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Grignard Cross-Coupling Amenable to Large Scale Production of α-Fluorostyryl and α-Fluorovinylthiophenes

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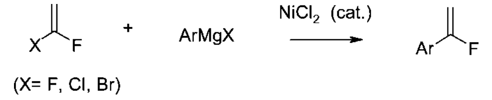

An efficient nickel-catalyzed Kumada-Corriu cross coupling enabled the introduction of an α-fluorovinyl functionality with excellent conversion and specificity.

The fluorovinyl group constitutes a useful synthetic functionality that has been introduced into several types of compounds to elicit improved pharmaceutical qualities. Most notable is the use of a fluorovinyl group as an amide bond isostere.[1] More recently 1-ary1−1-fluorovinyl compounds bearing an unsubstituted terminal 1-fluorovinyl group have been sited as mechanism-based enzyme inhibitors,[2] and as key functionality in synthetase inhibitors being developed as topical antibacterial agents.[3] Two general C−C bond-forming strategies for the assembly of α-fluorostyryls have been reported. These may be generally classified as a type *i* process in which a transition metal mediated cross coupling is carried out between a metallovinyl species and an aryl halide. This strategy has been described for the Pd-catalyzed cross-couplings of fluorovinylzinc reagents,[4] fluorovinylstannanes,[5] vinylzirconocenes,[6] and most recently with vinylsilanes.[7] A reversal of the coupling partners that employs a metallo-species (e.g., aryl, alkyl, alkenyl) to cross-couple with a fluorovinylhalide is referred to as a type *ii* process. This strategy has been described for the Pd-catalyzed cross-couplings with organoboranes or organostannanes.[8] (Figure 1). This approach has broadened the scope of the original vinyl to aryl C−C bond formation to include vinyl to vinyl and vinyl to alkyl bonds but has only been described in the case of a *β*-fluorosubstituted styrene substrate. Another type *ii* process via an atypical Heck Pd-catalyzed coupling has been described for the arylation of iodobenzene[9] or 5-iodotosylindole[10] with di or trifluoroethylene. In both cases moderate to high yields were achieved but reaction conditions required high temperature and developed very high pressure that required special apparatus and thus pose extra challenges for industrialization.

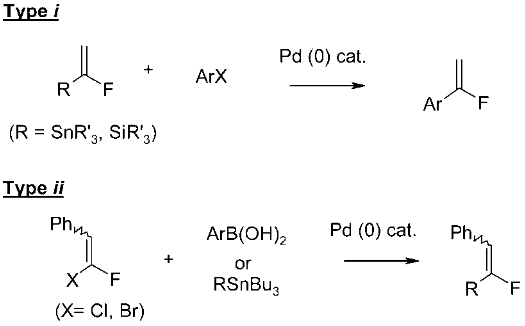

FIGURE 1. Example of type *i* and type *ii* coupling reactions.

In both of the type *i* and type *ii* approaches, the metallo species is prepared as a separate entity and thus bears the burden of extra manufacturing time and/or costs. In general boron, tin, zirconium or silicon containing reagents are less common and as a consequence are higher cost than a similar alkaline earth containing reagent (e.g., Grignard). The Grignard reagent is an extremely important reagent in the formation of C−C bonds and has been employed in a large variety of nucleophilic substitution reactions.[11] In 1972 Kumada,[12] Corriu,[13] and coworkers described an important C−C bond forming Grignard cross-coupling that has been used in a wide range of industrial fields since these early disclosures of this powerful method. Recently, Banno et al.[14] have described a type *ii* Grignard cross-coupling process for the industrial scale production of p-chlorostyrene. Described herein is a type *ii* nickel-catalyzed coupling between an aryl Grignard species and a α-fluoro,α-haloethylene (Figure 2) that expands the utility of this method substantially. The method has been studied for its generality and specificity with regard to sensitive functional groups in

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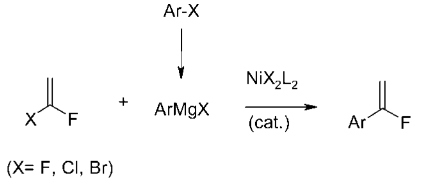


FIGURE 2. Example of Grignard type *ii* coupling reaction.

