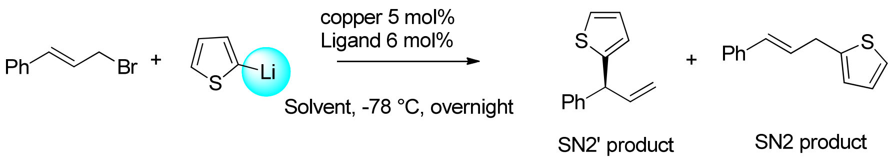
1. FINAL PUBLISHABLE SUMMARY REPORT

Catalytic asymmetric C-C bond formation with organo-lithium reagents

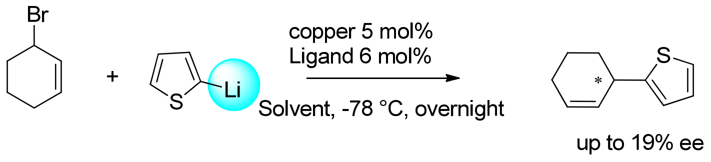
The aim of this project is the development of a catalytic asymmetric C-C bond formation using high reactive organolithium reagents. This methodology should solve the high reactivity of these kind of reagents to afford high selectivitiy in the C-C bond formation.

a) Catalytic asymmetric allylic substitution with heteroaryllithium reagents

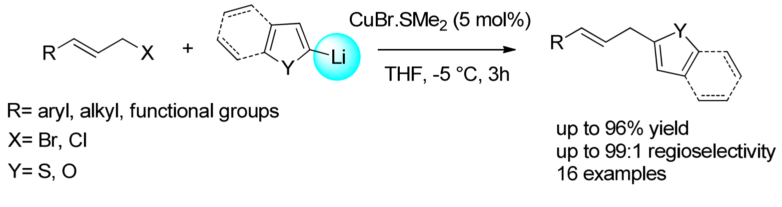
The chiral introduction of aryl lithium reagents was studied according to the research methodology described in the grant proposal. Initially, the addition of 2-thienyl lithium reagent was studied in the allylic substitution of cinnamyl bromide. An optimization study was carried out in order to investigate the reaction, and different chiral ligands, solvents, copper sources and temperatures were screened. Unfortunately, in all the cases the major product was the achiral SN2 product (ratio SN2':SN2 from 10:90 to 5:95).



In order to study more deeply the enantioselective allylic substitution, the researcher investigated the reaction between 2-thienyllithium and 3-bromocyclohex-1-ene, where the SN2 product is chiral. After a major optimization study with different chiral ligands (diphosphines, phosphoroamidates, carbenes), solvents, solvents, addition times, the highest enantiomeric excess was 19% ee (80% conversion).



In the view of the high conversion to the SN2 product, and considering that the allylic thiophenes represent an interesting compounds for organic synthesis or material science, we decided to optimize this reaction. The reaction conditions are very mild, using copper(I) bromide dimethyl sulfide (5 mol%) in THF at -5 C° and different allylic substrates and 2-heteroaryl lithium reagents were tested to obtain a broad scope of compounds.

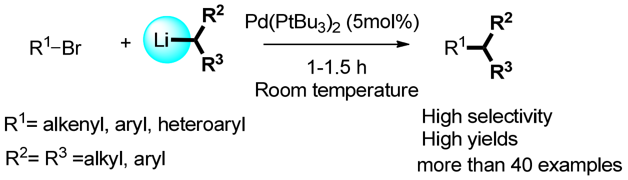


In conclusion, a copper catalyzed alkylation of 2-heteroaryl lithium reagents with allyl bromides highly regioselective have been developed.

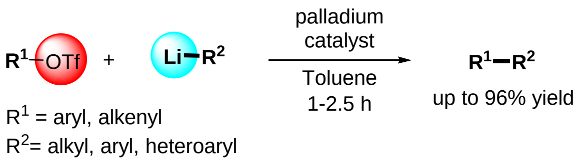
b) Palladium-catalysed direct cross-coupling of organolithium reagents.

The development of new methodologies for transition metal catalysed cross coupling reactions has attracted the attention of the chemistry community for the past 40 years. In this context, palladium mediated C-C bond formations, have played a crucial role, and methodologies involving palladium catalysis for cross-coupling have shown to be particularly effective. As a consequence Pd-catalysed cross-coupling has found widespread application in the industrial manufacturing of pharmaceuticals, fine chemicals and materials in the last decades. Meanwhile, organolithium reagents are cheap, readily available and commonly used reagents in chemical synthesis. However, due to their high reactivity, the use of these reagents has been hampered in the field of cross-coupling reactions. Recently, Feringa and coworkers develop a highly selective palladium cross-coupling of organolithium reagents with arylbromides (*Nature Chemistry*, **2013**, 5, 667-672). This breakthrough discovery offers exciting opportunities for a range of novel C-C bond forming reactions using organolithium reagents and several projects have been developed by the researcher Dr. Carlos Vila.

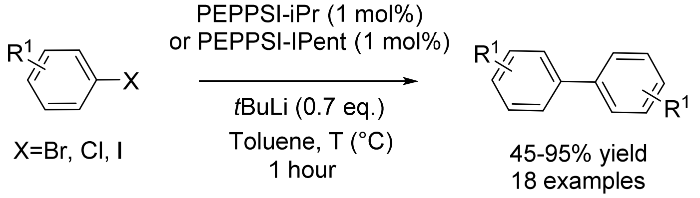
In particular, secondary organolithium reagents represent a formidable challenge owing to their even higher reactivity and basicity. Thus, we decided to study the Pd-catalysed cross-coupling of secondary alkyl lithium reagents with aryl and alkenyl bromides. The reaction proceeds at room temperature and in short times with high selectivity and very good yields using commercial $Pd(P^tBu_3)_2$ as a catalyst and toluene as a solvent. This new methodology shows the possibilities of using inexpensive and readily available secondary lithium reagents as complementary coupling partners.



