Cobalt-Catalyzed Vinylation of Functionalized Aryl Halides with Vinyl Acetates

Muriel Amatore,[a] Corinne Gosmini,*[a] and Jacques Périchon[a]

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A new method for the preparation of styrene derivatives is described on the basis of the activation of aryl halides by low-valent cobalt species. A combination of Co^{II} bromide and 2,2′-bipyridine is suitable as catalyst for the cross-coupling reaction of a wide range of aromatic halides (X = Cl, Br, I), mostly bearing sensitive moieties, with vinyl acetates. These reactions proceed under mild conditions in the presence of the appropriate reducing agent to afford α-substituted styrene compounds in satisfactory to high yields.

Introduction

Vinylation of aryl halides is a convenient route for synthesis of styrene derivatives. The Heck reaction is a common method[1] for their preparation, as well as classical palladium-catalyzed cross-coupling of vinylic stannanes,[2] silanes[3] and boronic acids[4] with aryl halides. Other methods using organometallic reagents such as alkenylgallium[5] and vinylaluminium compounds[6] allow the formation of these useful derivatives. However, all these reactions generally require palladium catalysts. Styrene derivatives can also be obtained by cross-coupling vinyl halides with arylboronic acids[7a] or aryl Grignard reagents.[7b] Because of their poor reactivity, simple vinyl acetates are not often used for these cross-coupling reactions. Heck was the first to report cross-coupling of "phenylpalladium chloride" and vinyl acetate, but only few traces of styrene were observed, the major products being substituted 2-arylaldehydes and ketones.[8] Daves et al. described the direct palladium-catalyzed vinylation from vinyl acetate and 5-iodopyrimidines[9] or iodobenzene.[10] Nevertheless, poor yields of the corresponding styrene derivative were isolated. Cross-coupling from reactive phenylvinyl acetate and various aryl halides affords better yields of *trans*-stilbenes[11] in a single step, yet, palladium catalysis is still required. In 2001, we described a cobalt-catalyzed electrochemical vinylation of aryl halides with vinyl acetates.[12] These reactions involved aryl bromides and chlorides and led to styrene derivatives in good yields. Although this electrochemical reaction compares favorably with known chemical process, its use is not generalized since electrochemical methods are often viewed as being difficult to handle and are not generally used on larger scales. Moreover, this process involves a large quantity of 2,2′-bipyridine. This paper focuses on a new chemical method for the vinylation of aryl halides using vinyl acetates (Scheme 1).[13] This reaction relies on our recent findings and demonstrates that in some cases a purely chemical procedure may be derived from an initial electrochemical approach, though requiring some important modifications.[14] Indeed low-valent cobalt may be generated by chemical reduction of cobalt halide and efficiently activate aryl halides to form the corresponding "aryl-cobalt" species prone to undergo cross-coupling with vinyl acetates.

This allows the replacement of expensive metal catalysts by cheap cobalt salts. Furthermore, aryl bromides, chlorides and obviously iodides substituted by electron-donating or -withdrawing groups result suitable, leading usually to short reactions times. We wish to report here the finalization of this reaction and to establish its versatility with several aryl halides and vinyl acetates.

Results and Discussion

We first investigated the reaction between methyl *p*-chlorobenzoate and isopropenyl acetate under the reaction conditions described in Scheme 1. The corresponding aryl-vinyl compound was synthesized in the presence of 5 mol% $CoBr_2$(2,2′-bipyridine) in a mixture of DMF/pyridine at 50 °C (GC yield 86%). The reducing metal was activated by traces of acid. The amount of the coupling product was determined by GC with internal alkane as the standard reference. The conversion was complete within 3.5 h. Two byproducts could be observed, the reduction product ArH and the homo-coupling product Ar–Ar. A mixture of acetonitrile/pyridine as reported in the electrochemical approach[12] could also be used. However, in this case, 40 mol% of $CoBr_2$ and 40 mol% of 2,2′-bipyridine were re-

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[a] Laboratoire d'Electrochimie, Catalyse et Synthèse Organique, UMR 7582, Université Paris 12-C.N.R.S.
2 rue Henri Dunant, 94320 Thiais, France
E-mail: gosmini@glvt-cnrs.fr

