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First Catalytic and Green Synthesis of Aryl-(*Z*)-vinyl Chlorides and Its Plausible Addition–Elimination Mechanism

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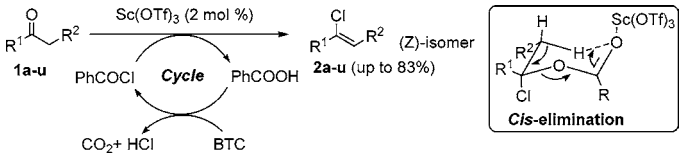
ABSTRACT



Via a catalytic cycle in the presence of scandium triflate (2 mol %)/DMF (1 mol %)/benzoyl chloride (5 mol %), aromatic ketones were treated with bis(trichloromethyl) carbonate (BTC) to afford aryl-(*Z*)-vinyl chlorides. All metal triflates tested in the reaction showed highly catalytic activity. A plausible addition–elimination mechanism was proposed. The present work describes the first catalytic and green route to the synthesis of aryl-(*Z*)-vinyl chlorides.

Vinyl chlorides are important intermediates in organic synthesis for C−C and C−N formation in Pd-catalyzed coupling reactions.[1] They have been prepared in various ways, among which the conversion of aromatic ketones to vinyl chlorides has been well studied. However, toxic phosphorus reagents such as PCl_5,[2] PCl_3,[3] and the Vilsmeier reagent[4] were involved in most cases where unpredictable byproduct formation was frequently observed.

Recently, Rolando et al. developed a new method for the direct synthesis of vinyl chlorides in strongly acidic solvents such as trifluoroacetic acid or methanesulfonic acid.[5] Besides producing a large amount of acid waste, the method required a lengthy reaction time (36 h) and the substrates were limited only to aryl ketones with a methyl-substituted or a nonsubstituted phenyl ring and 2-nonanone. Modification of the procedure exploited silica gel supported zinc halides to perform this transformation, but stoichiometric amounts of the catalyst and a large excess of acyl chloride have to be involved.[6] Obviously, the above methods are environmentally unfriendly due to the large waste and pollution.

With the increase of environmental consciousness in chemical research and industry, much attention has been paid to green chemistry. The challenge for a sustainable environment calls for clean procedures that can avoid using toxic organic reagents, large amounts of sensitive catalyst, and unnecessary waste. In the course of our research aimed at developing green organic processes, we have explored ionic liquids[7] as green solvents, metal triflate[8] as a reusable new type of Lewis acid catalyst, and BTC[9] as a safe reagent,[10]

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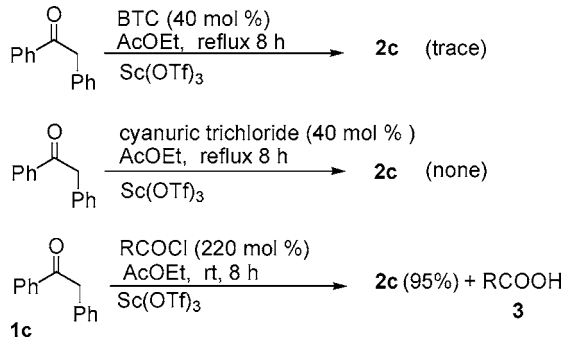
respectively. Herein, we wish to report an efficient and catalytic method for the preparation of vinyl chlorides from ketones.

The initial attempt to synthesize **2c** from 1,2-diphenyl ethanone using BTC or cyanuric trichloride in the presence of $Sc(OTf)_3$ (2 mol %) was unsuccessful (Scheme 1). Other

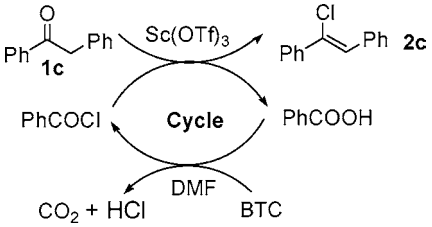
Scheme 1. Conversion of Phenylacetophenone (**1c**) to **2c**



metal triflates were also tried but proved inefficient under the reaction conditions. Even DMF (one of the most effective activators of BTC) addition could not improve the result, and only starting material was recovered. It is encouraging to find acyl chlorides were very active for the transformation, and a 95% yield of **2c** could be isolated when 1,2-diphenyl ethanone (**1c**) was treated with acetyl chloride or benzoyl chloride (2.2 equiv) in the presence of $Sc(OTf)_3$ (2 mol %). An aliquot of 2.0 equiv of acyl chloride was necessary due to the formation of carboxylic acids **3**, thus resulting in an equimolar amount of acid waste (Scheme 1).

