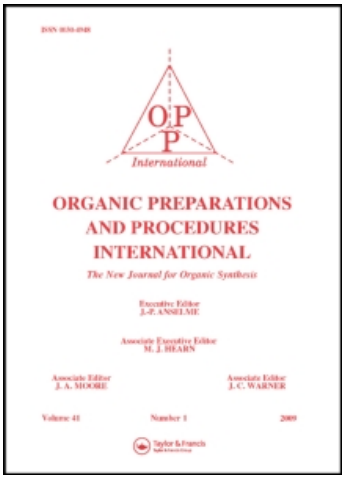


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# THE NICKEL(I) CATALYZED COUPLING OF A DIARYLZINC WITH AN ARYL CHLORIDE IN THE SYNTHESIS OF XENALIPIN

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# THE NICKEL(I) CATALYZED COUPLING OF A DIARYLZINC WITH AN ARYL CHLORIDE IN THE SYNTHESIS OF XENALIPIN

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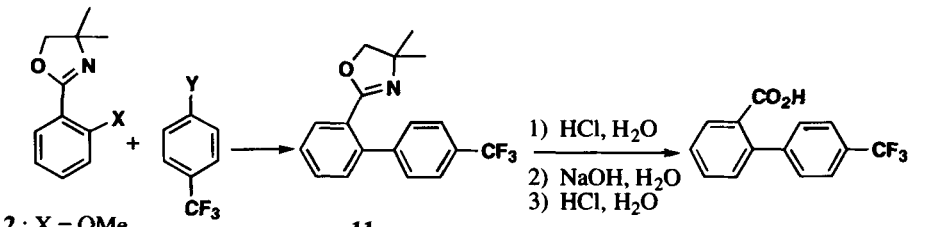
Epidemiological studies have strongly implicated elevated total plasma cholesterol as a major risk factor for coronary heart disease[1] and have shown that elevated plasma triglycerides can be positively correlated with the risk of the disease.[2] Xenalipin **1** (4'-trifluoromethyl-2-biphenylcarboxylic acid) has been shown to cause significant reductions in serum cholesterol and triglycerides in two animal species, and the results obtained suggest that xenalipin has a profile of activity which would be beneficial in therapy for hyperlipidemia.[3] To prepare the large quantities of xenalipin that would be needed to support clinical trials and to reduce the potential cost to the consumer for chronic therapy, we desired an efficient and inexpensive synthesis of **1**. The first published method for the synthesis of **1** was described by Bell, Burke, Hodgson, and Shumaker.[4] This method relied upon the work of Meyers[5] *et al* and involved the displacement of the 2-methoxy group of **2** by the Grignard **8** (Scheme 1). This method, however, was not amenable to large-scale synthesis, the yield of the biphenyloxazoline **11** being only 33% after vacuum distillation. Also this route, and any route which used a metallobenzotrifluoride, was considered hazardous based upon published reports of explosions during the formation of the organometallic intermediate.[6]




**2** : X = OMe
**3** : X = H
**4** : X = Li
**5** : X = ZnCl
**6** : X = 0.5 Zn

**7** : Y = Br
**8** : Y = MgBr
**9** : Y = I
**10** : Y = Cl

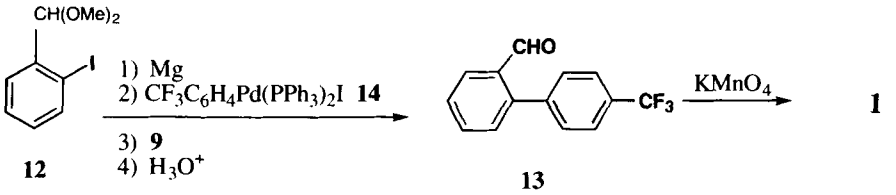
**11**

**1**

**Scheme 1**

To circumvent this possibility, our efforts focused upon forming the organometallic intermediate from the benzoic acid half of the biphenyl and coupling this with a 4-halobenzotrifluoride. Our

first successful synthesis (Scheme 2)[7] coupled the Grignard prepared from the dimethylacetal of 2-iodobenzaldehyde **12** with **9** in the presence of the catalyst **14**, iodo(4-trifluoromethylphenyl)*bis*(triphenylphosphine) palladium(II) (prepared from **9** and tetrakis(triphenylphosphine)palladium (0).[8] This resulted in a 96.4% yield of the aldehyde **13** after hydrolysis and chromatography. Oxidation to the acid **1** was accomplished in 85% yield. Although safer and higher yielding than the previous synthesis, this route was still not suitable for scale-up due to the difficulty in preparing and controlling large-scale Grignard reactions and the necessity for chromatographic purification of **13**, which contained substantial quantities of 2,2'-biphenyldialdehyde and 4,4'-bis(trifluoromethyl)biphenyl.