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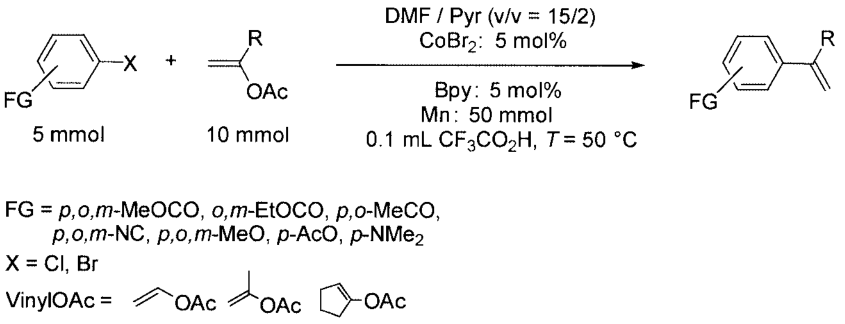


Scheme 1. General procedure for the cobalt-catalyzed cross-coupling process.

quired to achieve a similar efficiency (5 h, GC yield 84%). The use of pyridine as co-solvent is not indispensable, but it provides a spectacular acceleration. For example, in pure DMF, only 55% of aryl chloride was converted to coupling product in 8 h. This may be tentatively rationalized by considering that pyridine may play a stabilizating effect on the "aryl-cobalt" species. However, the coupling product was not observed in neat pyridine as the solvent. The efficiency of the reaction also depends on the amounts of catalyst and 2,2′-bipyridine (Table 1).

Table 1. Reaction efficiency upon using different amounts of $CoBr_2$/2,2′-bipyridine catalyst for cross-coupling of methyl *p*-chlorobenzoate with isopropenyl acetate (DMF/pyridine, 50 °C).

Entry	$CoBr_2$ (mol %)	Bpy (mol %)	Time (h)	Conversion (GC %)
1	10.0	0	68	19
2	10.0	5.0	3,5	84
3	10.0	10.0	1,5	80
4	2.5	2.5	6	10
5	5.0	5.0	3,5	86

The use of 2,2′-bipyridine was essential for the coupling reaction (Table 1, entry 1). However, when the reaction was carried out with one or two equivalents of cobalt bromide versus 2,2′-bipyridine, conversion of *para*-methylchlorobenzoate and reaction time were the same (Table 1, entries 2, 5). Thus cobalt salt excess versus 2,2′-bipyridine did not interfere in the catalytic process. In fact, only one equivalent of 2,2′-bipyridine was necessary, being presumably enough to stabilize $Co^{I or 0}$ species in the medium. Similar results were observed with 10 mol% of the equimolar complex $CoBr_2$(2,2′-bipyridine) though leading to a noticeable increase of the reaction rate (Table 1, entry 3). Conversely, poor yields were obtained with only 2,5 mol% of this complex (Table 1, entry 4). Several reducing metals were investigated showing that manganese seeming the most suitable for this system. Thus poor yields were observed with other reducing metals, e.g. Al or Mg. Similarly, though Zn was able to reduce the cobalt complex, this led to the corresponding aromatic organozinc chloride as byproduct.[15] The use of 10 equivalents of Mn versus ArCl was necessary to observe a fast conversion with good yields, yet decreasing its relative amount led to increasing reaction times. Nevertheless, the use of only 2 equivalents of Mn afforded the coupling product but required longer reaction time. Similar yields were obtained when the reaction was carried out at room temperature, but the reaction time increased in a two timefold. At 80 °C, the reaction time decreased but the proportion of byproducts resulted higher. Using two equivalents of vinyl acetate at 50 °C afforded necessary the coupling product with a short reaction time of 2h. Trifluoroacetic acid was required to activate the manganese powder. Iodine and acetic acid were also tested but resulted in less efficient activation.

We have thus extended the vinyl acetate coupling process to various aryl chlorides with isopropenyl acetate according to Scheme 1. Due to the low reactivity of C–Cl bond, these halides had to be activated by an electron-withdrawing group on the aromatic nucleus in order to react with reduced cobalt to form "arylcobalt" species. Results are reported in Table 2.

