# Chapter - 1

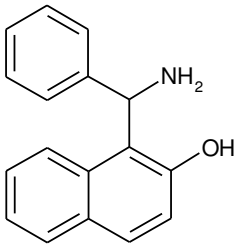
## Introduction: Synthesis and Applications of the Betti Base, Pd - catalyzed C - C bond formation via cross coupling reaction

# INTRODUCTION

## Part- I The Betti base: the awakening of a sleeping beauty

Senator Mario Betti (1875-1942) was a distinguished Italian chemist,[1,2] very active at the beginning of the 20th century. His main research interest in stereochemistry were directed towards the resolution of racemic compounds, the relationship between molecular constitution and optical rotatory power and asymmetric synthesis with the aid of chiral auxiliaries or in the presence of circularly polarized light. Prof. Noyori considered him to be the real pioneer of the asymmetric synthesis.[3] With respect to the other research topics, M. Betti is known for the so called Betti reaction[4-6] & for the resulting aminobenzyl naphthol **1** (**Figure 2**),[5-7] that was called the Betti Base.

**Figure 1**: Italian Senator Mario Betti




**1**

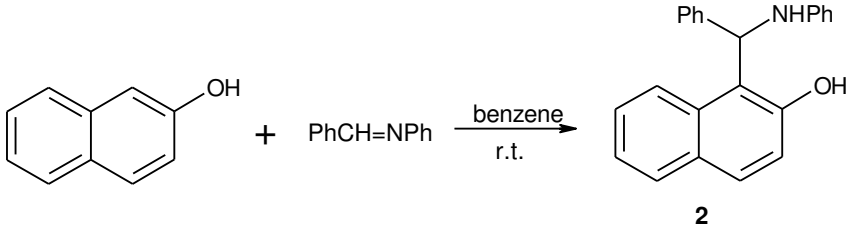
**Figure 2**: The Betti Base

### The Betti Reaction

This synthetic strategy originated between the end of the 19th & the beginning of the 20th century when research in several laboratories was performed on reactions between ammonia (or amines) formaldehyde and enolizable carbonyl compounds.[8] The first two components yield an imine that reacts with the carbonyl compound. These procedures are commonly classified as Mannich aminoalkylations, established by systemic work by other author, which began in 1912, subsequent to the Betti's research[5-7]. In 1990[5], Betti had hypothesized, and later proved that 2-naphthol should be a good carbon nucleophile towards the imine produced from benzaldehyde and aniline, as represented in **Scheme 1**.

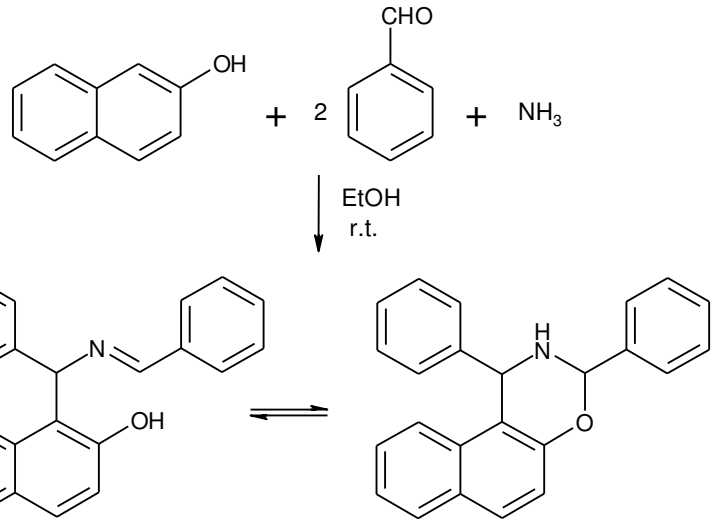
Eventually, Betti also reported[6] that the product **3** (**Scheme 2**) could be obtained from a three component condensation of 2-naphthol, an ethanolic solution of

ammonia and 2 equiv of benzaldehyde (91% yield). Actually, the product of the reaction is represented by the forms **3a** and **3b** in equilibrium.[9]




**2**

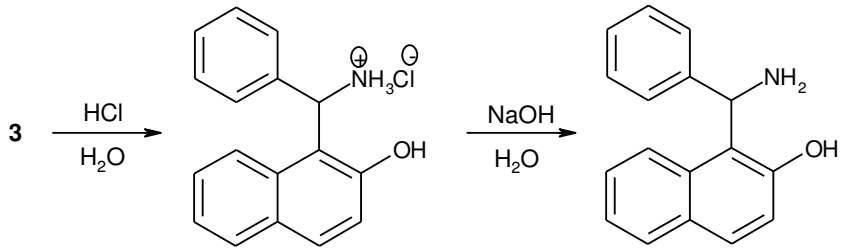
**Scheme 1:** Reaction between 2-naphthol and an imine




**3a** **3b**

**Scheme 2:** The Betti reaction

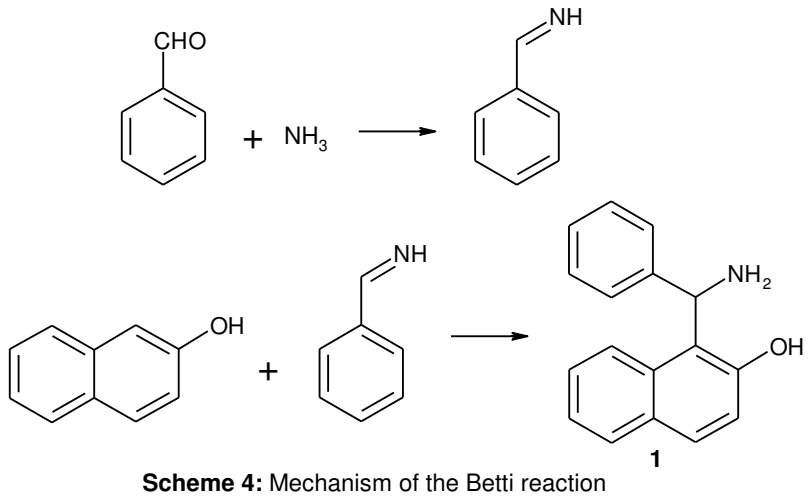
The intermediate **3** was treated with hydrochloric acid to obtain the salt of the Betti Base **1**- HCl in 91% yield (**Scheme 3**). Addition of a solution of sodium hydroxide to chloride, yielded Betti base **1** (75% yield).[4, 6]




**1**

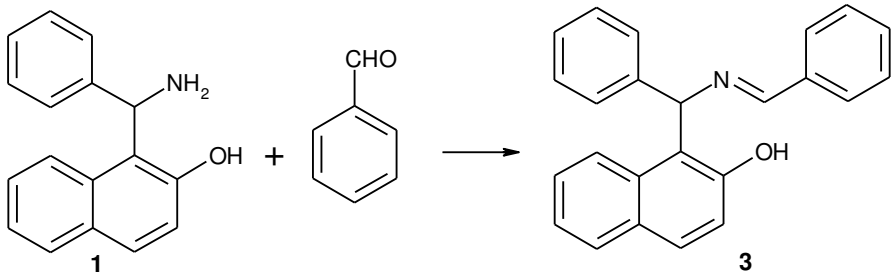
**Scheme 3:** The Betti base

Along the lines presented in **Scheme 1**,[5] **Scheme 4** reports the reaction of ammonia and benzaldehyde to yield the corresponding imine, that subsequently reacts with 2-naphthol.




**Scheme 4:** Mechanism of the Betti reaction

In the presence of benzaldehyde, Betti base **1** produces the imine/oxazine **3** (**Scheme 5**).