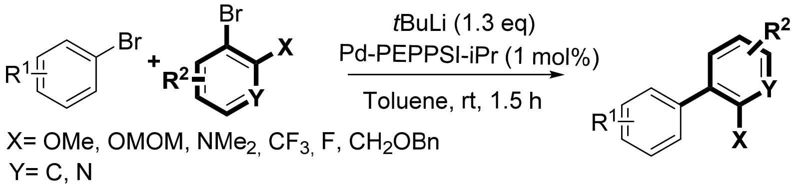
We also have developed a catalytic system for the direct palladium-catalysed cross coupling of aryl triflates with a range of alkyl and aryllithium reagents. This methodology is based on the use of commercially available catalytic system $Pd_2(dba)_3$/DavePhos. The transformation features readily available organolithium reagents and triflates in short reaction times (1-1.5 h), affording the corresponding alkylated or arylated products in moderate to high yields. Furthermore, this methodology has been applied for the coupling of alkenyl triflates and aryllithium reagents in a straightforward synthesis of olefins using a different commercial available catalytic system ($Pd_2(dba)_3$/SPhos). Although yields are generally high, even in the cases with modest yields the advantage of short reaction times and direct use of organolithium reagents it provides an available alternative to organic triflate based cross-coupling reactions.



The development of synthetic methodologies for the synthesis of symmetrical and unsymmetrical biaryls has been attracted great interest in chemistry over more than a century. Biaryls compounds are very important structures that have a widespread applications in many fields of chemistry. For example, the biaryl structural motif is present in many natural products and are common in pharmaceutical and agrochemical industry. Furthermore, biaryls, specially the chiral ones, played an important role as an efficient ligands in catalysis. Moreover, biaryls are very important in material science. Transition-metal-mediated reactions, among the innumerable methods for the construction of biaryls, constitute one of the leading strategies used. In this context, palladium-catalyzed cross-coupling of aryl metal reagents and aryl (pseudo)halides to form biaryl compounds is one of the most effective methods, and had played a fundamental role during the past 40 years. We were interesting in the direct cross-coupling of aryl halides, would be a more straightforward method for the synthesis of symmetrical or unsymmetrical biaryls, by generating the organometallic *in situ*. One easy and fast method to generate *in situ* a organometallic from an aryl bromide is the formation of the corresponding aryllithium reagent *via* halogen-lithium exchange. First we have developed an efficient catalytic system for the synthesis of symmetric biaryls from aryl halides in the presence of tBuLi (0.7 equivalents) using only 1 mol% of PEPPSI-IPr or PEPPSI-IPent catalyst loading. The reaction takes place under mild conditions, in short reaction times, compared with the previous reported procedures. Moreover, this methodology allows for the synthesis of tetra-ortho-substituted symmetric biaryls with high yields in only 1h.



Also, we have demonstrated that the cross-coupling between two different aryl bromides in the presence of tBuLi is possible. The Pd-PEPPSI-IPr or Pd-PEPPSI-IPent complex were shown to be an efficient catalyst for the synthesis of unsymmetrical biaryls at room temperature. The reaction needs an ortho-substituted bromides, in order to have a preference for the lithium/halogen exchange, and obtain good selectivities toward the unsymmetrical biaryl. We can use several groups in *ortho* position to the bromide, such as -OMe, -OMOM, -NMe2, -CF3, -F, -CH2OBn or a benzofurane ring. In the other hand, as an electrophilic partners, a series of (hetero)aryl bromides with electron-donating or electron-withdrawing groups had been used. Remarkably, we also had shown that is possible the cross-coupling with 3-bromo-2-methoxypyridine. This methodology is a fast and straightforward protocol to access of unsymmetrical biaryls in mild conditions.



Dr. Carlos Vila have been part in other palladium-catalysed direct cross-coupling of organolithium reagents for the C-C bomd formation, such the coupling of hindered aryllithium reagents or alkenyllithium reagents. As well, with the cross-coupling of less reactive aryl chlorides with aryllithium reagents. Furthermore, the fellow have been part in a project for a catalytic asymmetric conjugate addition of Grignard reagents to chromones.

Project management and deviations from the original project.

Dr C. Vila started the research work with the optimization of the catalytic allylic substitution using 2-thienyllithium and cinnamyl bromide. In all the conditions studied, the major product was the achiral S_N2 product, obtaining a very small amount of the desired S_N2'product. All the optimization, in order to obtain the S_N2'product were unsuccessfully. However, a free ligand protocol catalyzed by copper was developed using 2-heteroaryl lithium reagents and allyl bromides. Obtaining a broad scope with very high selectivity and good yields, and high functional group tolerability.

After this achievement, the researcher and the coordinator, were interested in the study of palladium catalytic processes for the formation of C-C bond using the challenging organolithium reagents that represent a great challenge in organic synthesis. For this purpose, different organolithium reagents such alkyl (highly challenging secondary alkyl), (heteroaryl)aryl and alkenyl were used tested with aryl bromides, chlorides and triflates. Different project have been accomplished by the researcher Carlos Vila in this 2 years of fellowship.