BTC is an efficient chlorinating reagent in organic synthesis,[11] which can transform carboxylic acids easily into acyl chlorides. Bearing this in mind, it occurred to us that a reaction cycle may be established between carboxylic acids and acyl chlorides in the above reaction. To our delight, when the protocol was applied, **2c** was successfully obtained (Scheme 2), indicating the reaction cycle could proceed

Scheme 2. Lewis Acid/DMF-Catalyzed Reaction Cycle



smoothly under the given conditions. It is worth noting that only a very small amount of benzoyl chloride was required

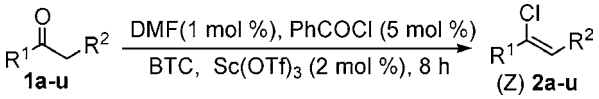
(10) It was clear that BTC was an efficient substitution of toxic phosgene, $SOCl_2$, PCl_3, $POCl_3$, PCl_5, etc.

(11) Previous review: Cotarca, L.; Delogu, P.; Nardelli, A.; Sunjic, V. *Synthesis* **1995**, 553.

(5 mol %), which reacted with ketone in the presence of $Sc(OTf)_3$ to form the desired product **2c**. The eliminated benzoic acid reacted in situ with BTC to form benzoyl chloride again, thus completing the cycle with CO_2 and HCl as the byproducts. The idea was environmentally friendly compared to most previous reports. It should be mentioned that DMF (1 mol %) was added as an activator so as to accelerate the reaction.

Because the eliminated benzoic acid could be transformed into benzoyl chloride in situ as demonstrated by the cycle, it may be reasonable to test the possibility of using carboxylic acid directly instead of benzoyl chloride to carry out the reaction. Indeed, the protocol afforded **2c** in moderate yield (Table 1, entry 3). Because the use of benzoyl chloride

Table 1. Synthesis of (*Z*)-Vinyl Chlorides in Refluxing AcOEt



entry	R^1	R^2	product	yield[a] (%)
1	Ph	CH_3	**2a**[b]	77
2	Ph	H	**2b**	31[d]
3	Ph	Ph	**2c**[b]	83 (51[c])
4	4-Me-Ph	Ph	**2d**[b]	79
5	4-Et-Ph	Ph	**2e**	81
6	3-NO_2-4-CN-Ph	H	**2f**	0[d]
7	3-Cl-Ph	CH_3	**2g**[b]	76
8	β-$C_{10}H_7$	Ph	**2h**	64
9	α-(β-MeO-$C_{10}H_6$)	Ph	**2i**	65
10	2-C_4H_3S	Ph	**2j**[b]	82
11	2-(5-Cl-C_4H_2S)	Ph	**2k**	80
12	2-(5-Br-C_4H_2S)	Ph	**2l**	79
13			**2m**	74
14	Ph	CH_2Cl	**2n**	0[d]
15	CH_2=CH	H	**2o**	trace[d]
16	n-C_5H_{11}	H	**2p**	27[d,e]
17	cyclohexanone		**2q**	30[d,e]
18	CH_3CH_2	CH_3	**2r**	33[d,e]
19	CH_3CH_2	CH_3CH_2	**2s**	25[d,e]
20	cyclohexyl	cyclohexyl	**2t**	trace[d]
21	cyclohexyl	CH_3	**2u**	18[d,e]

[a] Isolated yields based on ketones. [b] GC/MS analysis was performed to ascertain the absence of the *E* isomer. [c] Benzoic acid was used instead of benzoyl chloride. [d] Reaction time: 24 h. [e] Conversion determined by GC-MS.

afforded **2c** in better yields, the conditions developed for **2c** were further applied to a variety of ketones, and the results are summarized in Table 1.