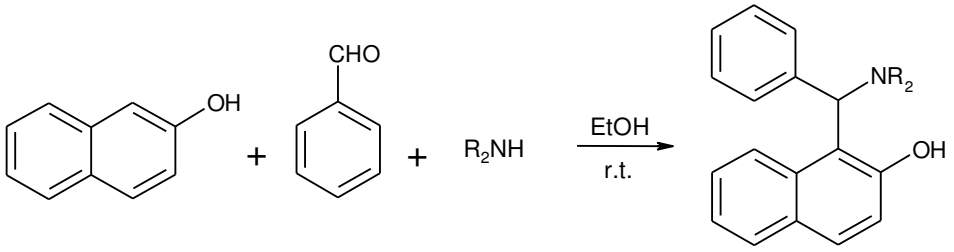



**Scheme 5:** The formation of the imine/oxazine

Betti base **1** was successfully resolved into two isomers using tartaric acid.[7] The Betti reaction, that is, a simple and straight forward condensation between 2-napthol, aryl aldehydes and ammonia, or amines could be used to synthesize more complex molecular structures by assembling these three simple components. However, a long period of silence occurred, after the initial interest that included the work performed by Littman and Brode, who used different amines instead of ammonia.[10] For example, the use of dimethylamine yielded the dimethylamino derivative of the Betti base **4** in a one-pot multicomponent process in 71% yield. On the other hand, the use of piperidine gave 1- (1-piperidylbenzy) -2- naphthol (73% yield) **5a**[10] (**Scheme 6**).

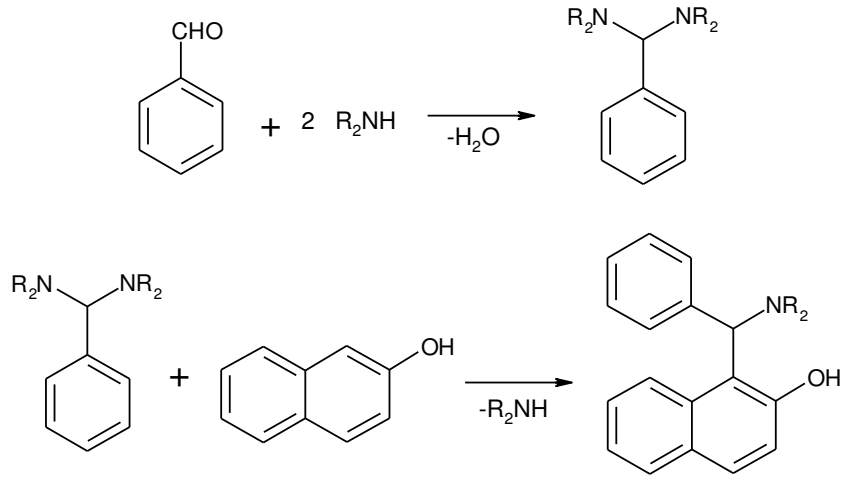
The compound **5a** was also resolved into its enantiomers with the aid of camphorsulfonic acid. A different mechanism should be operative in these reactions. According to Littmann and Brode,[10] secondary amines should react with benzaldehyde *via* the formation of a benzylidinediamine (**Scheme 7**). This

intermediate attacks 2-naphthol and yields aminobenzylnaphthol, after the elimination of an amine molecule.



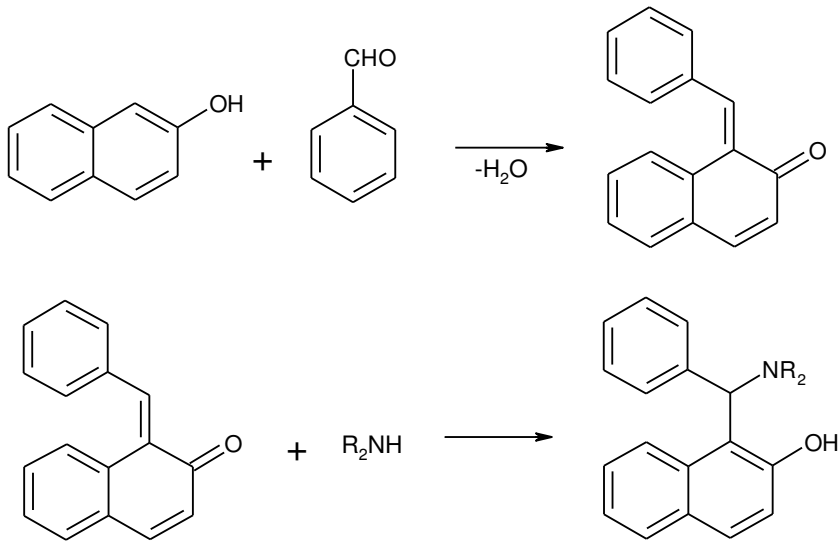

**4**, R = -$(CH_3)_2$
**5a**, R = -$CH_2(CH_2)_3CH_2$-

**Scheme 6:** The Betti reaction with secondary amine




**Scheme 7:** Mechanism of the Betti reaction with secondary amines

However, in principle the alternative mechanism represented in **Scheme 8**, based upon the reaction between the amine and an adduct formed between 2-naphthol and benzaldehyde cannot be ruled out.




**Scheme 8:** A different sequence for the Betti reaction.

A decade ago,[11,12] Cardellicchio et al. decided to 'awaken' the Betti base chemistry, due to their firm belief that its structure and all of the possible variations on them could be of special interest for organic chemists working in the field of ligand-metal catalyzed reaction.[3] In their work,[11] the original synthetic procedure was reconsidered and extended to other reactants; the absolute configuration of the Betti base hydrobromide was determined by an x-ray experiment (**Figure 3**) and the configuration of the other bases were also determined by chemical correlations with **1**.

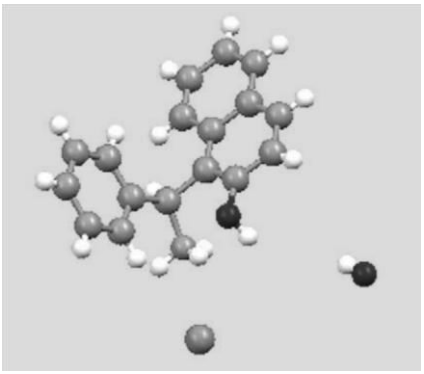


**Figure 3**: Crystal structure of the (S)-Betti base hydrobromide

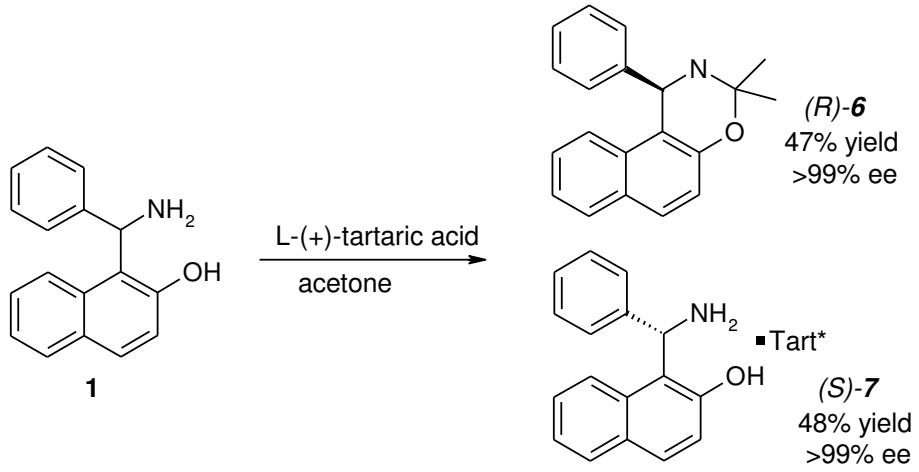
Finally they reported the first application of the aminobenzylnaphthols produced in asymmetric synthesis.[12] Since then, many other research groups in the world have investigated this reaction. In this chapter we represent the current state of the art and recent research[13] concerning this useful reaction and the bases produced that will be generally called Betti bases.

## New Synthesis And Resolution of the Original Betti Base 1

Fulop et al. reported a new synthesis of the archetypal Betti base **1** where ammonium carbamate or ammonium hydrogen carbonate under microwave irradiation was proposed as an alternative and convenient source of ammonia.[14] Cardellicchio et al.[11] improved the original Betti procedure for separation of enantiomers by preparing and separating the tartaric acid salts of the Betti base in a mixture of ethanol and methanol. They found that the separation of enantiomers became particularly easy if the tartaric acid salts were prepared in acetone. Under these conditions, these salts could be easily separated in a single step.

