ChemPubSoc Europe

DOI: 10.1002/chem.201402350

CHEMISTRY
A European Journal
Full Paper

Synthetic Methods

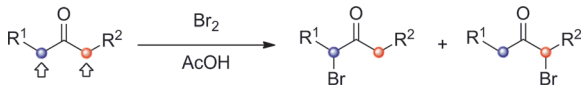
Iridium-Catalyzed Isomerization/Bromination of Allylic Alcohols: Synthesis of α-Bromocarbonyl Compounds

Antonio Bermejo Gómez,[a, b] Elis Erbing,[a, b] María Batuecas,[a] Ana Vázquez-Romero,[a] and Belén Martín-Matute*[a, b]

Abstract: α-Brominated ketones and aldehydes, with two adjacent electrophilic carbon atoms, are highly valuable synthetic intermediates in organic synthesis, however, their synthesis from unsymmetrical ketones is very challenging, and current methods suffer from low selectivity. We present a new, reliable, and efficient method for the synthesis of α-bromocarbonyl compounds in excellent yields and with excellent selectivities. Starting from allylic alcohols as the carbonyl precursors, the combination of a 1,3-hydrogen shift catalyzed by iridium(III) with an electrophilic bromination gives α-bromoketones and aldehydes in good to excellent yields. The selectivity of the process is determined by the structure of the starting allylic alcohol; thus, α-bromoketones formally derived from unsymmetrical ketones can be synthesized in a straightforward and selective manner.

Introduction

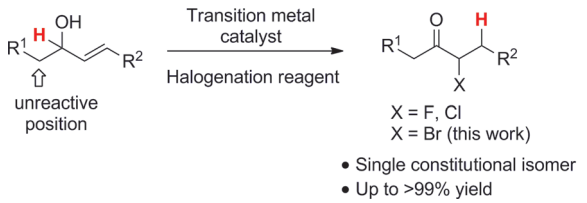
Brominated compounds are highly versatile intermediates in organic synthesis that can undergo various transformations including nucleophilic substitution[1] and transition-metal-catalyzed cross-coupling reactions.[2] Consequently, the development of efficient and selective methods for their preparation is important.[3] Bromination reactions have traditionally been accomplished by using bromine. However, because of the toxicity and high reactivity of bromine, a number of safer alternative reagents have been prepared in recent years. Among them, *N*-bromoamide reagents have been used in a great number of efficient and even diastereo- and enantioselective transformations.[4] Difficulties commonly encountered during the synthesis of halogenated compounds include a lack of selectivity and an incompatibility of the reaction conditions with certain functional groups. For example, in the halogenation of unsymmetrical ketones with two enolizable positions (α and α′), a mixture of products is usually obtained (Scheme 1). This selectivity may be controlled in some instances by an electronic and/or steric differentiation of the two enolizable positions, which can result in selective halogenation.[5] Low selectivities may also be seen with substrates containing benzylic positions, or with electron-rich aromatics, because both of these are prone to bromination.



Scheme 1. α-Bromination of unsymmetrical ketones.

During the last few years, we have reported alternative selective methods for the synthesis of α-fluoro[6a–b] and α-chloro ketones and aldehydes[6c] in excellent yields and under mild reaction conditions. The methodology formally relies on the formation of in situ catalytic amounts of enolates from allylic alcohols. This is achieved by using transition-metal catalysts that can promote a 1,3-hydrogen shift.[7] In the presence of electrophilic halogenating reagents,[6] α-fluoro and α-chlorocarbonyl compounds are obtained in excellent yields and, more importantly, as single constitutional isomers (Scheme 2).[8,9]

A major challenge to be overcome in this tandem process is the compatibility of the transition-metal catalysts with the halogenating agents.[10,11] We found that $[Cp^*IrCl_2]_2$ in aqueous



Scheme 2. Synthesis of α-halocarbonyl derivatives from allylic alcohols.

[a] A. B. Gómez, E. Erbing, M. Batuecas, A. Vázquez-Romero, B. Martín-Matute
Department of Organic Chemistry
and Berzelii Center EXSELENT
Arrhenius Laboratory
Stockholm University,
SE-106 91 Stockholm, Sweden.
Fax: (+) 46815 49 08
E-mail: belen@organ.su.se

[b] A. B. Gómez, E. Erbing, B. Martín-Matute
Berzelii Center EXSELENT
on Porous Materials
Stockholm University,
SE-106 91 Stockholm, Sweden.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402350.

solvent mixtures was an excellent catalyst that was compatible with halogenating agents such as Selectfluor and *N*-chlorosuccinimide (NCS).[6] Furthermore, the reactions could be carried out under an atmosphere of air and at room temperature in short reaction times.

Inspired by their unique reactivities and important roles as synthetic intermediates in organic synthesis, in this paper, we present the results of our investigations into the synthesis of α-bromocarbonyl compounds from allylic alcohols. Reaction conditions, including the nature of the catalyst and the solvent system, were evaluated so that the tandem 1,3-hydrogen shift/bromination process could be achieved. Furthermore, due to the high reactivity of common brominating agents such as bromine and *N*-bromosuccinimide (NBS), a key factor in the development of this new transition-metal-catalyzed bromination method was the use of a mild and underexplored brominating reagent. The scope and limitations of this bromination reaction are presented.