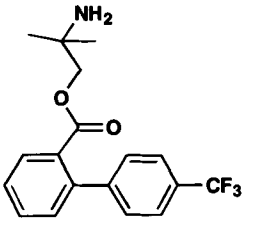



**Scheme 2**

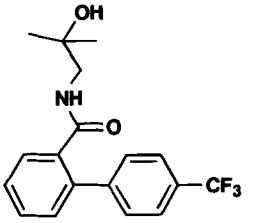
Efforts were next directed to the *ortho*-lithiation of the phenyloxazoline **3** followed by transmetallation to an arylzinc compound, a species which has been shown to give good yields in coupling reactions with either palladium or nickel catalysts (Scheme 1).[9] The lithiation and transmetallation could be successfully performed at a temperature of -25 to -35°. Addition of one molar equivalent of anhydrous zinc chloride gave the arylzinc compound **5**. Addition of catalyst **14** (3 mole %) and **9** resulted in a 79.4% yield of **1** after hydrolysis.[10] Use of one-half an equivalent of zinc chloride to give the stable diarylzinc species **6** also resulted in good yields of **1** (84%).

Our next concern was to replace the palladium with a less expensive nickel catalyst. Grignard reagents have been reported to couple with aryl halides in the presence of Ni(II) catalysts.[11,12] Both Grignard and arylzinc reagents couple with aryl iodides and bromides in the presence of Ni(0) catalysts.[9] Based upon the works of Kochi[13] and Schwartz,[14] however, it appeared that Ni(I) might actually be the reactive catalytic species. We thus decided to investigate the preparation and use of Ni(I) in our coupling reaction. The catalyst was prepared by the reduction of Ni(II) with one equivalent of diisobutylaluminum hydride (DIBAH). In our first attempt, a suspension of an equimolar amount of nickel(II) acetylacetonate and DIBAH was prepared and kept at 0° for 5.5 hrs and then added to a solution of **6**, followed by a solution of **9**. No reaction occurred after stirring overnight at ambient temperature. However, when $PPh_3$ (2 equivalents based on nickel) was added, the reaction proceeded immediately to completion, showing that $PPh_3$ was needed to promote the coupling. After hydrolysis of the resulting biphenyloxazoline **11**, a 66% yield of **1** was obtained. In subsequent reactions, we used a 50% excess of **3** to ensure conversion of the expensive benzotrifluoride **9** to **11**. The catalyst (7 mole %) was prepared in a separate pot using a 1:2:1 ratio of $Ni(acac)_2$:$PPh_3$:DIBAH and aged 1-3 hrs at 0° before adding to **6** and then following with a solution of **9**. The coupling reaction was complete within 1 hr at temperatures between 0° and ambient, and was conveniently monitored

by $^1$H NMR spectroscopy of a sample by the ratio of the oxazoline methylene protons of **11** to **3**. Rather than purify the resulting oily mixture of **11** and unreacted **3**, we found it best to hydrolyze the mixture to the crystalline carboxylic acids and then to purify by recrystallization. Although simple acid hydrolysis easily opened the oxazoline ring of **11**, a further two-day reflux never completely converted the resulting amino ester **15** to **1**. We found the best conditions for hydrolysis to be a two-step, one-pot sequence. Treatment with acid for 1-4 hrs gave predominantly the amino ester **15** and some **1**. Replacing the acid with strong base gave mostly **1** and some of the hydroxy amide **16**. Conversion of **16** to **1** required an overnight reflux.




**15**




**16**



Having found a successful synthesis using the inexpensive phenyoxazoline **3** (derived from benzoyl chloride) and a cheap catalyst, we turned our attention to the 4-halobenzotrifluorides. Substitution of the less expensive bromo compound **7** also worked well in the coupling reaction, but required about 3.5 hrs at ambient temperature to reach completion. Workup and hydrolysis gave a 76.6% yield of **1**. We also found in this reaction that the use of 4 equivalents of $PPh_3$ in the catalyst preparation slowed the coupling reaction rate by about one-half but still gave an acceptable yield of **1** (82%). The reaction also worked with one equivalent of $PPh_3$ but was slower and gave slightly lower yields of **1**.