Along this line of research, Hu et al. reported a new protocol for the separation of the enantiomers of the original Betti base **1**[15] by using L-(+)-tartaric acid and acetone as the solvent. Protic solvents were not used because they could cause a retro-Betti reaction during the separation, with a consequent decrease in the yields of the collected enantiomers. On the other hand, when acetone was used as a solvent, two

different compounds were formed, the N,O-ketal of the (*R*)-enantiomer of the Betti base **1** and the tartaric acid salt of the (*S*)-enantiomer of the same base (**Scheme 9**).

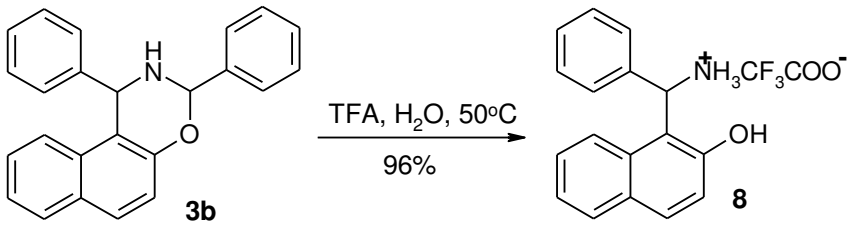



**Scheme 9**:A new resolution of the Betti base **1**

They proved that tartaric acid first causes the acid catalyzed N,O-ketalisation of both the enantiomers with acetone. Then, the chiral non-racemic acid catalyses the N,O-deketalisation of the (*S*)-enantiomer to yield the desired free base which, eventually, reacts with the same tartaric acid to form the tartarate. In summary, this new procedure for the separation of enantiomers of the Betti base **1** is simple, easily scalable and produces both the enantiomers in high yields.

## A New Method for the Synthesis of Enantiomerically Pure Betti Base

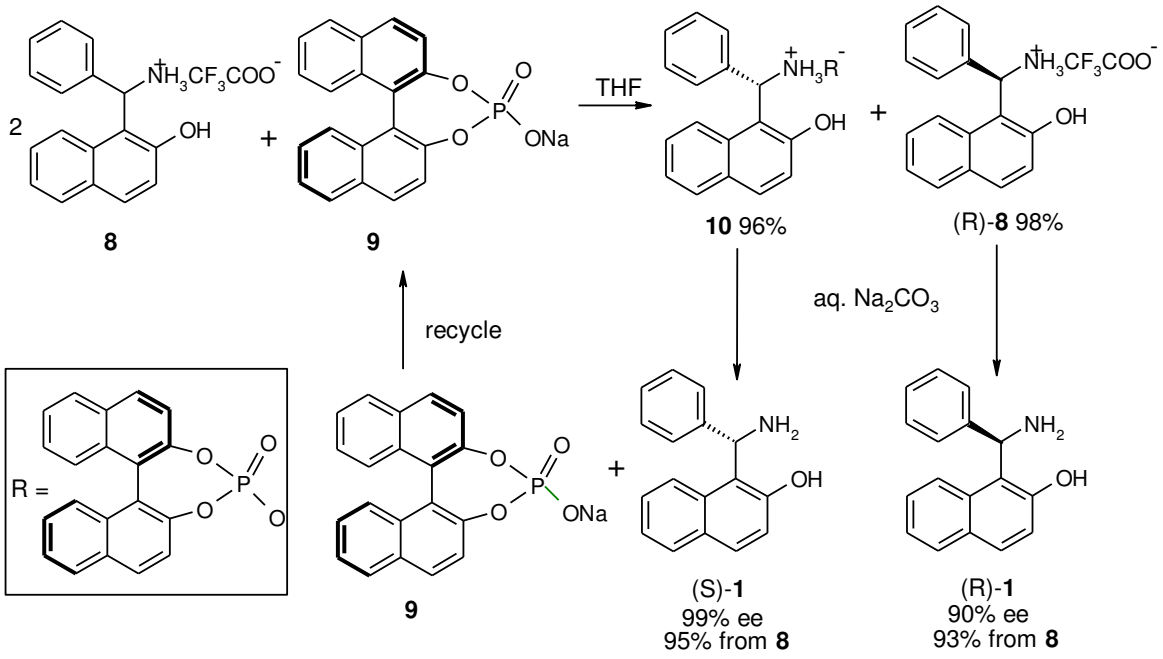
Traditionally, the hydrolysis of oxazine **3b** consists of steam distillation in hydrochloric acid to remove benzaldehyde. However, this hydrolysis procedure is difficult to take to completion even with prolonged reaction times and increased hydrochloric acid concentrations due to the insolubility of oxazine **3b** and Betti base hydrochloride. So Bian et al. have introduced an improved hydrolysis method with the use of trifluoroacetic acid.[16] The trifluoroacetic acid catalyzes the hydrolysis of **3b** and proceeds smoothly to form salt **8** with the hydrolysate under milder conditions in up to 96% yield (**Equation 1**). The Betti base•trifluoroacetate **8** is not only easy to separate by simple filtration because it is almost insoluble in cold dichloromethane but also stable and can be stored for extended periods after vacuum drying.




**Equation 1**: TFA catalyzed hydrolysis of **3b**

Until now, the reported synthesis of enantiomerically pure Betti base have been mainly based on the resolution of racemic Betti base **1** with chiral tartaric acid as discussed before. In the above reported resolution procedures, the method of Hu can also give (*R*)-Betti base with good chemical yield and enantiomeric excess, but another resolution process was necessary. In contrast, the resolution method of Cardellicchio can simultaneously provide the two desired enantiomerically pure Betti bases by one-step resolution, but the yield and reproducibility are not satisfactory. So Bian et al. reported a one-step resolution method for racemic Betti base with good reproducibility and high chemical yields and enantiomeric excess of the two enantiomers. A recyclable resolving agent (*R*)-1,1'-binaphthalene -2,2'-diyl sodium phosphate (**9**) is used to directly separate racemic Betti base•trifluoroacetate **8** (**Scheme 10**).

The reaction of two equivalents of **8** with one equivalent of **9** in tetrahydrofuran gives a mixture of (*S*)-Betti base diastereomeric salt **10**, (*R*)-Betti base trifluoroacetate (*R*)-**8** and sodium trifluoroacetate. The salt **10** is insoluble in THF and can be easily separated by filtration. Dilution of the mother liquor with water results in the precipitation of salt (*R*)-**8**, which can be easily separated. Neutralization of salt **10** gives the free Betti base (*S*)-1-(α-aminobenzyl)-2-naphthol [(*S*)-**1**] and releases the chiral acid **9**. The chiral acid **9** can be recycled from the water phase by simple filtration. This recycled **9** can be efficiently reused without significantly decreasing the yields and enantiomeric excess of (*S*)-Betti base (**Table 1**). Following the same procedure for obtaining (*S*)-**1** from salt **10** gives (*R*)-**1** from salt (*R*)-**8**. This one-step resolution of racemic Betti base•trifluoroacetate by recyclable **9** provides (*S*)-Betti base in 95% yield with 99% *ee* and (*R*)-Betti base in 93% yield with 90% *ee*.