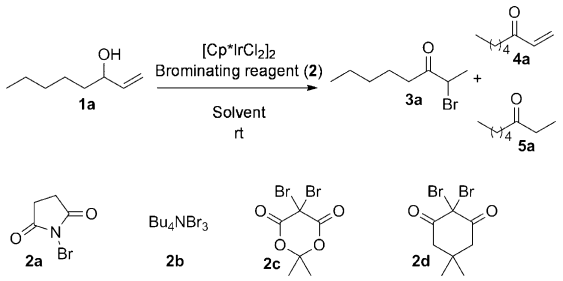
Results and Discussion

We first investigated the tandem 1,3-hydrogen shift/bromination of allylic alcohols using the conditions previously reported by our group for the corresponding fluorination or chlorination process.[6] The chosen system was oct-1-en-3-ol (**1a**) as starting allylic alcohol, in a mixture of tetrahydrofuran (THF) and water (1:1 v/v), with $[Cp^*IrCl_2]_2$ (0.5 mol%) as the catalyst in the presence of common electrophilic brominating reagents (**2a**–**c**; 1.1 equiv, Table 1). When *N*-bromosuccinimide (NBS; **2a**) was used, only the undesired nonbrominated ketone **5a** was formed almost quantitatively (>99%; Table 1, entry 1). Although full conversion was achieved by using tetrabutylammonium tribromide (**2b**), a mixture of unidentified products was obtained in which neither **3a**, **4a**, nor **5a** were detected (Table 1, entry 2). The best result was obtained when 5,5-dibromo-2,2-dimethyl-1,3-dioxane-4,6-dione (5,5-dibromo Meldrum's acid; **2c**) was used, which gave full conversion into a mixture of brominated (**3a**) and nonbrominated (**5a**) ketones in a 79:21 ratio (Table 1, entry 3). When the less common 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione (2,2-dibromodimedone; **2d**) was used, the conversion into the desired product **3a** was lower under the chosen reaction conditions, but the selectivity was significantly improved (Table 1, entry 4).

To improve these results, we screened a range of reaction conditions including the concentration and the THF/water ratio, the catalyst loading, and the number of equivalents of brominating agent **2c**. The reactions were stopped after 3 h in the optimization study to detect differences in the reaction outcomes. When the number of equivalents of **2c** was decreased to 0.55 in THF/H_2O (1:1, 0.2 M), the ratio **3a**/**5a** was improved (Table 1, entry 5 vs. 3). Interestingly, even though less than 1 equiv of **2c** was used, **3a** was obtained in a yield as high as 70%, indicating that this brominating agent is able to deliver both of its Br atoms to form the product. Increasing the relative amount of THF in the solvent system gave better **3a**/**5a** ratios, although the conversion gradually decreased as the amount of THF was increased (Table 1, entry 6 and Table S1). When the relative amount of H_2O was increased under otherwise identical conditions, moderate yields and inferior **3a**/**5a** ratios were obtained (Table 1, entry 7 and Table S1). A drastic decrease in the amount of water in THF or acetone afforded yields of less than 10% (See Tables S1 and S2), which may be explained by the low solubility of the iridium complex in organic solvents.

Further optimization studies were then conducted with a THF/H_2O ratio of 2:1. The concentration of allylic alcohol **1a**, the number of equivalents of **2c**, and the catalyst loading were varied (Table 1, entries 8–10 and Table S1). It can be concluded that the best results [99% conv. into **3a** (90%) and **5a** (9%)] were obtained with 0.7 equiv of **2c**, 0.5 mol% $[Cp^*IrCl_2]_2$ (i.e., 1 mol% Ir), and [**1a**] = 0.1 M (Table 1, entry 10). Better results were not achieved when acidic, basic, or neutral buffers, or different reaction temperatures were used (40 or 0 °C). It is worth mentioning that α,β-unsaturated ketone **4a** was not detected, except under the conditions described in entries 3 and 4 (Table 1), for which less than 1% **4a** was formed.

Table 1. Screening of reaction conditions.[a]

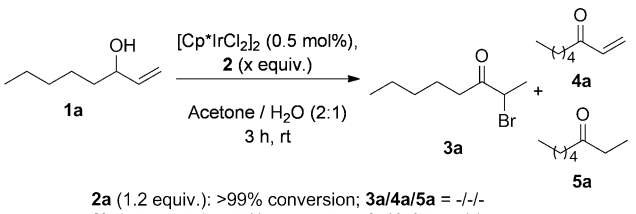


	Solvent (v/v)	2 (equiv)	Conv. [%][b]	Yield [%][b] 3a	4a	5a
1	THF/H_2O (1:1)	**2a** (1.1)	>99	–	–	>99
2[c]	THF/H_2O (1:1)	**2b** (1.1)	>99	–	–	–
3	THF/H_2O (1:1)	**2c** (1.1)	>99	79	<1	21
4	THF/H_2O (1:1)	**2d** (1.1)	44	42	<1	1
5	THF/H_2O (1:1)	**2c** (0.55)	84	70	–	14
6	THF/H_2O (5:1)	**2c** (0.55)	38	36	–	2
7	THF/H_2O (1:5)	**2c** (0.55)	68	42	–	25
8	THF/H_2O (2:1)	**2c** (0.7)	93	86	–	7
9[d]	THF/H_2O (2:1)	**2c** (0.7)	46	44	–	4
10[e]	THF/H_2O (2:1)	**2c** (0.7)	>99	90	–	9
11[e]	Et_2O/H_2O (2:1)	**2c** (0.7)	2	1	–	1
12[e]	2-MethylTHF/H_2O (2:1)	**2c** (0.7)	3	3	–	<1
13[e]	$MeCN/H_2O$ (2:1)	**2c** (0.7)	11	7	–	4
14[e,f]	$EtOH/H_2O$ (2:1)	**2c** (0.7)	>99	26	–	8
15[e]	THF/EtOH (2:1)	**2c** (0.7)	<1	<1	–	<1
16[e]	1,4-Dioxane/H_2O (2:1)	**2c** (0.7)	66	46	–	20
17[e]	**Acetone/H_2O (2:1)**	**2c (0.7)**	**>99**	**91**	–	**9**
18[e]	Acetone/H_2O (5:1)	**2c** (0.7)	70	66	–	4
19[e]	Acetone/H_2O (1:1)	**2c** (0.7)	95	84	–	10
20[e]	Acetone/H_2O (1:2)	**2c** (0.7)	76	54	–	22