Table 2. Cross-coupling of isopropenyl acetate with different aryl chlorides (5 mol% $CoBr_2$(2,2′-bipyridine), Mn, DMF/pyridine, 50 °C, unless stated otherwise).

Entry	ArCl	Yield (%) (conversion 100%)	
1	*p*-$MeOCOC_6H_4Cl$	75	**1**
2	*o*-$MeOCOC_6H_4Cl$	0[a]	**2**
3	*m*-$MeOCOC_6H_4Cl$	56[a,b]	**3**
4	*p*-$MeCOC_6H_4Cl$	65	**4**
5	*o*-$MeCOC_6H_4Cl$	27[a]	**5**
6	*p*-NCC_6H_4Cl	76	**6**
7	*o*-NCC_6H_4Cl	73	**7**
8	*m*-NCC_6H_4Cl	63[c]	**8**

[a] GC yield. [b] Reaction required 10 mol% $CoBr_2$(2,2′-bipyridine) and compound **3** was difficult to separate from ArH. [c] Reaction run at 80 °C.

Satisfactory yields were observed when the electron-withdrawing substituent was in *para* or *meta* position. The *ortho* substitution with an ester or a carbonyl group prevented the formation of the coupling product reflecting steric requirements and involvement of chelation. Indeed, a nitrile group in *ortho* position did not affect the cross coupling.

The reactivity of aryl bromides was also investigated. The coupling reactions took place with good yields with isopropenyl acetate. The increased C–Br bond reactivity allowed good yields even in the presence of electron-donating groups. Results are reported in Table 3. Again, the *ortho* position was not very compatible with this process.

Table 3. Cross-coupling of isopropenyl acetate with different aryl bromides (5 mol% $CoBr_2$(2,2′-bipyridine), Mn, DMF/pyridine, 50 °C, unless stated otherwise).

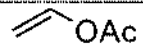
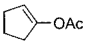
Entry	ArBr	Yield (%) (Conversion 100%)	
1	p-$MeOC_6H_4Br$	78	**9**
2	o-$MeOC_6H_4Br$	48[a,b]	**10**
3	m-$MeOC_6H_4Br$	81	**11**
4	p-$AcOC_6H_4Br$	74	**12**
5	p-$NMe_2C_6H_4Br$	44[c]	**13**
6	p-$MeOCOC_6H_4Br$	75	**1**
7	o-$EtOCOC_6H_4Br$	0[a]	**14**
8	m-$EtOCOC_6H_4Br$	82[a,d]	**15**
9	p-$MeCOC_6H_4Br$	51	**4**
10	p-NCC_6H_4Br	42[a]	**6**
11	o-NCC_6H_4Br	16[a]	**7**

[a] GC yields. [b] Reaction required 10 mol% $CoBr_2$(2,2′-bipyridine). [c] Compound **13** was recrystallized from methanol. [d] Compound **15** was difficult to separate from ArH.

Aryl iodides such as p-iodoanisole and ethyl p-iodobenzoate could be coupled with isopropenyl acetate. However, the corresponding "arylcobalt" species were too reactive in the medium leading essentially to the formation of ArH and Ar–Ar.[16]

The process was finally extended to halopyridines and isopropenyl acetate. The cross coupling reaction was efficient with 3- and 4-halopyridines notably with chloropyridines. The 3-chloropyridine could be coupled in 83% yield (compound **22**) with 5 or 10 mol% of $CoBr_2$(2,2′-bipyridine). However, the reaction time was increased with 5 mol% (24 h instead of 4.5 h). The more reactive 4-chloropyridine hydrochloride led to 67% yield (compound **23**) with only 5 mol% of catalyst within 4 h. On the other hand, the major product was the reduction one upon using the more activated 3- and 4-bromopyridines. Table 4 demonstrates the scope of the reaction upon using various vinyl acetates and different aryl halides.