**Scheme 10**: Resolution of Betti base by salt **9**

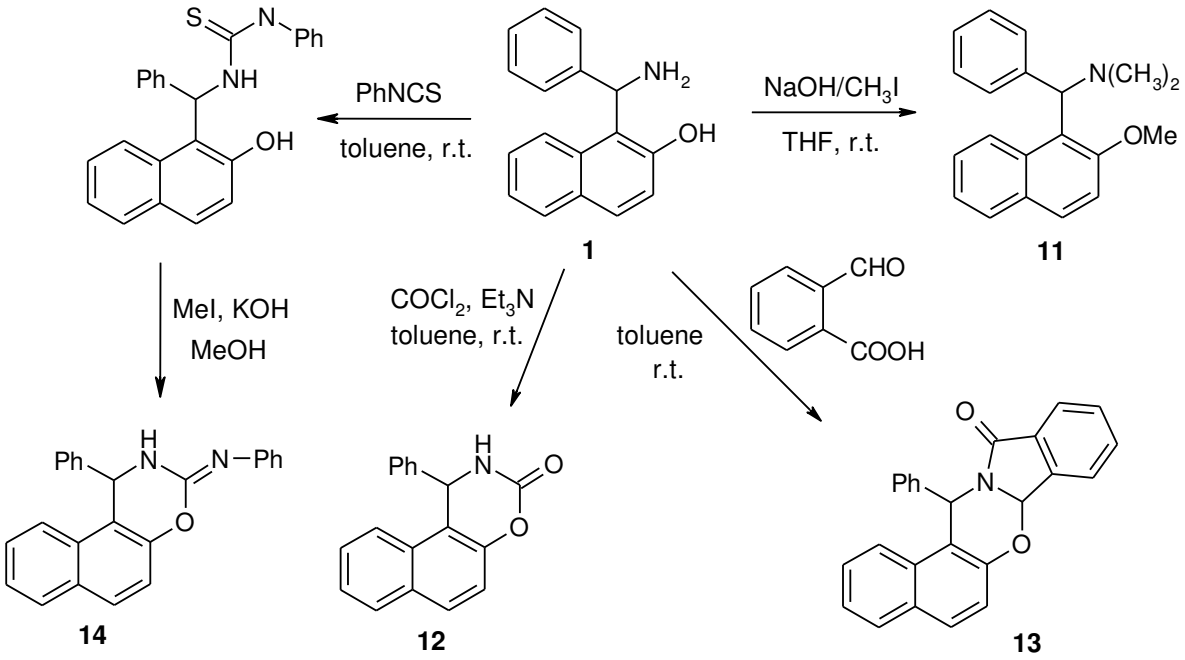
**Table 1**: Resolution of Betti Base by Recycled (*R*)-1,1'-Binaphthalene-2,2'-diyl Sodium Phosphate (**9**)

| Sodium phosphate **9** | Yield (%) of **10** | Yield (%) of (*S*)-**1** | *ee* (%) of (*S*)-**1** | Recovery (%) of **9** |
|---|---|---|---|---|
| 1st use | 96 | 95 | 99 | - |
| Recycle 1 | 94 | 93 | 99 | 90 |
| Recycle 2 | 90 | 89 | 98 | 89 |

## Synthesis of New Derivatives of Betti Base

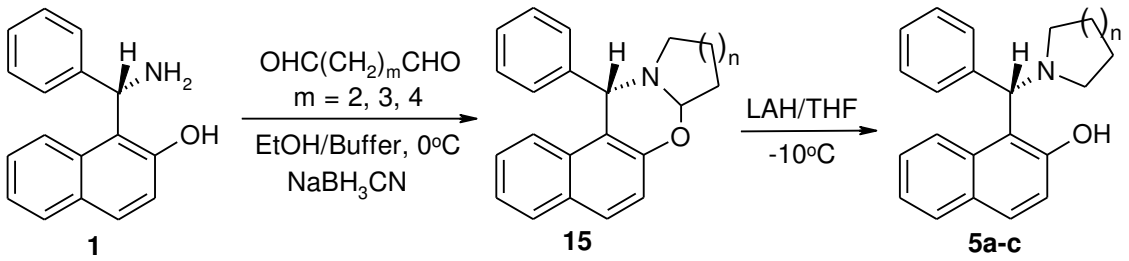
### (A) Transformation of the original Betti base (1)

New chiral molecules were synthesized starting from the Betti base. Cardelicchio et al. observed that simultaneous N- and O- methylation of the Betti base (**11**) could be accomplished by simple treatment with $NaOH/CH_3I$ (90% Yield, **Scheme 11**).[11] Betti base **1** was also transformed into polycyclic 1,3 – oxazines through domino ring closure reactions.[17] Towards this end, the base was reacted with phosgene or salicylaldehydes to give product **12** (54% yield) or **13** (63% yield) respectively. On the other hand, the reaction of base **1** with phenyl isothiocyanate, followed by methylation, yielded **14** (25% overall yield).[17]




**Scheme 11**: Synthesis of derivatives of Betti

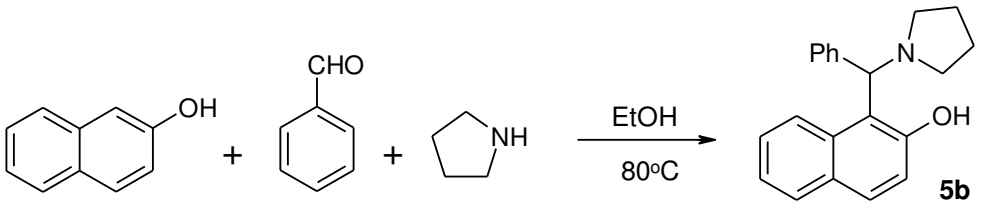
In addition to racemic Betti bases, non racemic products were synthesized by suitable reactions of (*S*)-Betti base **1** (**Scheme 12**) with 1, n-dialdehydes and $NaBH_3CN$ in an ethanol/buffer solution (51-61% yields),[18] with formation of the intermediates **15**. Compound **15** were than reacted with $LiAlH_4$ to obtain the corresponding (*S*)-1-(α-cycloaminobenzyl)-2- naphthols **5a-c** in high yields (94-98% yields).




**Scheme 12**: Synthesis of 1-(α -cycloaminobenzyl)-2-naphthols

**(B) Betti reaction with different achiral Amines and/or Aldehydes:**

The Betti procedure could be extended to different amines, as shown by the earlier work of Littman and Brode (**Schemes 6**).[10] In another work,[19] Betti reaction of 2-naphthol, benzaldehyde and pyrrolidine yielded 1-(pyrrolidinylbenzyl)-2-naphthol **5b** (**Scheme 13**) in 95% yield.




**Scheme 13**: Betti reaction with pyrrolidine

Various patents have described the use of Betti reaction to prepare intermediates of pharmacological interest. In one of these patents, Betti reaction was used to produce a range of products **16** & **17** (**Figure 4**), tested as analgesic agents, due to their affinity towards the N-methyl-D-aspartate (NMDA) receptor family, and towards α-adrenergic and opioid receptors.[20] The experimental procedure started with the preliminary reaction between the amines and aryl aldehydes. The isolated intermediates were then reacted with 2-naphthol in hot acetonitrile.

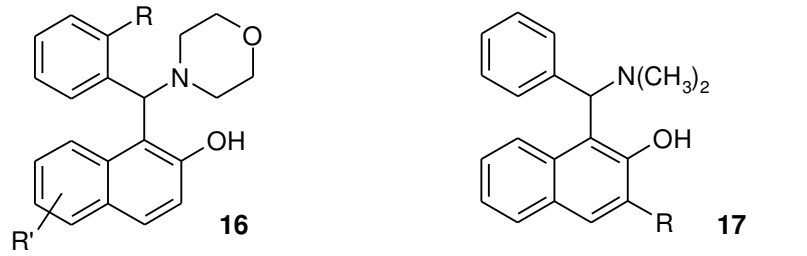
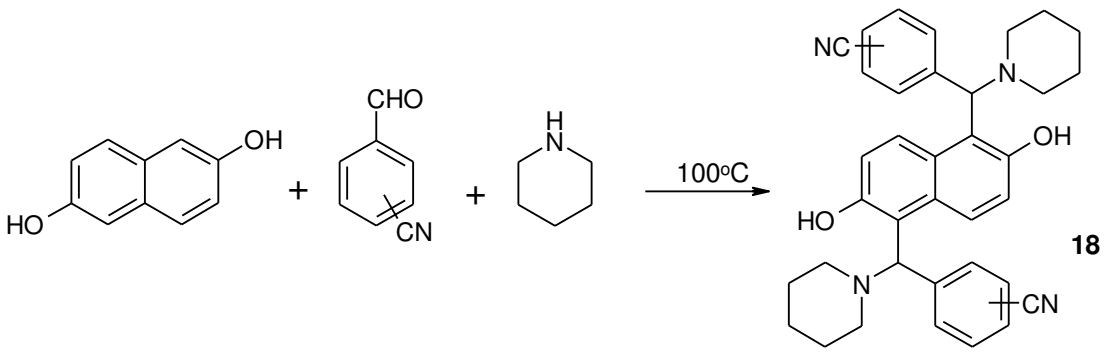