[a] Unless otherwise noted: [**1a**] = 0.2 M, $[Cp^*IrCl_2]_2$ (0.5 mol%) at room temperature. Reaction time for entries 1–4 = 16 h and for 5–20 = 3 h. All reactions were run under an atmosphere of air. [b] Determined by ^1H NMR spectroscopic analysis using 2,3,5,6-tetrachloronitrobenzene as internal standard. [c] Full conversion into an unidentified mixture of products. [d] 0.4 M. [e] 0.1 M. [f] A complex mixture of by-products was formed.

We then studied the effect of different solvent mixtures on the 1,3-hydrogen shift/bromination of **1a** (0.1 M concentration) with **2c** (0.7 equiv) catalyzed by $[Cp^*IrCl_2]_2$ (0.5 mol%). The use of Et_2O, 2-methyltetrahydrofuran (2-methylTHF), or MeCN, in combination with H_2O (2:1) (Table 1, entries 11–13), gave very low conversions of the starting allylic alcohol. In EtOH/H_2O (2:1), most **1a** decomposed and bromoketone **3a** was obtained in only 26% yield (Table 1, entry 14). In the absence of water, when a mixture of EtOH/THF (1:2) was used, no reaction occurred (Table 1, entry 15). In 1,4-dioxane/H_2O (2:1), a moderate conversion and low selectivity were achieved (Table 1, entry 16). On the other hand, acetone/H_2O (2:1) gave essentially the same results as obtained with THF/H_2O (2:1) (Table 1, entry 17 vs. 10). Because acetone is a more environmentally friendly solvent than THF, which is particularly important for large-scale applications, further optimization was carried out in aqueous acetone (Table 1, entries 18–20 and Table S2). However, the conversion and the selectivity decreased as the solvent ratio was varied by either increasing or decreasing the acetone/H_2O ratio.

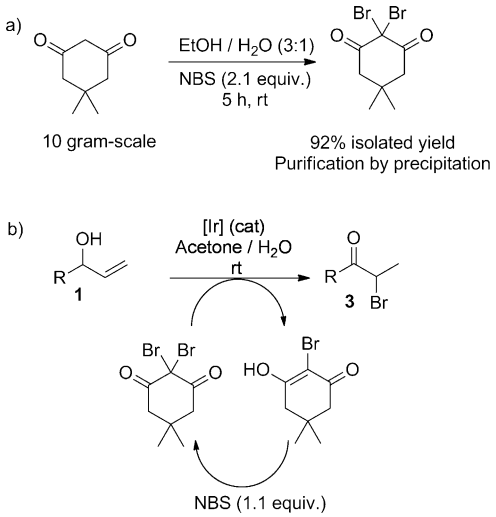
Despite the high conversions achieved, the formation of ketone **5a** diminishes the applicability of this bromination methodology because challenging purifications are needed to separate this by-product from **3a**. In the best cases described so far, high conversion into an approximate 91:9 mixture of **3a**/**5a** was obtained in either a THF/H_2O or an acetone/H_2O solvent mixture (Table 1, entries 10 and 17). The effect of the nature of the brominating agent on the outcome of the reaction had, however, only been evaluated in THF/H_2O mixtures (see Table 1). We therefore tested brominating agent **2a**, **2b** and **2d** again in acetone/H_2O (Scheme 3). The use of NBS (**2a**, 1.2 equiv) or tetrabutylammonium tribromide (**2b**, 1.2 equiv) resulted in decomposition of allylic alcohol **1a** to give complex reaction mixtures in which neither ketone **4a** nor **5a** was detected. We were delighted to observe that with **2d** (1.2 equiv), **1a** was fully converted into a mixture containing the desired α-bromoketone **3a** (99%) and enone **4a** (1%). The formation of **5a** was completely suppressed under these conditions. The number of equivalents of **2d** could not be decreased further (Table S3), because **2d** was able to transfer only one of its bromine atoms to the product. Interestingly, formation of traces of **4a** may indicate the formation of iridium hydride intermediates, which may act as catalytically active species.[7b,11]



2a (1.2 equiv.): >99% conversion; **3a/4a/5a** = -/-/-
2b (1.2 equiv.): >99% conversion; **3a/4a/5a** = -/-/-
2c (0.7 equiv.): >99% conversion; **3a/4a/5a** = 91/-/9
2d (1.2 equiv.): >99% conversion; **3a/4a/5a** = 99/1/-

Scheme 3. 1,3-Hydrogen shift/bromination of **1a** with **2a**–**d**. Conversions and ratios were determined by ^1H NMR spectroscopy using 2,3,5,6-tetrachloronitrobenzene as internal standard.