Unfortunately, at the time of this work, we could find no bulk suppliers of either **9** (*ca* \$8/g catalog price) or **7** (*ca* \$1-2/g). By contrast, 4-chlorobenzotrifluoride **10** was an agricultural intermediate and available in bulk quantities (\$16.50/kg). Although aryl chlorides are generally inactive in palladium-catalyzed coupling reactions, some precedent existed for the reaction using a nickel catalyst. Kumada[12] *et al* have found that $Ni(dppp)_2Cl_2$ was especially useful for the coupling of chlorobenzene with various Grignard reagents, although they reported that $Ni(acac)_2$ alone was inactive as a catalyst. Only one report existed of a coupling reaction using an arylzinc reagent. Phenylzinc, used in large excess, had been found to couple with the reactive substrate 1,8-dichloroanthracene using $Ni(acac)_2$.[15] We thus chose to investigate the use of our pre-reduced nickel catalyst with **10**. When **10** was first reacted with **6** in the presence of the pre-reduced catalyst mixture at 0°, very little reaction was observed. However, stirring overnight at ambient temperature gave complete conversion to **11**. We also found that the $Ni(acac)_2$ could be reduced with two molar equivalents of $NaBH_4$. This reduction gave off 0.5 equivalent of $H_2$ within the first 5 minutes, corresponding to a bulk reduction of Ni(II) to Ni(I), a result consistent with Schwartz's[14] observation of the evolution of 0.5 equivalent of

isobutane when DIBAH was used as the reducing agent. As judged by $H_2$ evolution, full reduction to Ni(0) required an additional 90 minutes at ambient temperature. The $NaBH_4$-reduced catalyst, in the presence of 2 equivalents of $PPh_3$, was also effective in the coupling of **6** with **10**. Ni(acac) + 2 $PPh_3$ without pre-reduction was ineffective as a catalyst, showing that the arylzinc **6** was incapable of reducing Ni(II) to a catalytically active oxidation state. We also found that the diarylzinc **6** was stable at higher temperatures and that this reaction could be driven to completion by refluxing for two hrs. Hydrolysis and recrystallization gave overall yields of 64-72% of **1** from **10**. We were also able to reduce the excess of **3** from 50 % to 10% with no reduction in yield. This reaction has been successfully used at the 100-gal scale (350 moles) in our pilot plant, giving us a safe, efficient, and inexpensive synthesis of xenalipin.

## EXPERIMENTAL SECTION

4,4-Dimethyl-2-phenyl-2-oxzaline, 4-iodobenzotrifluoride, 4-bromobenzotrifluoride, and triphenylphosphine were purchased from Aldrich. 4-Chlorobenzotrifluoride was purchased from Marshallton. 2.6 M *n*-Butyllithium in hexane was purchased from Lithium Corporation. Nickel bis(acetylacetonate) was purchased from Strem Chemicals and anhydrous zinc chloride from Alfa. Diisobutylaluminum hydride was purchased from Ethyl Corporation as a 1.21 M solution in hexane. All other reagents and solvents were of reagent grade. Tetrahydrofuran was dried over 4A molecular sieves. NMR proton spectra were obtained on a Perkin-Elmer R-24B (60MHz) spectrometer. HPLC conditions: System A, C-18 5μ column using 7:3 $CH_3CN$:$H_2O$, 1 mL/min flow rate, 260 nm uv detector wavelength; System B, C-18 10μ column using 45:55:0.05 $CH_3CN$:$H_2O$:HOAc, 2 mL/min flow rate, 237 nm uv detector wavelength. TLC (System 1) was performed on C-18 plates using 7:3 $CH_3CN$:$H_2O$ or (System 2) on silica using diethyl ether.



**Preparation of the Nickel Catalyst**.- To a stirred suspension of anhydrous nickel bis(acetylacetonate) (0.162 mol) and triphenylphosphine (0.324 mol) in dry THF (420 mL) at -15° was added DIBAH (134 mL, 0.162 mol) at a rate to keep the temperature ≤0°. The resulting black suspension was kept at 0° under $N_2$ for 1-3 hrs.