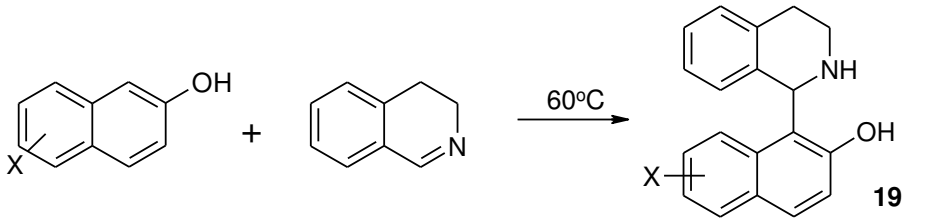

**Figure 4**: A selection of intermediates of pharmacological interest prepared by a Betti reaction

On the other hand, Xiong exposed 2, 6-dihydroxynaphthalene with 2 equiv of piperidine or morpholine and cyanobenzaldehyde at 100°C. As shown in **Scheme 14**, the use of di-naphthol produced the bis-Betti bases **18** in good yields (81-86%).[21] As suggested by the author, the reaction should occur through two sequential Betti reactions.




**Scheme 14**: Betti reaction with 2,6-dinaphthols

A procedure that could be considered as an extended Betti reaction was reported by Li et al.[22] They reacted 2-naphthol with 3,4-dihydroisoquinoline, a cyclic imine molecule, thus forming 1-naphtholyl tetrahydroisoquinolines **19** (45-97% yields, **Scheme 15**) which, in principle, could represent potential ligands in asymmetric synthesis.

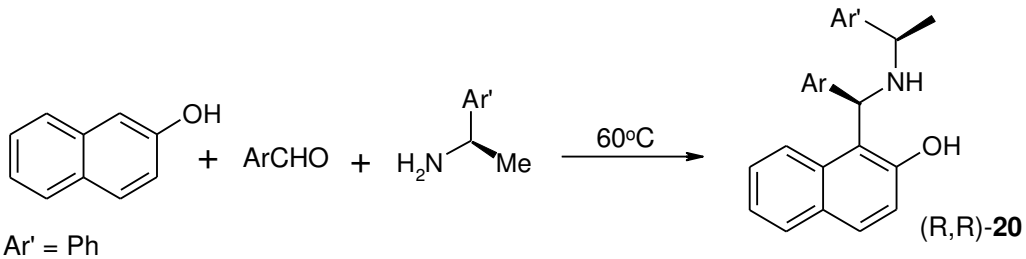



**Scheme 15**: Betti reaction with 3,4-dihydroisoquinoline

For such applications, the racemic isoquinolines were subjected to resolution by using L-tartaric acid in methylene chloride. However, the best enantiomeric excess was only 58% and extensive racemisation was found to occur subsequently. On the other hand, the methyl derivative (6-MeO and 7-MeO) could be easily resolved and a stable (-)-enantiomer was obtained.

## (C) Betti reaction with chiral non racemic reactants

A new fruitful research topic began when the Betti reaction was performed with enantiopure amines. In this approach, the presence of a resolved stereogenic centre on the amine induced the formation of a new stereogenic centre with high stereoselectivity. By this procedure, involving a simple crystallization, the formation of the desired aminobenzylnaphthol having two fully resolved stereogenic centres was achieved. Palmieri et al. reported the Betti reaction of 2-naphthol, aryl aldehydes and (*R*)-1-phenylethylamine or (*R*)-1-(1-naphthyl)ethylamine.[23]

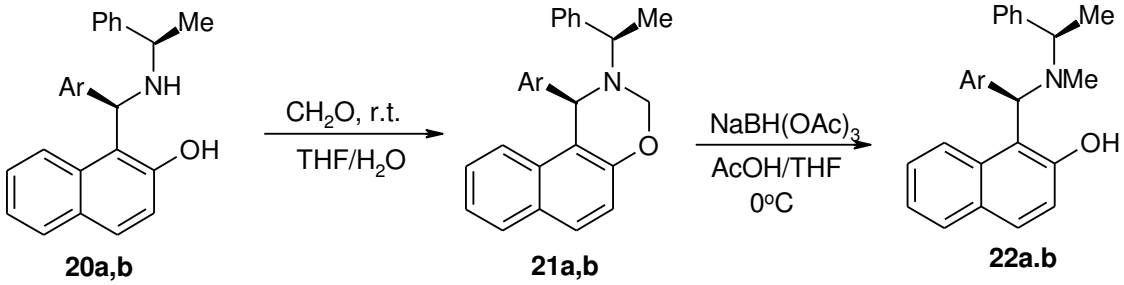



Ar' = Ph
Ar=Ph, **20a**; Ar=p-tol, **20b**; Ar=4-$MeOC_6H_4$, **20c**; Ar=2-$MeOC_6H_4$, **20d**; Ar=4-$ClC_6H_4$, **20e**; Ar=3-$NO_2C_6H_4$, **20f**; Ar=1-Np, **20g**; Ar=2-Np, **20h**; Ar=$C_6H_5$, **20i**; Ar=2-pyridyl, **20j**; Ar=2-furyl, **20k**; Ar=2-thienyl, **20l**; Ar'=1-Np, Ar=Ph, **20m**

**Scheme 16**: Betti reaction with (R)-1-arylethylamine

At the end of this solvent-free reaction, the addition of ethanol favoured the precipitation of the predominant (*R*,*R*)-**20** (**Scheme 16**), that could be easily collected.

When benzaldehyde was used, this solvent free procedure resulted in high yields (93%) and in a very high diastereomeric ratio (99:1). In the case of other aryl aldehydes, lower yields (54-86%) and a lower diastereomeric ratio (from 3:1 to 24:1) were observed. The high diastereoselectivity obtained in the first case was explained by invoking the intervention of a crystallization-induced asymmetric transformation, that would favour the predominance of the (*R*,*R*)-stereoisomer. The aminobenzylnaphthols **20a** and **20b** (**Scheme 17**) were reacted with formaldehyde to produce the corresponding oxazine **21a** and **21b**,[23c] that were than reduced with $NaBH(OAc)_3$ in acetic acid (50-63% yields) to the corresponding N-methyl-aminobenzylnaphthol **22a** and **22b**.[23c]

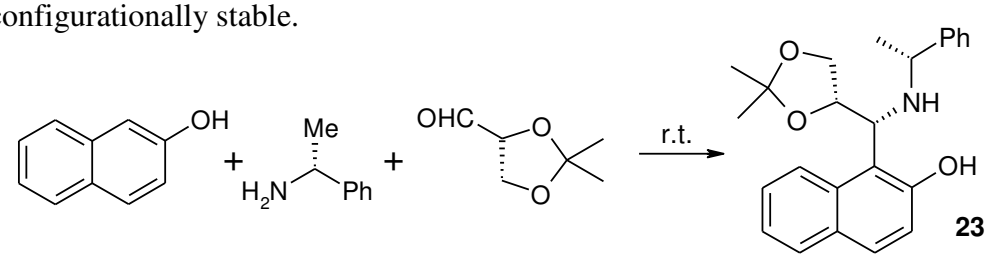



**Scheme 17**: Selective N-methylation of bases **20**

Similar reactions were independently reported by Chen et al,[24] where benzldehyde was added to a solution of 2-naphthol in ethanol. Subsequent addition of (*S*)-1-phenylethylamine and stirring for six days led to the formation of the (*S*,*S*)-**20a** (70% yield). This secondary amine **20a** was also reacted with paraformaldehyde and $NaBH_4$ in the presence of TFA to prepare the corresponding N-methylamine **22a** (65% yield) as already presented in **Scheme 17**.