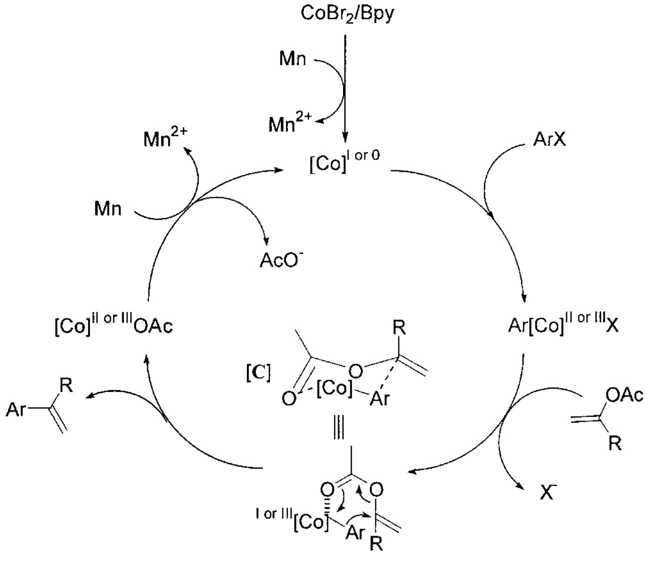
Table 4. Coupling between different vinyl acetates and aryl halides in the cobalt-catalyzed cross-coupling (5 mol% $CoBr_2$(2,2′-bipyridine), Mn, DMF/pyridine, 50 °C).

Entry	ArX	Vinyl acetate	Yield (%), (Conversion 100%)	
1	p-$MeOCOC_6H_4Cl$	A = 	81	**16**
2		B = 	79	**17**
3	p-$MeOCOC_6H_4Br$	A	59	**16**
4		B	16[a]	**17**
5	p-NCC_6H_4Cl	A	37[a]	**18**
6		B	23[a]	**19**
7	p-$MeOC_6H_4Br$	A	72	**20**
8		B	39[a]	**21**

[a] GC yields.

Yields were lower than with isopropenyl acetate. These differences in reactivity may reflect in the one hand the poor solubility of vinyl acetate in the medium and its trend towards polymerization and, on the other hand, the steric bulk of cyclopentenyl acetate.

From a mechanistic point of view, Co^{II} associated to 2,2′-bipyridine is reduced either in $Co^{I \text{ or } 0}$ by manganese powder, which needs to be previously activated by acid traces. As shown in our previous work where Co^I is stabilized by vinyl acetate in acetonitrile/pyridine,[17] cobalt species is also probably coordinated to vinyl acetate. The low-valent cobalt most likely reacts with aryl halide by oxidative addition to form an "arylcobalt" species. This species could undergo a substitution reaction with the carbon attached to the acetate group after ligand exchange. (Scheme 2). The electronically preferred direction of addition appears to favour a transfer of the aryl group onto the carbon attached to the ester group. This suggests the involvement of the a six centers transition state [**C**] in which the aryl group is well-positioned to be added on the most substituted carbon atom of the double bond. With vinyl ethers instead of vinyl acetates, no reaction was occurred. In this last case, the formation of the six centers transition state is not possible, this confirms our hypothesis. Once styrene derivative released, cobalt is reduced again by the excess of Mn to regenerate $Co^{I or 0}$ catalyst. Electrochemical studies are still in progress in order to establish more soundly the mechanism of this chemical reaction and to identify the "arylcobalt" species.



Scheme 2. Mechanism proposal for the vinylation of aryl halides with vinyl acetates.

Conclusions

In conclusion, we have developed a Co-catalyzed chemical process devoted to the preparation of aryl-vinyl compounds from various aryl or heteroaryl halides and vinyl acetates. This catalytic process using $CoBr_2$(2,2′-bipyridine) appears extremely suitable as catalyst for a broad range of aryl chlorides and bromides bearing an electron-donating or withdrawing group. To the best of our knowledge, this is the first palladium-free direct preparation of α-substituted styrene derivatives with satisfactorily good yields. Moreover, this very versatile process compares favourably with the procedures using palladium catalysis since aryl bromides and chlorides do not bring difficulties in the cross-coupling. Work is now in progress to elucidate the mechanism of this reaction.