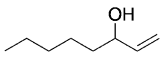
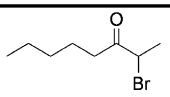
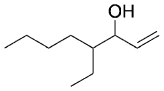
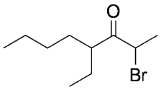
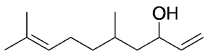
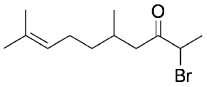
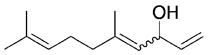
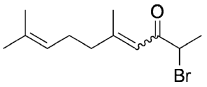
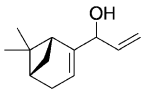
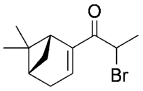
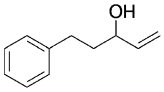
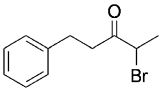
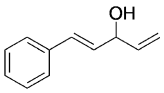
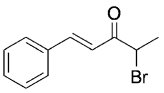
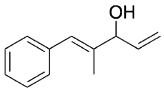
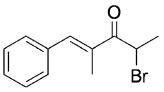
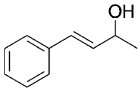
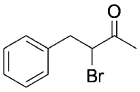
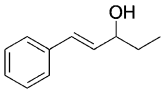
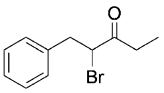
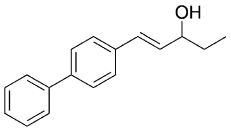
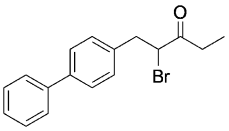
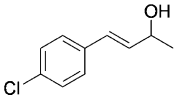
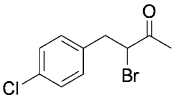
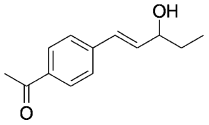
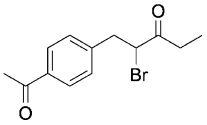
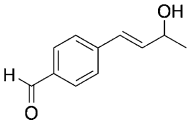
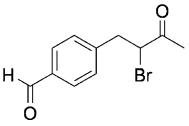
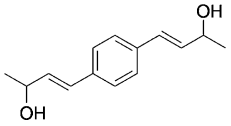
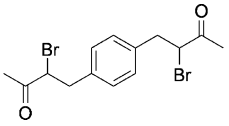
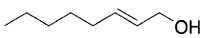
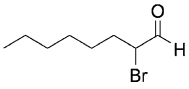
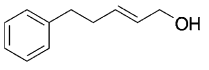
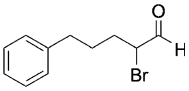
The formation of nonbrominated ketone **5a** occurs when transition-metal-catalyzed isomerization of the allylic alcohol[12,13,14] competes with the desired 1,3-hydrogen shift/bromination. The former process occurs in the absence of brominating agent. We have previously observed that the isomerization of allylic alcohols into carbonyl compounds is accelerated when the transition-metal-catalyzed reaction is carried out under acidic conditions.[6a] The formation of **5a** when **2c** was used as the brominating agent could thus be ascribed to the lower stability of this reagent compared with that of **2d**, which results in the formation of traces of acid in the aqueous reaction medium. Furthermore, **2c** can deliver both bromine atoms forming Meldrum's acid, which decomposes under the reaction conditions to give acidic species. In contrast, 2,2,-dibromodimedone (**2d**) does not decompose in solution so the formation of unwanted **5a** is suppressed. Other important advantages of using **2d** as brominating agent are: i) it can be prepared easily on a multi-gram scale from available and inexpensive starting materials in one step,[15] and ii) although only one bromine atom is used, the monobrominated by-product can be recovered from the reaction medium to be transformed back into **2d** (Scheme 4).



Scheme 4. a) Synthesis of 2,2-dibromodimedone **2d**. b) Reusability of the monobrominated by-product after catalytic bromination with **2d**.

The scope of the reaction was then investigated by exploring the 1,3-hydrogen shift/bromination of a variety of allylic alcohols under the conditions shown in Scheme 3 (i.e., with **2d** as brominating agent). We observed that substrates with aromatic groups and, in particular those in which these groups were conjugated with the double bond of the allylic alcohol (e.g., **1i**–**l** in Table 2), required reaction times as long as 42 h. With the aim of finding a more active catalyst with a broad substrate scope, we investigated the use of other related Ir^{III} complexes: $[Cp^*Ir(H_2O)_3]SO_4$[16a] and $[(Cp^*Ir)_2(OH)_3]OH{\cdot}11H_2O$.[16b] Reactions were carried out in NMR tubes using deuterated solvents, and were followed by ^1H NMR spectroscopy. Figure 1 shows the conversion of **1f** as a function of time. The bromi-

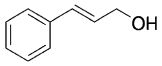
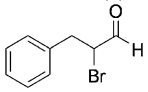
Table 2. Scope of the 1,3-hydrogen shift/bromination of allylic alcohols.[a]

		Allylic alcohol (**2**)	*t* [h]		Product (**3**)	Yield [%][b]
1	**1a**		0.5	**3a**		90 (99)
2	**1b**		1.5	**3b**		97 (98)[c]
3	**1c**		3	**3c**		73 (86)[d]
4	**1d**		2	**3d**		76 (98)[e]
5	**1e**		3.5	**3e**		71 (80)[f]
6	**1f**		0.5	**3f**		96 (98)
7	**1g**		24	**3g**		46 (92)
8	**1h**		4	**3h**		79 (88)
9[g]	**1i**		24	**3i**		85 (92)
10[g]	**1j**		24	**3j**		83 (96)
11[g]	**1k**		24	**3k**		82 (94)
12[g]	**1l**		24	**3l**		88 (96)
13[g]	**1m**		24	**3m**		87 (90)
14[g]	**1n**		24	**3n**		45 (52)
15[g,h]	**1o**		24	**3o**		87 (92)
16	**1p**		5	**3p**		91 (96)
17	**1q**		6	**3q**		86 (99)

nation was faster with hydroxo complex $[(Cp^*Ir)_2(OH)_3]OH{\cdot}11H_2O$, which gave 90% of **3f** in only 10 min, and reached full conversion within 20 min. None of the catalysts produced the by-product **5f**.