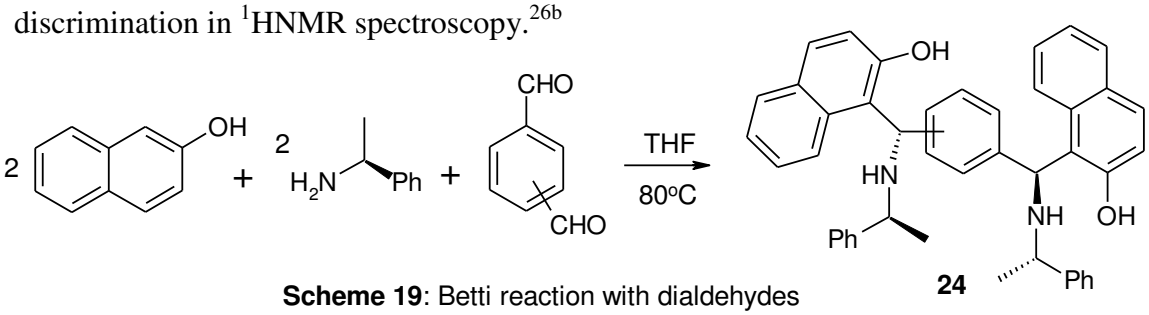
The diastereoselecive synthesis of aminnonaphthols from chiral aldehydes (for example 2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde) was reported by Palmieri et al (**Scheme 18**).[25] The reaction occurred between 2-naphthol with primary (or secondary) amines and chiral aldehydes at room temperature and under the solvent-free condition. Best results were obtained with primary amines (52-62% yields; stereoisomeric ratios in the range from 75:25 to 89:11). The aminoalkyl naphthol **23** was treated with aqueous hydrochloric acid in THF to remove the ketal protection and

prepare the corresponding diol (40-95% yields). The pure diasteromers were found to be configurationally stable.



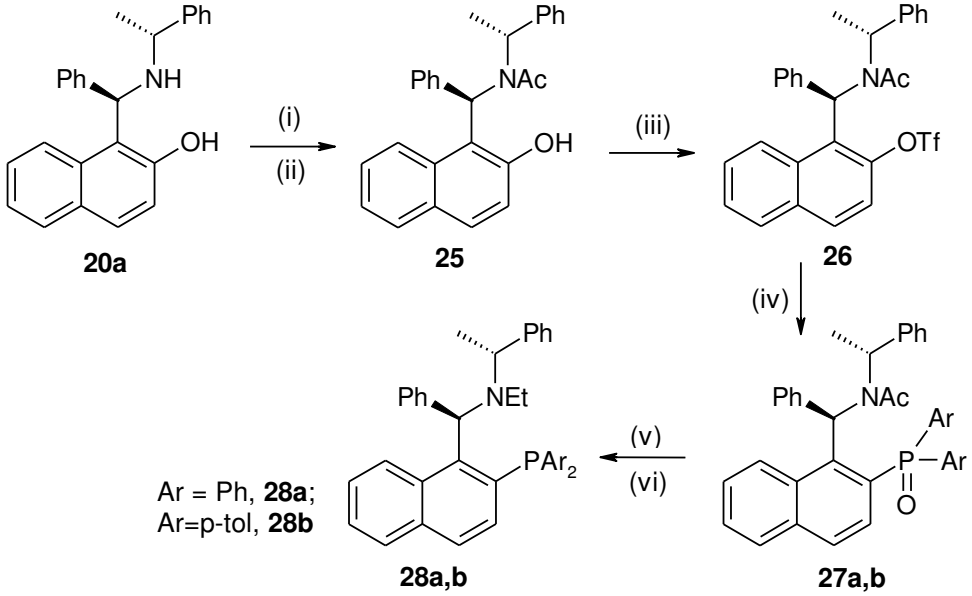

**Scheme 18**: Betti reaction with chiral non-racemic aldehydes and amines

Diamines **24** (**Scheme 19**) bearing two naphthalene units were prepared by reacting 2-naphthol with phenylethylamine and *m*- or *p*-benzenedialdehydes (32-45% yield).[26a] The dinaphthols **24** were also reacted with 2,6 bis-chloromethylpyridine to yield a macrocyclic product (88% yield), which was tested for molecular discrimination in $^1$HNMR spectroscopy.[26b]




**Scheme 19**: Betti reaction with dialdehydes

Aminobenzylnaphthol **20a** was transformed into the corresponding aminobenzylphosphines **28a** and **28b**[27] molecules that were used as chiral ligands in asymmetric catalysis. The complete synthetic strategy is summarized in **Scheme 20**.




Scheme 20: Preparation of chiral aminobenzylphosphine. Reagents and conditions: (i) AcCl, pyridine, rt; (ii) NaOH, MeOH, rt; (iii) $Tf_2O$, DCM, $Et_3N$, -78°C; (iv) $Pd(OAc)_2$, dppp, $HP(O)Ar_2$, $(i\text{-}Pr)_2NEt$, DMSO, 100°C; (v) $BH_3{\cdot}Me_2S$, THF, 0°C–reflux; (vi) $HSiCl_3$, $Et_3N$, toluene, 100°C.

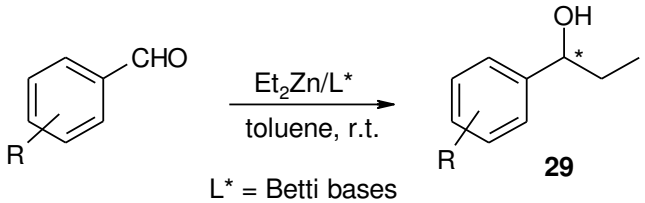
Apart from the protection/deprotection steps, the crucial points of the procedure are represented by the transformation of naphthol **20a** into triflate **26** (three steps with 74% overall yield), and coupling between triflate **26** and diphenylphosphine oxide in the presence of a palladium catalyst (61-64% yields). The final reduction step (51-56% yields) produced the interesting aminophosphines **28a** and **28b**.

## Application of Betti bases in Asymmetric Synthesis

### 1. Organozinc chemistry

#### (a) Addition of diethylzinc to aryl aldehydes

The enantioselective addition of orgonozinc reagents to aldehydes in the presence of a chiral ligand is a very useful synthetic method leading to secondary chiral alcohols.[28] This reaction requires the presence of a suitable ligand of the metal that can be also used on a catalytic scale (typically the ratio between the substrate and the chiral ligand should be in the range of 20:1-5:1). The process is commonly used in asymmetric synthesis to test the effectiveness of the chiral ligands. Enantiopure amines, alcohols, aminoalcohols, sulfur compounds, and many other molecules were tested with this easy and useful reaction.[28] Accordingly, several aminobenzylnapthols obtained as the Betti protocol were tested as chiral ligands for the standard reaction (**Scheme 21**). The results that were reported can be considered to be of special interest taking in to account the easy accessibility of the chiral ligand.




**Scheme 21**: Enantioselective diethylzinc addition to aryl aldehydes in the presence of Betti bases.

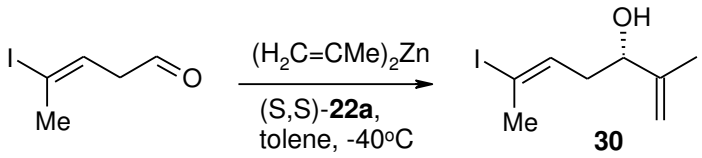
As a matter of fact Cardellicchio et al., first performed the addition of diethylzinc to aryl aldehydes in the presence of Betti base ligands.[12] Solvents such as THF, n-hexane and toluene were found to be effective. Lower *ee* values of the secondary alcohol (35% *ee*) were measured with Betti base **1**. The best asymmetric induction (92 - > 99% *ee*) was obtained by using tertiary base **4** (63–94% isolated yield). In the work of Hu et al. diethylzinc was added to aryl aldehydes in toluene in the presence of ligands **5a-c**,[19,29] when 93-96% yield of the ethyl phenyl carbinol with

73-99% *ee* were observed. Screening of different aminobenzylnapthols was performed by Palmieri et al. for the same reaction.[23] Ethyl phenyl carbinol was obtained with 15-89% *ee* values with good chemical conversions. The highest enantioselectivity (89% *ee*) was observed with aminobenzylnapthol **20d**.