Experimental Section

GC analysis was carried out using a gas chromatograph Varian 3300 provided with a 25-m CPSIL5CB capillary column. Mass spectra were recorded with a GCQ Thermoelectron spectrometer coupled to a gas chromatograph Varian (25-m CPSIL5CB/MS capillary column). Column chromatography was performed on silica gel 60, 70-230 mesh with pentane/ether as eluent. ^{1}H, and ^{13}C spectra were recorded in $CDCl_3$ at 200 and 400 MHz. All solvents and reagents were purchased and used without further purification. No inert atmosphere was required.

1. Typical Procedure for Vinylation of Aryl Halides: To a solution of DMF (15 mL) and pyridine (2 mL) were successively added $CoBr_2$ (0.025 mmol, 55 mg), 2,2′-bipyridine (0.025 mmol, 39 mg) and manganese powder (50 mmol, 2.75 g). Aryl halide (5 mmol) and vinyl acetate (10 mmol) were then introduced into the solution. The medium was activated by traces of trifluoroacetic acid (100 µL) and stirred at 50 °C until aryl halide was consumed. The amount of the corresponding coupling product was measured by GC by using an internal reference (dodecane, 200 µL). The reaction mixture was poured into a solution of 2 N HCl (40 mL) and extracted with diethyl ether (3 × 40 mL). The organic layer was washed with a saturated solution of NaCl (20 mL) and dried with $MgSO_4$. Evaporation of diethyl ether and purification by column chromatography on silica gel (pentane/diethyl ether) afforded the styrene derivatives that were characterized by NMR (^{1}H, ^{13}C) and mass spectrometry.

2. Typical Vinylation Procedure for Cyano-, Aminoaryl Halides and Pyridyl Halides (Compounds 6, 7, 8, 13, 22, 23): The procedure for vinylation of cyano-, aminoaryl halides and halopyridines was the same as for the other aryl halides except for the standard work-up procedure. The reaction mixture was filtered through Celite, poured into a saturated solution of NH_4Cl (40 mL) and extracted with diethyl ether (3 × 40 mL). The organic layer was washed with saturated solution of NaCl (20 mL) and dried over $MgSO_4$. Evaporation of diethyl ether and purification by column chromatography on silica gel (pentane/diethyl ether) afforded the styrene derivatives that were characterized by NMR (^{1}H, ^{13}C) and mass spectrometry.

3. CAS Registry Numbers (Provided by the Authors): methyl 4-isopropenylbenzoate (**1**), 26581-23-7; methyl 2-isopropenylbenzoate (**2**), 62291-44-5; 1-(4-isopropenylphenyl)ethanone (**4**), 5359-04-6; 4-isopropenylbenzonitrile (**5**), 19956-03-7; 2-isopropenylbenzonitrile (**6**), 23877-63-6; 3-isopropenylbenzonitrile (**7**), 53097-35-1; 1-isopropenyl-4-trifluoromethylbenzene (**8**), 55186-75-9; 4-isopropenyl-1-methoxybenzene (**9**), 1712-69-2; 2-isopropenyl-1-methoxybenzene (**10**), 10278-02-1; 3-isopropenyl-1-methoxybenzene (**11**), 25108-57-0; 4-isopropenylphenyl acetate(**12**), 2759-56-0; 4-isopropenyldimethylaniline (**13**), 25108-56-9; ethyl 2-isopropenylbenzoate (**14**), 143769-34-0; ethyl 3-isopropenylbenzoate (**15**), 105640-23-1; methyl 4-ethenylbenzoate (**16**), 1076-96-6; methyl 4-(cyclopent-1-enyl)benzoate (**17**), 579472-58-5; 4-ethenylbenzonitrile (**18**), 3435-51-6; 4-(cyclopent-1-enyl)benzonitrile (**19**), 19936-20-0; 4-methoxystyrene (**20**), 637-69-4; 4-(cyclopent-1-enyl)-1-methoxybenzene (**21**), 709-12-6; 3-isopropenylpyridine (**22**), 15825-89-5, 4-isopropenylpyridine (**23**), 17755-30-5.

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[15] Unpublished results.

[16] With *p*-iodoanisole and ethyl *p*-iodobenzoate, we observed respectively 41% (GC yield) and only few traces of the corresponding coupling products. This work was not optimized because aryl bromides and chlorides were best candidates for this cross-coupling reaction and it was more interesting to develop a process using less expensive starting materials.

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