The scope of the reaction was therefore investigated by using $[(Cp^*Ir)_2(OH)_3]OH{\cdot}11H_2O$ and **2d** (1.2 equiv) in acetone/H_2O (2:1). In general, aliphatic allylic alcohols reacted much more quickly than those containing a conjugated aromatic ring. Increased steric hindrance at the aliphatic chain was well tolerated (Table 2, entries 2–5 vs. entry 1). For substrates containing two olefinic substituents on the alcohol carbon, bromination only occurred at the least substituted double bond (Table 2, entries 4, 5, 7, and 8). Trisubstituted double bonds further away from the allylic alcohol moiety did not react (Table 2, entries 3 and 4). The presence of a nonconjugated aromatic ring did not slow down the reaction (Table 2, entry 6 vs. 1). However, when the aromatic ring was conjugated, longer reaction times were needed (Table 2, entries 7–8 vs. 6). This was particularly so for those substrates in which the aromatic ring was conjugated with the reactive double bond, which may be due to a loss of conjugation during the reaction. For these substrates, a higher catalyst loading was needed (Table 2, entries 9–15). An excellent example showing the efficiency of this methodology is shown in Table 2, entry 15, whereby **1o**, with two allylic alcohol moieties, was transformed into bis(α-bromoketone) **3o** in excellent yield. The attempted preparation of **3o** directly from the corresponding nonbrominated diketone would result in a complex mixture of brominated products with the Br group at either of the α or α′ carbon atoms of each of the carbonyl groups or

Table 2. (Continued)

	Allylic alcohol (**2**)	*t* [h]	Product (**3**)	Yield [%][b]
18[g]	**1r** 	24	**3r** 	70 (85)

[a] Reaction conditions: allylic alcohol (**1**, 1.0 mmol), 2,2-dibromodimedone (**2d**, 1.2 mmol), $[(Cp^*Ir)_2(OH)_3]\cdot 11H_2O$ (1.0 mol%, 2 mol% Ir), acetone/H_2O (2:1 v/v, 0.1 M on allylic alcohol), RT under air atmosphere. [b] Isolated yield; yields determined by ^1H NMR spectroscopy using 2,3,5,6-tetrachloronitrobenzene as internal standard are given in parentheses. In cases were a quantitative yield was not obtained, the remainder was starting material. [c] d.r. = 1:2 [d] d.r. = 1:1. [e] *E*/*Z* = 1:1. [f] d.r. = 1:1. [g] $[(Cp^*Ir)_2(OH)_3]\cdot 11H_2O$ (2.0 mol%). [h] **2d** (2.4 equiv).

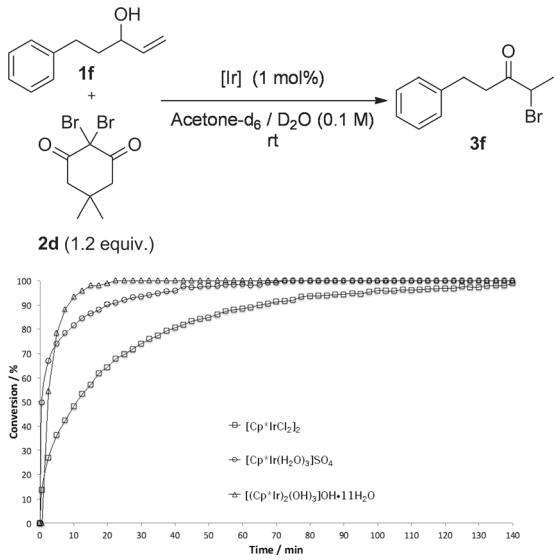
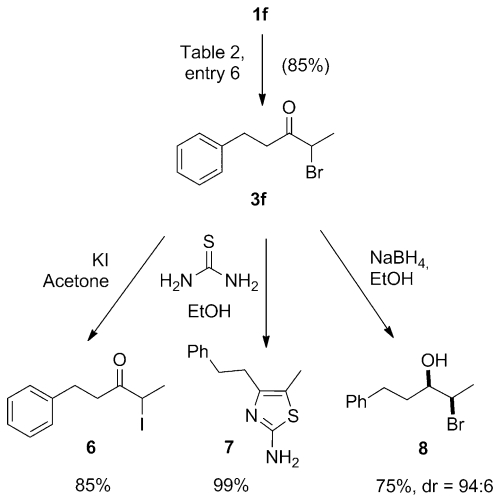


Figure 1. Conversion of **1f** catalyzed by three Ir^{III} complexes (1 mol% Ir).

at either of the benzylic positions. Importantly, primary allylic alcohols also reacted to give α-bromoaldehydes in good yields (Table 2, entries 16–18). All the products were isolated in very good yields, except for **3n**, which was produced in a moderate yield, and **3g**, which, although it was formed in very good yield, decomposed during purification. A control experiment performed with allylic alcohol **1f** in the absence of the iridium catalyst for 72 h afforded exclusively starting material.



