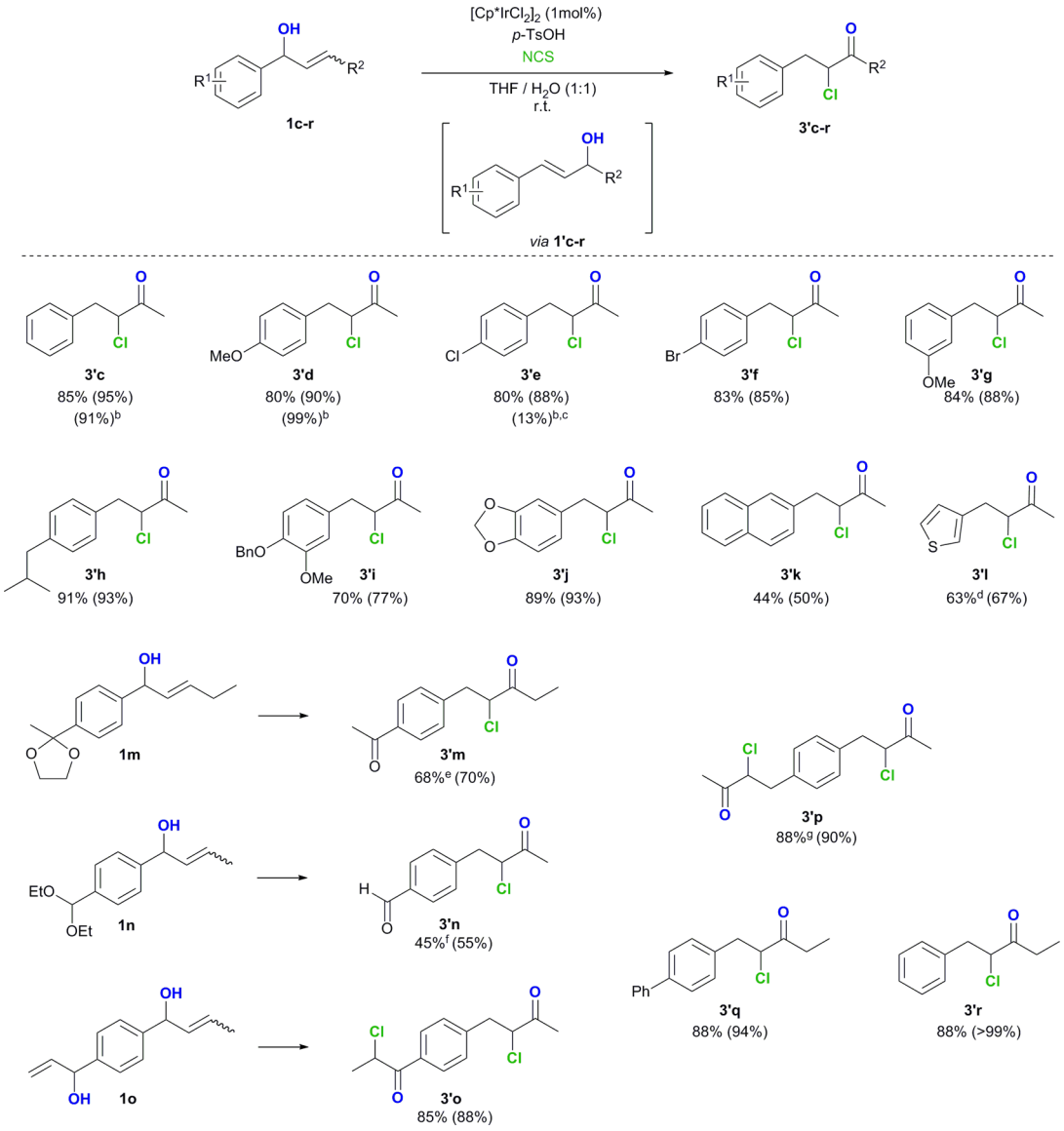
Scheme 2. Scope: 1,3-Transposition/Redox Isomerization/Chlorination of α-(Hetero)Aromatic Allylic Alcohols[a]



[a]Unless otherwise noted: reactions were carried out with 1 mmol of allylic alcohol in THF/H_2O (1:1, concentration 0.2 M) with *p*-TsOH (1 equiv) at r.t. After 60 min, NCS (1.2 equiv) and $[Cp^*IrCl_2]_2$ (1 mol %) were added at r.t, and the mixtures were stirred for 12 h (full conversion). 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). [b]Reactions carried out with 10 mol % of *p*-TsOH. [c]35% of transposed allylic alcohol **1e′** was remaining and decomposition was observed. [d]A mixture THF/H_2O (2:1) was used. [e]3 equiv of $BF_3{\cdot}Et_2O$ was used. [f]3 equiv of *p*-TsOH was used. [g]2 equiv of *p*-TsOH was used.

Substrates **1m** and **1n** were synthesized with acetal protecting groups, in order to avoid undesired reactions on the ketone or aldehyde functional groups. 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/H_2O mixtures (Supporting Information Table S3). The best result for **1m** was obtained using 3 equiv of $BF_3{\cdot}Et_2O$, 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

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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%) when using catalytic amount of *p*-TsOH.

The versatility of this method therefore gives access to variety of α-chlorocarbonyls in good to excellent yields. These compounds can be transformed into functionalized molecules through cross-coupling[11] and substitution reactions.[12] Very commonly, they are used as building blocks in the synthesis of heterocyclic compounds, which are important scaffolds in medicinal chemistry.[7b,13,14]

CONCLUSIONS

A mild and efficient methodology based on a tandem 1,3-transposition/3,1-hydrogen shift/chlorination of α-aryl secondary 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/H_2O 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

The following file is available free of charge on the ACS Publications website at DOI: 10.1021/cs501618h.

Experimental details, characterization data, and NMR spectra of organic compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: belen@organ.su.se.

Notes

The authors declare no competing financial interest.

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