**4,4-Dimethyl-2-(4'-trifluoromethyl-2-biphenylyl)-2-oxazoline (11)**. To a solution of 4,4-dimethyl-2-phenyl-2-oxazoline (**3**, 4.97 mol) in dry THF (1.57 L) under nitrogen at -35° was added dropwise *n*-butyllithium at a rate to keep the temperature ≤-25°. More THF (150 mL) was added to facilitate stirring of the resulting yellow precipitate. After 2 hrs at -30°, solid zinc chloride (2.55 mol) was added at a rate to keep the temperature <-27°. The temperature was then allowed to rise to 7° during a 1.5-2 hrs period (*Note*: If the temperature was allowed to rise rapidly much past 10°, butane evolution was vigorous and can cause a violent boil). The mixture was then cooled back to 0°, the nickel catalyst mixture was poured in followed by the addition of 4-chlorobenzotrifluoride (3.24 mol). The mixture was allowed to warm to ambient temperature with stirring overnight. The reaction may be monitored by TLC System 1 (**3**, $R_f$ 0.44; **11**, $R_f$ 0.28) or HPLC System A (**3**, RT 5.1 min; **11**, RT 10.5 min). Alternatively, a sample may be quenched with 2*N* acetic acid, extracted with ether, dried and evaporated for NMR in $CDCl_3$. For the reaction described, completion was reached when the ratio of the

methylene protons of **11** (δ 3.7) and 3 (δ 4.0) reaches 2. Upon completion, the solvent was evaporated, toluene (1 L) was added, the mixture chilled to 10°, and a cold solution of 2.5 *N* acetic acid was added at a rate to keep the temperature <20°. The two phases were separated and the organic was washed with 2.5 *N* acetic acid (2 x 500 mL). The combined aqueous extracts were washed with toluene (2 x 300 mL). The combined toluene extracts were washed with water (2 x 500 mL), dried over $MgSO_4$, and evaporated to leave crude **11** as an orange oil. A sample chromatographed on the Waters Prep 500 using 3:2 $CH_3CN$:$H_2O$ gave a pure sample of **11** as a colorless oil. $^1H$ NMR ($CDCl_3$): δ 1.22 (s, 6 H, Me), 3.71 (s, 2 H, $CH_2$), 7.1-7.8 (m, 8 H, ArH).

**4'-Trifluoromethyl-2-biphenylcarboxylic Acid (1).**- The crude **11** obtained above was refluxed for 3 hrs in 6 *N* HCl (1 L). The solvent was evaporated under reduced pressure until a thick yellow syrup was obtained. Methanol (1 L) and 50% sodium hydroxide (1 kg) were added and the mixture was refluxed for 12 hrs. The hydrolysis may be monitored by TLC System 2 (**1**, $R_f$ 0.72; **15**, $R_f$ 0.06; **16**, $R_f$ 0.45; benzoic acid, $R_f$ 0.61) or HPLC System B (**1**, RT 15.3 min; **15**, RT 10.3 min; **16**, RT 12.6 min; benzoic acid, RT 3.2 min). The solvent was evaporated and water (1 L) added to the pasty mass. The mixture was heated to 90° to give a solution. Concentrated HCl (1 L) was added with cooling to keep the temperature ≤80°. The resulting yellow precipitate was cooled to 10°, collected and washed with water. The solid was then dissolved in 9% NaOH (1.7 kg) by heating to 90°. The hot aqueous base was extracted with toluene (4 x 500 mL), treated with charcoal, filtered, and acidified with concentrated HCl (400 mL). The precipitate was collected, washed with water (4 x 700 mL), and dried in a vacuum oven at 65° overnight. The yield was 103% of a product containing about 79% **1** and 13% benzoic acid by HPLC System B.

The crude **1** (50 g) obtained above was dissolved in refluxing toluene (100 mL) and the solution was filtered hot through a thin bed of Celite and then cooled to ambient temperature. The resulting white suspension was chilled, and the solid was collected, washed with cold toluene, and dried at 65° in a vacuum oven to afford 31.16 g (64.4% overall from **10**) of white solid, mp. 168-169, lit.[4] 167-169°. HPLC System B: **1**, 99.7%; benzoic acid, 0.3%. $^1H$ NMR ($CDCl_3$): δ 7.2-7.7 (m, 7 H, ArH), δ 8.0 (m, 1 H, H-3), δ 10.3 (broad s, 1 H, $CO_2H$).

*Anal.* Calcd. for $C_{13}H_9F_3O_2$: C, 63.16; H, 3.41. Found: C, 63.23; H, 3.45

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