Scheme 5. α-Bromoketones as synthetic intermediates

α-Bromocarbonyl compounds are important synthetic intermediates in organic chemistry. This bromination methodology can be used as the key step in the selective preparation of a variety of functionalized molecules. Selected examples are shown in Scheme 5. Upon treatment of **3f** with KI, α-iodoketone **6** is obtained in good yields. α-Iodoketones are also important synthons in organic synthesis. α-Bromocarbonyl compounds contain two consecutive electrophilic carbon atoms, which makes them important precursors in the synthesis of a variety of heterocyclic compounds. For example, treatment of **3f** with thiourea afforded 2-aminothiazole **7** in excellent yield.[6c] Additionally, reduction of the carbonyl functional group of α-bromocarbonyls affords another highly versatile building block in organic synthesis. Thus, treatment of **3f** with $NaBH_4$ gave bromohydrin **8** in good yields and with excellent diastereoselectivity.

Conclusions

We have developed a new method for the synthesis of α-bromoketones in excellent yields as single constitutional isomers from allylic alcohols. The method can also be used to synthesize α-bromoaldehydes. The reactions are catalyzed by $[(Cp^*Ir)_2(OH)_3]OH\cdot 11H_2O$ and carried out in aqueous acetone, and they do not require the use of an inert atmosphere. As brominating agent, 2,2-dibromodimedone afforded the best results, because it suppressed the formation of nonbrominated carbonyl by-products and was compatible with functionalized alcohols without yielding undesired polybrominated species. Mechanistic investigations are in progress, and the results will be reported in due course. α-Bromocarbonyl compounds are very versatile synthetic intermediates. Thus, this new procedure is expected to be of great interest to the scientific community, both in academia and in industry, because it opens up new and efficient synthetic routes for the preparation of a large variety of building blocks.

Experimental Section

General Information

All iridium-catalyzed reactions were carried out in closed glass vials under an atmosphere of air. Air- and moisture-sensitive reactions used to prepare the starting allylic alcohols were carried out in oven-dried glassware under an atmosphere of dry nitrogen. Reagents were used as obtained from commercial suppliers without further purification. Acetone was used as obtained from a commercial supplier (puriss p.a.). Flash chromatography was carried out on

60 Å (35–70 μm) silica gel (Acros Kieselgel 60) using pentane or pentane/EtOAc or pentane/Et_2O mixtures as eluent. Analytical TLC was carried out on aluminum-backed plates (1.5 Å, ca. 5 cm) precoated (0.25 mm) with silica gel (Merck, Silica Gel 60 F254). Compounds were visualized either by exposure to UV light or by dipping the plates in a solution of 0.75% $KMnO_4$ (w/v) in an aqueous solution of K_2CO_3 0.36 M. Melting points were recorded in a metal block and are uncorrected. ^1H NMR spectra were recorded at 400 or 500 MHz; ^{13}C NMR spectra were recorded at 100 or 125 MHz with a Bruker Advance spectrometer. ^1H and ^{13}C NMR chemical shifts (δ) are reported in ppm from tetramethylsilane, using the residual solvent resonance ($CHCl_3$: $\delta_H = 7.26$ ppm and $CDCl_3$: $\delta_C = 77.0$ ppm) as an internal reference. Coupling constants (*J*) are given in Hz. High-resolution mass spectra (HRMS) were recorded with a Bruker microTOF ESI-TOF mass spectrometer. NMR yields were calculated using 2,3,5,6-tetrachloronitrobenzene as internal standard.

Synthesis

Synthesis of 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione (2d): Prepared by a modification of a reported procedure.[15] 5,5-Dimethylcyclohexa-1,3-dione (10 g, 71.3 mmol) was dissolved in a mixture of EtOH and H_2O (3:1 v/v, 140 mL), and *N*-bromosuccinimide (26.8 g, 150 mmol, 2.1 equiv) was added in four portions (5 min between each portion). The reaction mixture was stirred for 5 h, then the resulting white solid formed was collected by filtration and washed several times with water. The residual solvent was removed under rotatory evaporation at 40 °C for 2 h, and the remaining material was kept under reduced pressure (< 2 mmHg) overnight. Compound **2d** was obtained as a white solid (19.5 g, 65.4 mmol, 92%). M.p. 148–150 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 2.99$ (s, 4H), 1.00 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 192.9$, 66.6, 48.3, 30.7, 27.8 ppm; HRMS (ESI): *m/z* calcd for $C_8H_{12}O_3{}^{79}Br_2 + Na^+$: 336.9045 $[M+H_2O+Na]^+$; found: 336.9045.

General procedure for tandem iridium-catalyzed 1,3-hydrogen shift/C–Br bond formation: The corresponding allylic alcohol (1 mmol, 1 equiv) was dissolved in a mixture of acetone and water (2:1 v/v, 9.6 mL). 2,2-Dibromo-5,5-dimethylcyclohexane-1,3-dione (**2d**; 358 mg, 1.2 mmol, 1.2 equiv) was added and the mixture was stirred for 3 min. Then $[(Cp^*Ir)_2(OH)_3]OH{\cdot}11H_2O$ (1–2 mol%) was added, and the reaction mixture was stirred at RT for the time indicated (TLC monitoring). Then the acetone was removed under reduced pressure, and the mixture was extracted with CH_2Cl_2 (3× 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash silica gel column chromatography (pentane/EtOAc or pentane/Et_2O) to give the corresponding α-bromoketone/aldehyde.