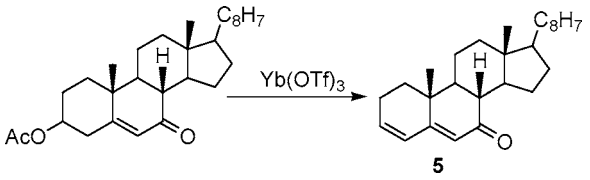
Acetophenone afforded only 31% yield of **2b** even after 24 h with the majority of the substrate unchanged (entry 2). 3-Nitro-4-cyano-acetophenone bearing two strong electron-withdrawing groups did not undergo the transformation and was recovered almost quantitatively (entry 6). A similar result was obtained with ω-chloroacetophenone (entry 14). Otherwise, *m*-chloropropiophenone gave the desired **2g** in good

yield (entry 7). Reactions of phenylacetothiophene derivatives with a catalytic amount of benzoyl chloride in the presence of BTC/DMF could also proceed smoothly, and the corresponding products were obtained with 82%, 80%, and 79% yields, respectively (entries 10−12). Naphthyl-benzyl ketones bearing a bulky group were also suitable substrates (entries 8 and 9). It could be concluded that electron-withdrawing groups decrease the electronic density of keto-carbonyls and therefore disfavor the carbonyl addition with acyl chloride.

1-Tetralone was efficiently converted into **2m** under the same conditions in 74% isolated yield (entry 13). However, strong acid or other Lewis acid catalysts[5] could not realize the transformation with such efficiency, so the vinyl chloride was contaminated with other byproducts. It should be noted that product **2** did not react further under the present reaction conditions, thus avoiding byproduct formation to a large extent. Our protocol ensured a clean and facile route to the synthesis of vinyl chloride.

Unfortunately, dienyl chloride was not obtained from unsaturated ketone under the same conditions (entry 15). Cholest-3,5-dien-7-one (**5**, Scheme 3) was easily formed

Scheme 3. Lewis Acid Catalyzed Elimination Reaction



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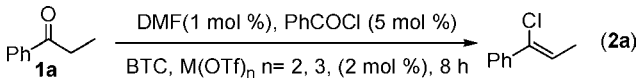
when 7-oxocholesterol acetate was treated with a catalytic amount of $Yb(OTf)_3$. Aliphatic ketones were also converted to vinyl chlorides though in lower yields (entries 16−21). Effects of metal triflates were also examined with aliphatic ketones (**2u**) in different solvents such as $CHCl_3$, CH_2Cl_2, THF, CH_3CN, CH_3NO_2, etc., but the yield was not increased obviously. It seems aromatic ketones should be more suitable in the above reaction.

In addition, when catalytic $Yb(OTf)_3$, $Zn(OTf)_2$, $Ga(OTf)_3$, $Bi(OTf)_3$, $In(OTf)_3$, and $Cu(OTf)_2$ were used instead of $Sc(OTf)_3$, the reaction of the aromatic ketone (**1a**) also proceeded well (Table 2). However, conventional $AlCl_3$ (5

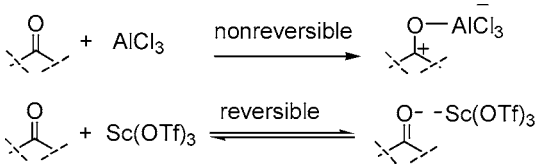
Table 2. Effect of Different Metal Triflates[a]



entry	metal	yield[b] (%)	entry	metal	yield[b] (%)
1	Yb	76	4	Bi	74
2	Zn	64	5	In	73
3	Ga	69	6	Cu	70

[a] Anhydrous metal triflates were used. [b] Isolated yield based on propiophenone.

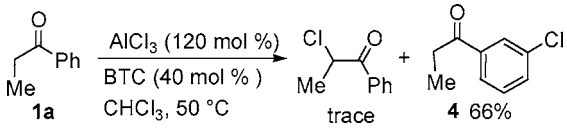
mol %) was inefficient in the reactions and only gave trace amounts of product. We supposed the strongly coordinate oxygen−aluminum bond has lost the Lewis acid catalysis, so conventional Lewis acid could not be recycled and reused (eq 1).



Eq. 1

When propiophenone was treated with BTC (0.4 mol) in the presence of excess $AlCl_3$ (1.2 mol) for 4 h, an unexpected reaction occurred and chlorinated ketone **4** was obtained in 66% yield (Scheme 4).