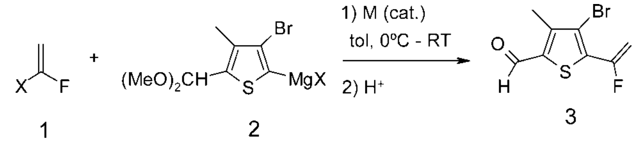
producing highly substituted phenyl or thiophene α-fluorovinyl derivatives. In one particular substrate, a highly functionalized thiophene, this method was employed at multikilo scale. To our knowledge, a Grignard type method for the synthesis of α-fluorostyrenes or α-fluorovinylthiophenes has not been disclosed and would serve as an important new option for the introduction of this key functional group.

The goals of the study were several, identify process conditions that would (a) be applicable to demanding substrates with sensitive functionality (b) short reaction times, (c) labor efficient, (d) high yield, (e) low energy demand, and (f) avoid special apparatus (e.g., high temperatures and pressures). A variety of reaction parameters including reactant types were studied in the development of this methodology. The α-fluoro−α-haloethylene substrate and the transition-metal catalyst had a profound effect on reaction outcome. Other parameters such as solvent and temperature played a lesser role but were also studied.

Mild temperature conditions of 0−5 °C were found optimal for the efficient formation of the aryl Grignard species and the subsequent cross-coupling reaction. In the case when α,α-difuoroethylene was utilized, the coupling reaction was started at −78 °C and slowly raised to ambient. Elevated temperatures or pressures were not studied as they were not required for good conversion and were anticipated to lead to side reactions or reaction/degradation of the desired product. Care was taken in the generation of aryl Grignard species to avoid moisture and oxygen and generally required 2−3 h for complete formation. Standard 1 or 2 M THF solutions of isopropyl or ethylmagnesium chloride were utilized to generate the aryl Grignard species. The Grignard species is very stable in THF but did not promote high yield in the subsequent cross-coupling step. Nonpolar cosolvents, in particular toluene, gave reliable high yields. The two-step one pot transformation was found to proceed to completion in generally 6−8 h.

The commercial availability of α-fluoro, chloro, and bromo α-fluoroethylenes, **1**, allowed the facile study of halogen effect on reaction outcome. In our case, the highly substituted thiophene acetal **2** was utilized to investigate the halogen effect on coupling outcome. Both α-fluoro and α-chloro α-fluoroethylene were reactive, but gave higher amounts of proton quenched substrate, **4**, in comparison to α-bromo−α-fluoroethylene. Overall the coupling reaction was found to proceed best in the order Br > Cl > F (Table 1).

TABLE 1. Halogen and Catalyst Study



entry	α-fluoro, α-X-ethylene X	catalyst-M	yield (%) **3**
1	F	NiCl$_2$	15−20
2	Cl	NiCl$_2$	30−60
3	Br	NiCl$_2$(dppp)	80−90
4	Br	NiCl$_2$	80−90
5	Br	Ni(acac)$_2$	80−90
6	Br	Ni(COD)$_2$	30−50
7	Br	Ni on C	80−90
8	Br	Pd(dba)$_2$	0
9	Br	Co(OAc)$_2$	<20
10	Br	FeCl$_2$	25−30

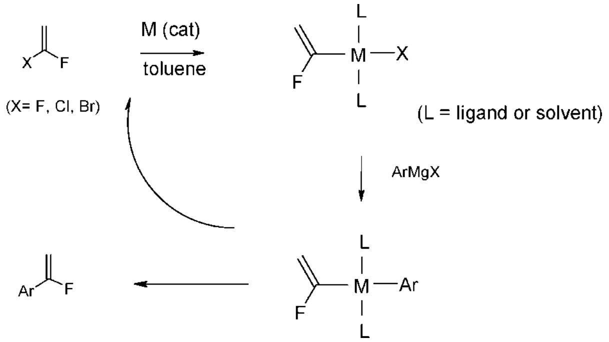


FIGURE 3. Proposed mechanism of coupling reaction.