Chen et al. added diethylzinc to benzaldehyde in toluene in the presence of ligands **20a** and **22a**.[24] Yields (70-97%) of the secondary alcohol were obtained (*ee* values 52-100%). Tertiary amine **22a** showed better selectivity (*ee* > 99%) compared to the secondary amine **20a**. Fulop et al. performed the addition of diethylzinc to aryl aldehydes in the presence of bases **20** under microwave irradiation.[30] The yields of the procedure were 94-98% with *ee* values in the range of 10-92%, the 92% *ee* peak value being obtained with aminobenzylnapthol **20m**.

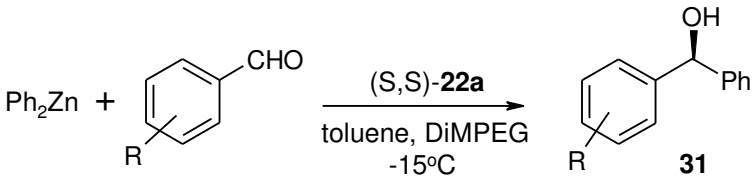
**(b) Alkenylation or arylation of aldehydes**

The addition of diisopropenyl zinc to 4-iodo-3-pentenal in the presence of ligand **22a** yielded the corresponding alcohol (68% yield, 83% *ee*, **Scheme 22**).[31] This intermediate was used in the synthesis of octalactin A, a lactone isolated from marine microorganisms, which showed significant cytotoxic activity against some tumor cell lines.[31]




**Scheme 22**: Enantioselective addition of diisopropenylzinc to the 4-iodo-3-pentenale in the presence of the aminobenzylnaphthol **22a**

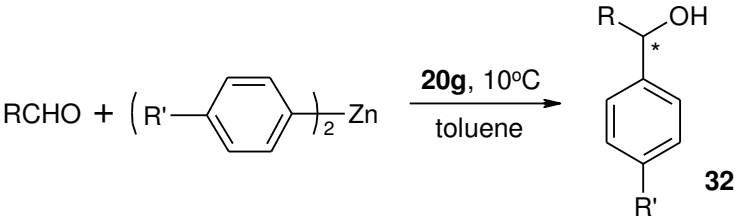
In order to perform the aldehyde arylation, Chen et al. prepared a phenylzinc reagent by mixing phenylboronic acid with diethylzinc. The zinc reagent was added to aldehydes in the presence of aminobenzylnapthol **22a** to produce chiral diarylmethanols, as shown in **Scheme 23**.[32] High yield (87-95%) and excellent selectivity (92-99% *ee*) were observed for this case. This protocol seems to be particularly interesting, due to low cost of both the reagents and of the chiral auxiliary and also due to the pharmaceutical relevance of the optically active diarylmethanols obtained.




R = 2-Me, 3-Me, 4-Me, 2-F, 2-Cl, 4-Cl, 2-Br, 4-Br, 2-OMe

**Scheme 23**: Enantioselective arylation of aryl aldehydes in the presence of the aminobenzylnaphthol **22a**

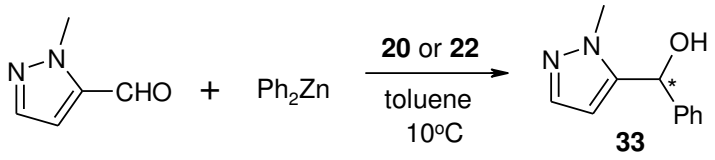
Dahmen and Lohrmann reported a different aryl transfer to aldehydes.[33] Arylzinc was produced *in situ* by reacting diethylzinc with triphenylborane, or with stable and readily available borane complexes with ammonia or amine. These arylzinc species were added to alkyl or aryl aldehydes in the presence of the aminobenzylnapthol **20g**, according to **Scheme 24**.




R = Ph, 2-$BrC_6H_4$, 2-$MeC_6H_4$, 2-$MeOC_6H_4$, 3-$ClC_6H_4$, 4-$ClC_6H_4$, 4-$MeOC_6H_4$,cyclohexyl,n-heptyl.
R' = H, Cl, Me, OMe

**Scheme 24**: Enantioselective arylation of aldehydes in the presence of a Betti base

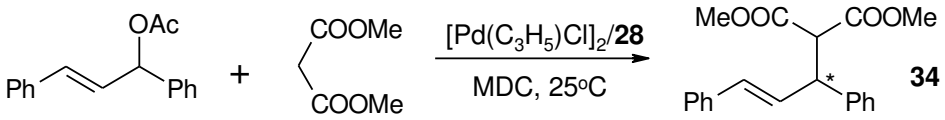
The zinc complex that originated from the triphenylborance was highly reactive, but less stereoselective (36% *ee*). Better results were obtained when borane/aminoethanol complexes were employed. In this case, chiral diarylmethanols were prepared in high yields (86-97%) and high selectivity (92-98%). This process was successfully applied by the same authors[34] for the synthesis of valuable pharmaceutical intermediates. For example a chiral precursor **33** (**Scheme 25**) of the analgesic Cizolirtine was obtained by reacting diphenylzinc (prepared from triphenylborane and diethylzinc) with pyrazol carbaldehyde in the presence of a series of chiral ligands, including aminobenzylnapthols **20a**, **d**, **g** and **22g**. Selectivity in the range of 78–85% *ee* was observed.[34a]




**Scheme 25**: Preparation of a precursor of Cizolirtine by the arylation of an aldehyde in the presence of Betti bases

## 2. Tsuji-Trost allylic substitution

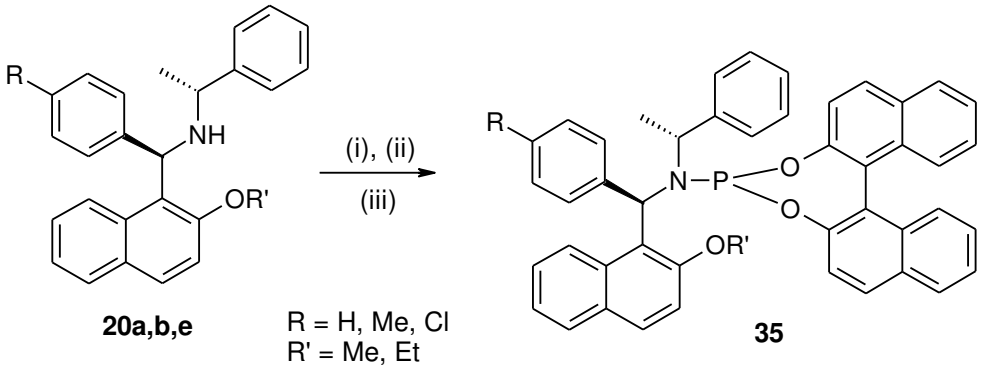
The Tsuji – Trost palladium-catalyzed allylic substitution of 1,3-diphenylprop-2-en-l-ylacetate with dimethyl malonate is a common asymmetric induction test for new phosphine ligands. When phosphines **28a** and **b** were used in this reaction (**Scheme 26**), moderate yields and enantioselectivities of **34** were observed (41–99% yields, 12–70% *ee*). The highest asymmetric induction was observed in methylene chloride.[27]




**Scheme 26**: Catalytic allylic substitution in the presence of phosphine **28** derived from Betti bases

## 3. Hydrosilylation of aryl alkenes

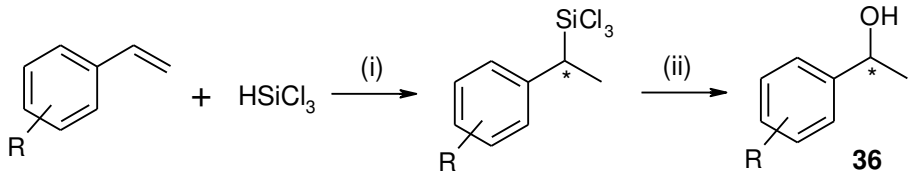
Aminobenzylnapthols **20a**, **b**, and **e** were treated with (*S*)- or (*R*)-BINOL and phosphorous trichloride (**Scheme 27**) to synthesize the corresponding new chiral phosphoramidites **35** (32–74%) yields.[35]




**Scheme 27**: Synthesis of a chiral phosphoramidite from a Betti base. Reagents and conditions: (i) n-BuLi, -78°C ; (ii) $PCl_3$, -78°C to 0°C; (iii) BINOL, $Et_3N$, 0°C to rt.