General procedure for the recovery of unreacted 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione (2d) and of 2-bromo-3-hydroxy-5,5-dimethylcyclohex-2-en-1-one from the reaction mixture: After chromatographic purification of α-bromocarbonyl **3f** (reaction performed on a 5.96 mmol scale of **1f**), the eluent was changed to EtOAc/pentane (1:10) for elution of the excess of 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione (**2d**; $R_f = 0.58$ in EtOAC/pentane (1:10), 326 mg, 91%, 0.18 equiv). The eluent was then changed to EtOAC/pentane (2:1) and 2-bromo-3-hydroxy-5,5-dimethylcyclohex-2-en-1-one ($R_f = 0.23$ in EtOAC/pentane (2:1)) was recovered after evaporation of the solvent and washing the orange solid with EtOAc. The monobrominated by-product was recovered as white crystals after drying under reduced pressure (790 mg, 61%, 0.61 equiv). M.p. 174–176 °C; ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 6.60$ (br. s, 1H), 2.52 (br. s, 2H), 2.43 (br. s, 2H), 1.11 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = 190.6$, 169.7, 100.8, 50.9, 42.6, 32.2, 28.2 ppm; HRMS (ESI): *m/z* calcd for $C_8H_{11}O_2{}^{79}Br + Na^+$: 240.9835 $[M+Na]^+$; found: 240.9828.

Synthesis of 2,2-dibromo-5,5-dimethylcyclohexane-1,3-dione (2d) from 2-bromo-3-hydroxy-5,5-dimethylcyclohex-2-en-1-one: *N*-Bromosuccinimide (446 mg, 2.5 mmol, 1.1 equiv) was added in one portion to a solution of 2-bromo-3-hydroxy-5,5-dimethylcyclohex-2-en-1-one (0.50 g, 2.28 mmol) in a mixture of EtOH and H_2O (3:1 v/v, 8 mL). The reaction mixture was stirred for 3 h and the resulting white solid formed was collected by filtration and washed several times with water. The residual solvent was removed under rotatory evaporation at 40 °C for 2 h, and then the material was kept under reduced pressure (< 2 mmHg) overnight. Compound **2d** was obtained as a white solid (664 mg, 2.23 mmol, 98%).

Acknowledgements

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, and M. B. thanks the Spanish MEC for a predoctoral grant.

Keywords: allylic compounds · bromination · iridium · ketones · synthetic methods

[1] Selected examples: a) T. Ankner, M. Fridén-Saxin, N. Pemberton, T. Seifert, M. Grøtli, K. Luthman, G. Hilmersson, *Org. Lett.* **2010**, *12*, 2210–2213; b) A. Herath, N. D. P. Cosford, *Org. Lett.* **2010**, *12*, 5182–5185; c) S. G. Li, S. Z. Zard, *Org. Lett.* **2013**, *15*, 5898–5901.

[2] a) P. M. Lundin, J. Esquivias, G. C. Fu, *Angew. Chem.* **2008**, *121*, 160–162; *Angew. Chem. Int. Ed.* **2008**, *48*, 154–156; b) P. M. Lundin, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029; c) S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 1264–1266; d) S. Lou, G. C. Fu, *J. Am. Chem. Soc.* **2010**, *132*, 5010–5011.

[3] a) I. Pravst, M. Zupan, S. Stavber, *Tetrahedron Lett.* **2006**, *47*, 4707–4710; b) I. Pravst, M. Zupan, S. Stavber, *Tetrahedron* **2008**, *64*, 5191–5199; c) R. E. Boyd, C. R. Rasmussen, J. B. Press, *Synthetic Commun.* **1995**, *25*, 1045–1051; d) C. Ye, J. M. Shreeve, *J. Org. Chem.* **2004**, *69*, 8561–8563; e) K. Tanemura, T. Suzuki, Y. Nishida, K. Satsumabayashi, T. Horaguchi, *Chem. Commun.* **2004**, 470–471.

[4] C. K. Tan, Y. Y. Yeung, *Chem. Commun.* **2013**, *49*, 7985–7996.

[5] C. R. Rasmussen, J. B Press. R. E. Boyd, *Synth. Commun.*, **1995**, *25*, 1045–1051.

[6] a) N. Ahlsten, B. Martín-Matute, *Chem. Commun.* **2011**, *47*, 8331–8333; b) N. Ahlsten, A. Bartoszewicz, S. Agrawal, B. Martín-Matute, *Synthesis* **2011**, 2600–2608; c) N. Ahlsten, A. Bermejo Gómez, B. Martín-Matute, *Angew. Chem.* **2013**, *125*, 6393–6396; *Angew. Chem. Int. Ed.* **2013**, *52*, 6273–6276.

[7] a) T. D. Sheppard, *Synlett* **2011**, 1340–1344; b) N. Ahlsten, A. Bartoszewicz, B. Martín-Matute, *Dalton Trans.* **2012**, *41*, 1660–1670.

[8] For selected examples using carbon electrophiles (i.e., aldehydes and imines), see: a) X.-F. Yang, M. Wang, R. S. Varma, C.-J. Li, *Org. Lett.* **2003**, *5*, 657–660; b) V. Branchadell, C. Crévisy, R. Grée, *Chem. Eur. J.* **2004**, *10*, 5795–5803; c) D. Cuperly, J. Petrignet, C. Crévisy, R. Grée, *Chem. Eur. J.* **2006**, *12*, 3261–3274; d) J. Petrignet, I. Prathap, S. Chandrasekhar, J. S. Yadav, R. Grée, *Angew. Chem.* **2007**, *119*, 6413–6416; *Angew. Chem. Int. Ed.* **2007**, *46*, 6297–6300; e) A. Bartoszewicz, M. Livendahl, B. Martín-

Matute, *Chem. Eur. J.* **2008**, *14*, 10547 – 10550; f) N. Ahlsten, B. Martín-Matute, *Adv. Synth. Catal.* **2009**, *351*, 2657 – 2666; g) A. Mizuno, H. Kusama, N. Iwasawa, *Chem. Eur. J.* **2010**, *16*, 8248 – 8250; h) H. T. Cao, T. Roisnel, A. Valleix, R. Grée, *Eur. J. Org. Chem.* **2011**, 3430 – 3436; i) L. Lin, K. Yamamoto, S. Matsunaga, M. Kanai, *Angew. Chem.* **2012**, *124*, 10421 – 10425; *Angew. Chem. Int. Ed.* **2012**, *51*, 10275 – 10279; j) A. Bartoszewicz, M. M. Jeżowska, K. Laymand, J. Möbius, B. Martín-Matute, *Eur. J. Inorg. Chem.* **2012**, 1517 – 1530.