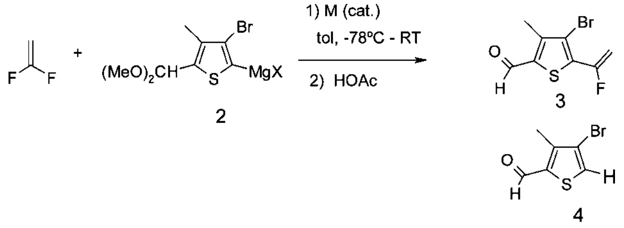
Early work in our laboratories had revealed that Ni(II) carbene ligand catalysts gave equivalent conversion to Ni(II) catalyst without any ligand (e.g., ligand-less) when cross coupling with α-bromo−α-fluoroethylene. A study was conducted of representative d^8 metals of Groups 8−10 to search for an optimal catalyst species (Table 1). In this survey it was found that a Ni(II) species, which gets reduced in situ to the catalytically active Ni(0) oxidation state by aryl Grignard, was superior to using a preformed Ni(0) species, such as the capricious Ni(COD)$_2$. The use of a solid supported nickel (II) catalyst on carbon was also studied; however, the results were found comparable to that of unsupported nickel (II) chloride.

Interestingly, the Pd catalyst studied was completely nonreactive under the conditions employed. Other Pd(0) and Pd(II) species were not tried. One possible explanation is that sterically crowded aryl Grignard species, such as those studied in this work, are less reactive and require a reasonably electrophilic metal species such as a nickel (Figure 3.). Palladium (II) fluorovinyl intermediates have previously been proposed as moderately active electrophiles.[8] Single examples from the Group 9, cobalt acetate, and Group 10 iron chloride were studied. Fe(II) chloride did provide reasonable catalytic activity but significantly lower than nickel species. The overall reactivity of the metal catalyst was found to be Ni > Co = Fe > Pd. The amount of catalyst was also studied and herein it was determined that ≥ 0.005 equiv of NiCl$_2$ provided maximal conversion.

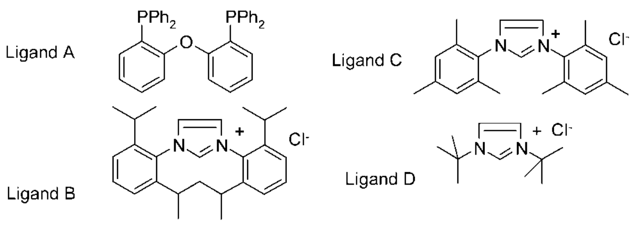
A study was also conducted with α,α-difuoroethylene to determine the feasibility of utilizing this low cost feedstock gas. Lower reaction temperatures were utilized to avoid the generation of high pressures while working with this gas. This reaction partner differed in reactivity with that of its higher halogen congeners. In particular Ni(II) catalysts with phosphine ligands were found to provide somewhat improved yield over ligand-less Ni(II). The yield was relatively good, 60%, but the amount of uncoupled product, approximately 30% was significant. In the case of this particular product it was also difficult to separate from the desired product. These results reflect that this low cost fluorovinyl synthon is suitably reactive and should be evaluated as a raw material on a case by case basis.

The generality of the cross-coupling reaction with representative examples of aryl iodides, aryl bromides, and bromothiophenes was studied using the optimized reaction condi-

TABLE 2. Catalyst Study with α,α-Difuoroethylene



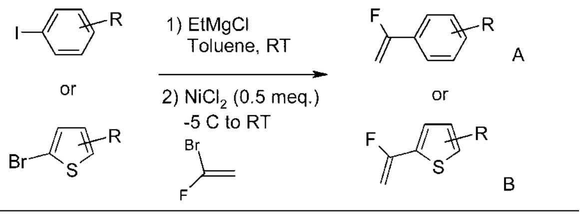
entry	catalyst-M	ligand	ratio 3:4
1	NiCl$_2$ or Ni(acac)$_2$	no	0
2	Ni(acac)$_2$	A	0
3	Ni(acac)$_2$	B	64:36
4	Ni(acac)$_2$	C	14:86
5	Ni(acac)$_2$	D	15:85



tions. Representative substituents of both electron withdrawing and electron donating nature were investigated. In general, the reaction afforded higher yield with electron withdrawing groups versus electron donating groups. Notable in the group is that a highly substituted substrate was selectively converted in high yield to the desired fluorostyryl product 6. It is worth noting that the manner in which the aryl Grignard is generated must be taken into account with highly functionalized substrates. Specifically, transmetalation of aryl lithium species generated by the reaction of alkyl lithium with a substituted aryl iodide or bromide precursor gave much lower yields compared to transmetalation via alkyl Grignard.