Scheme 4. $AlCl_3$-Catalyzed Chlorination on the Aromatic Ring



A very small amount of DMF was used as an activator in the protocol, but when stoichiometric amounts or excess DMF was used, the results were greatly different. Chloroformylation reaction occurred, and a β-chloro-α,β-unsaturated aldehyde was formed.[12]

Obviously, the mechanism was different from Vilsmeier halogenation or haloformylation. The reaction probably proceeded with an acyl chloride mediated carbonyl addition, where 1-chloroalkylester was formed in the presence of $Sc(OTf)_3$[13] followed by cis elimination[6,14] of a carboxyl acid to give (*Z*)-vinyl chloride (Scheme 5). The cis elimination may be performed via six-membered ring transition states. The intermediate **6** (in Scheme 5) with the Cl, Ar, and O group attached on the same α-carbon, and a β-H should be unstable and could not be isolated under such reaction conditions. But interestingly, previous literature reported that aromatic aldehydes could react with acyl chloride to give stable 1-chloroalkylesters via carbonyl addition.[8c,13]

Moreover, it is favorable when the phenyl group is oriented at an equatorial position on this six-membered transition state.

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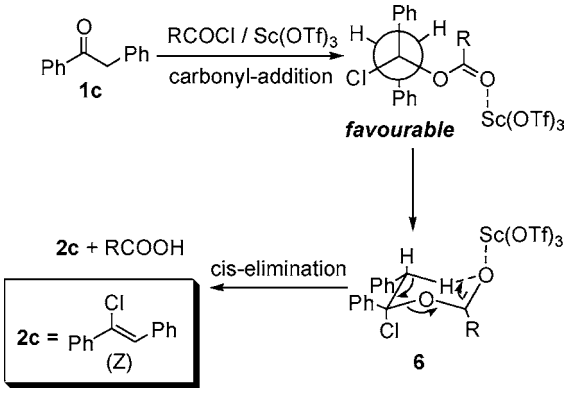
Scheme 5. Plausible Mechanism



The stereochemistry of the double bond was exclusively (*Z*)-configuration. Previous literature reported that ^{1}H NMR shift values of vinylic protons as well as methyl protons between the (*Z*) and (*E*) configuration were obviously different.[15] The unambiguous stereochemical assignments of our results agreed with the (*Z*)-configuration according to the literature. The stereochemistry was also established by NOE experiments and X-ray analysis[16] (Figure 1). Further, to ascertain the absence of the *E* isomer, GC/MS analysis was performed during the reaction (Table 1).

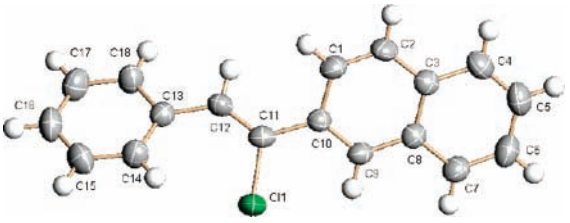


Figure 1. X-ray structure of **2h**.

In conclusion, we have developed a useful route to the preparation of aryl-(*Z*)-vinyl chlorides, very useful materials in transition metal promoted coupling reactions, with moderate to good yields under mild conditions catalyzed by scandium triflate.[17] The confirmed stereochemical assignments of the final products accorded with the mechanism involved in the process. To the best of our knowledge, it is the first catalytic and green synthesis of aryl-(*Z*)-vinyl chloride. The advantages of this method include high stereoselectivity, good atom economy, decreased waste formation, the use of safer non-phosphorus reagents, and the requirement of a very small amount of catalyst.

Acknowledgment. We thank the National Basic Research Program of China [973 Program: 2003CB 114400] and the National Natural Science Foundation of China [20476098 and 20676123] for financial support.

Supporting Information Available: General procedure for the synthesis of aryl-(*Z*)-vinyl chlorides and characterization of the products, including copies of ^{1}H and ^{13}C NMR spectra of all products, NOESY, and the X-ray crystal structure of **2h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) CCDC-295191 contains the supplementary crystallographic data for **2h**, which is available free of charge via www.ccdc.cam.ac.uk.

(17) **General procedure**: To a solution of ketone (5 mmol) and benzoyl chloride (0.25 mmol, 0.035 g) in ethyl acetate (2 mL) was added $Sc(OTf)_3$ (0.1 mmol, 0.049 g) successfully. The solution was heated to reflux for 10 min, and DMF (0.05 mmol) was added successively. Then, BTC (2 mmol, 0.594 g in 5 mL of ethyl acetate) was added dropwise very carefully over 8 h at reflux. After completion (monitored by TLC), the mixture was treated with ammonia and extracted with ether. After dryness and condensation, the products vinyl chlorides were obtained by preparative TLC.