[9] For other relevant transition-metal-catalyzed transformations relying on catalytic formation of enolates, see: a) B. M. Bocknack, L. C. Wang, M. J. Krische, *Proc. Natl. Acad. Sci.* **2004**, *101*, 5421 – 5424; b) C. Bee, S. B. Han, A. Hassan, H. Iida, M. J. Krische, *J. Am. Chem. Soc.*, **2008**, *130*, 2746 – 2747; c) A. Hassan, J. R. Zbieg, M. J. Krische, *Angew. Chem.* **2011**, *123*, 3555 – 3558; *Angew. Chem. Int. Ed.* **2011**, *50*, 3493 – 3496; d) S. Ogawa, Y. Obora, *Chem. Commun.* **2014**, *50*, 2491 – 2493.

[10] For relevant examples of transition-metal-catalyzed electrophilic halogenations, see: a) N. Schröder, J. Wencel-Delord, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 8298 – 8301; b) N. Kuhl, N. Schröder, F. Glorius, *Org. Lett.*, **2013**, *15*, 3860 – 3863.

[11] For a one-pot consecutive iridium-catalyzed isomerization/halogenation, see: A. Quintard, A. Alexakis, C. Mazet, *Angew. Chem.* **2011**, *123*, 2402 – 2406; *Angew. Chem. Int. Ed.* **2011**, *50*, 2354 – 2358.

[12] For selected reviews on the isomerization of allylic alcohols, see: a) R. C. van der Drift, E. Bouwman, E. Drent, *J. Organomet. Chem.* **2002**, *650*, 1 – 24; b) R. Uma, C. Crévisy, R. Grée, *Chem. Rev.* **2003**, *103*, 27 – 51; c) V. Cadierno, P. Crochet, J. Gimeno, *Synlett* **2008**, 1105 – 1124; d) L. Mantilli, C. Mazet, *Chem. Lett.* **2011**, *40*, 341 – 344; e) P. Lorenzo-Luis, A. Romerosa, M. Serrano-Ruiz, *ACS Catalysis*, **2012**, *2*, 1079 – 1086.

[13] For isomerization of allylic alcohols in H_2O, see: a) V. Cadierno, S. E. García-Garrido, J. Gimeno, A. Varela-Álvarez, J. A. Sordo, *J. Am. Chem. Soc.* **2006**, *128*, 1360 – 1370; b) N. Ahlsten, H. Lundberg, B. Martín-Matute, *Green Chem.* **2010**, *12*, 1628—1633; For isomerization in THF and MeOH, see: c) R. Uma, M. K. Davies, C. Crévisy, R. Grée, *Eur. J. Org. Chem.* **2001**, 3141 – 3146.

[14] For recent selected examples of asymmetric or enantiospecific isomerization of allylic alcohols, see: a) R. Wu, M. G. Beauchamps, J. M. Laquidara, J. R. Sowa Jr., *Angew. Chem.* **2012**, 124, 2148 – 2152; *Angew. Chem. Int. Ed.* **2012**, *51*, 2106 – 2110; b) V. Bizet, X. Pannecoucke, J. L. Renaud, D. Cahard, *Angew. Chem.* **2012**, 124, 6573 – 6576; *Angew. Chem. Int. Ed.* **2012**, *51*, 6467 – 6470; c) J. Q. Li, B. Peters, P. G. Andersson, *Chem. Eur. J.* **2011**, *17*, 11143 – 11145.

[15] G. Papori, B. Abhilasha, D. Babulal, *Adv. Synth. Catal.* **2009**, *351*, 1483 – 1487.

[16] a) S. Ogo, N. Makihara, Y. Watanabe, *Organometallics* **1999**, *18*, 5470 – 5474; b) A. Nutton, P. M. Bailey, P. M. Maitlis, *J. Chem. Soc., Dalton Trans.* **1981**, *9*, 1997 – 2022.

Received: February 25, 2014
Revised: March 31, 2014
Published online on ■■ ■■, 0000

FULL PAPER

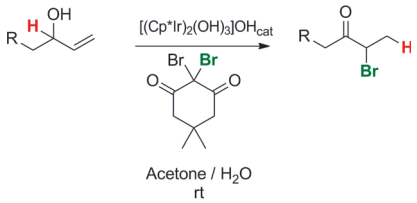
Synthetic Methods

*A. B. Gómez, E. Erbing, M. Batuecas, A. Vázquez-Romero, B. Martín-Matute**

■■ – ■■

Iridium-Catalyzed Isomerization/Bromination of Allylic Alcohols: Synthesis of α-Bromocarbonyl Compounds

1,3-Hydrogen shift / bromination of allylic alcohols



- Up to 97% isolated yields
- Single constitutional isomers
- 18 examples of α-bromoketones and α-bromoaldehydes

Synthon shuffle: An efficient and high-yielding synthetic route to prepare α-bromoketones and aldehydes is presented (see scheme). The method relies on 1,3-hydrogen shift/bromination of allylic alcohols catalyzed by Ir^{III} complexes. The products are obtained in excellent yields and as single constitutional isomers.