In summary, we have developed an expedient synthesis of α-fluorostyryls and α-fluorothiophenes via a Kumada-Corriu type Ni-catalyzed cross coupling reaction. The process accomplished key constraints in allowing for sensitive functionality to be tolerated, low cost equipment and starting materials to be used and overall high yields achieved. This process may hold applicability as technique in the synthesis of other fluorovinyl-substituted heterocycles of biological interest or in the industrial scale manufacture of fluorostyrl monomers for fine chemical or polymer chemistry uses.

TABLE 3. Coupling Reaction with Various Iodo and Bromo Substrates



compd	R	yield (%) A	yield (%) B
4	4-CO$_2$Me	70	na
5	4-OMe	52	na
6	2-OEt, 3-CH(OMe)$_2$, 5-Br	67	na
7	2,3-diBr	na	80

Experimental Section

4-Bromo-5-(1-fluoroethenyl)-3-methylthiophene-2-carboxaldehyde 3. To a 3 L, three necked, round-bottom flask equipped with a mechanical stirrer, nitrogen inlet, thermometer and addition funnel was added 75.0 g (227.25 mmol) of 2,3-dibromo-4-methyl-5-dimethoxymethyl thiophene followed by 600 mL of anhydrous toluene under a nitrogen atmosphere. The clear, colorless solution was cooled to 5 °C with an ice-bath and 123.0 mL (258.3 mmol, 1.15 equiv, 2.1 M solution, titrated) of ethylmagnesium chloride in tetrahydrofuran added while maintaining the reaction temperature below 11 °C. (addition took approximately 30 min). After complete addition, the reaction was stirred in the ice-bath for 2.5 h. After 2 h, an aliquot was drawn, quenched with methanol and analyzed by HPLC. No starting dibromothiophene adduct was present. Nickel chloride (0.15 g, 1.16 mmol, 0.005 equiv) was then added followed by 115.0 mL (274.85 mmol, 1.21 equiv of a 2.39 M solution in toluene) of 1-bromo-1-fluoroethylene.*(the solution was prepared by bubbling 1-bromo-1-fluoroethylene in a flask cooled in an ice bath containing a known amount of toluene. The flask was weighed before and after addition to determine quantity added and then a molarity calculated)* The mixture was stirred in the ice-bath while monitoring by HPLC. After 3 h, HPLC analysis of an aliquot drawn and quenched with methanol indicated less than 1% of the monobromo thiophene adduct resulting from halogen−metal exchange.

The reaction was quenched with the addition of 200 mL (400.0 mmol) of 2 M hydrochloric acid. The mixture was stirred at room temperature while monitoring for completion of hydrolysis of the acetal by HPLC. After less than 10% acetal remained, the reaction was diluted with 200 mL of water and the organic phase separated. The organic phase was washed with water (200 mL) and the combined aqueous layers extracted with 250 mL of ethyl acetate. The combined organic layers were concentrated under reduced pressure to afford 56.5 g (99.8%) of crude FVT as a yellow-orange solid.

Recrystallization of 4-Bromo-5-(1-fluoroethenyl)-3-methylthiophene-2-carboxaldehyde 3 [FVT] with 30% Charcoal. To a 500 mL round-bottom flask equipped with heating mantle, nitrogen inlet, magnetic stirrer, condenser and thermometer was added the crude FVT (28.0 g) followed by 275 mL of heptane and 50 mL of toluene. The mixture was heated to 80 °C. To the clear amber color solution was added 9.0 g of decolorizing charcoal and stirring continued at 80 °C for 30 min. The mixture was filtered through a pad of celite 503 (previously washed with heptane) and the filter cake rinsed with 50 mL of hot heptane (80 °C). The filtrate (clear yellow color) was allowed to stand at room temperature and then placed in an ice-bath for 15 min. The solids were filtered, washed with 150 mL of heptane, and dried under vacuum to afford 18.95 g (67.7%) of product as a pale-yellow solid.

Acknowledgment. This work is dedicated to the memory of A. I. Meyers who touched so many people with his love of life and chemistry. We thank Professor Lou Hegedus for helpful discussions during the course of this work.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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