The hydrosilyation reaction of arylethenes was performed with phosphoramidites **35** in the presence of a palladium catalyst.[35] The silane obtained

could be oxidised to the corresponding aryl methyl carbinol **36** (**Scheme 28**). Good yields (65–96%) and high enantioselectivities (73–97% *ee* values) were observed by using the ligands **35**.

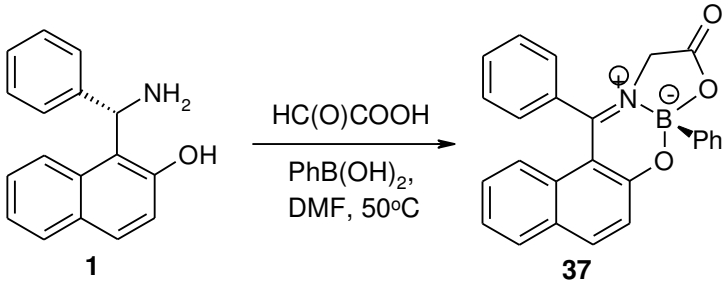



R = H, 2-Cl, 3-Cl, 4-Cl, 4-F, 4-Me, 4-OMe

**Scheme 28**: Hydrosilylation of arylethenes in the presence of a derivative of the Betti base. Reagents and conditions: (i) $[Pd(C_3H_5)Cl]_2$/**35**, 0°C; (ii) $H_2O_2$, KF, $KHCO_3$, MeOH/THF, rt.

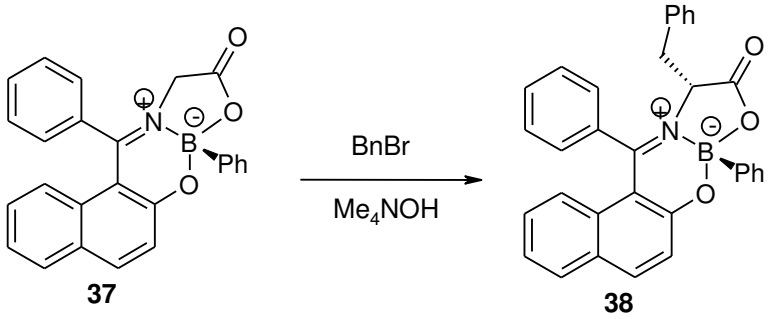
## 4. Preparation of a *β*-chiral boronate complex

Betti base **1** was used to prepare the first stable boronate complex **37** (**Scheme 29**) that is stereogenic only at the boron centre.[36] Accordingly, Betti base **1** was reacted with glyoxylic acid and phenylboronic acid in DMF.




**Scheme 29**: Preparation of a *β*-chiral boronate complex by using the Betti base

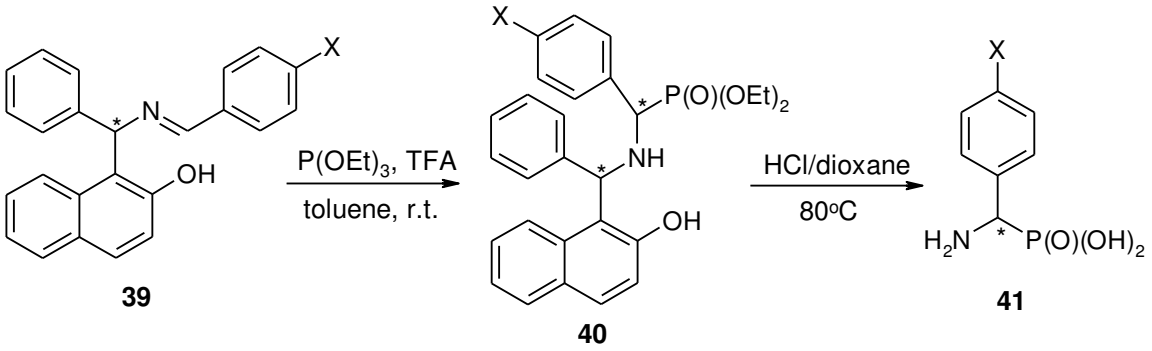
A chirality transfer process occurred from the stereogenic carbon of the Betti base to the boron atom, complex **37** was then alkylated with benzyl bromide (**Scheme 30**) with a good stereoselectivity (*dr* 10.5:1), to yield the amino acid precursor **38**.[36]




**Scheme 30**: Alkylation of a boronate complex derived from the Betti base.

## 5. Preparation of enantiopure α-aminophosphonic acids

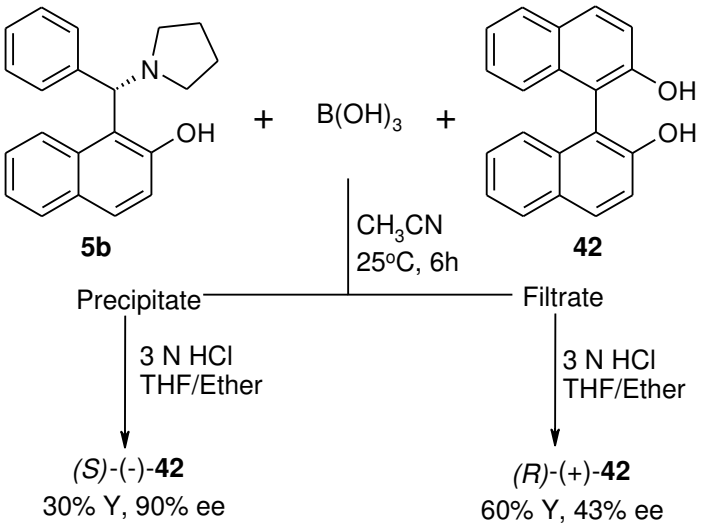
Imines **39** were treated with triethyl phosphite in the presence of trifluoroacetic acid to yield benzylaminonapthol derivative **40** (74-90% yields; 66-84% de).[37] When compound **40** was hydrolysed, chiral aminophosphonic acid **41** was produced, as summarized in **Scheme 31**.[37]




**Scheme 31**: Synthesis of chiral aminophosphonic acids starting from the imine of Betti bases **39**.

## 6. Betti bases in the separation of enantiomers

Due to their easy preparation in an enantiomerically pure form, Betti bases can be legitimately added to the chiral pool of the compounds used in the separation of enantiomers, and also of industrial interest. For example 1-(pyrrolidinylbenzyl)-2-naphthol **5b** and boric acid in acetonitrile were used in an innovative methodology that was devised for achieving the separation of the enantiomers of the racemic BINOL ligand **42**.[19]




**Scheme 32**: Resolution of BINOL by using Betti bases **5b**.

# Part - II Pd catalyzed C-C bond formation via cross-coupling

The Chemistry Nobel Prize for the year 2010 was shared by Prof. Richard F. Heck, Prof. Ei-ichi Negishi, Prof. Akira Suzuki. The Royal Swedish Academy of Sciences rewarded these three chemists for: "Palladium-catalyzed cross couplings in organic synthesis." The discoveries by the three organic chemists have had a great impact on academic research, the development of new drugs and materials, and are used in many industrial chemical processes for the synthesis of pharmaceuticals and other biologically active compounds. It concerns the development of methods for palladium-catalyzed formation of carbon-carbon bonds *via* so-called cross-coupling reactions. The formation of new carbon-carbon bonds is of central importance in organic chemistry and a prerequisite for many biochemical steps. Through the assembly of carbon atoms into chains, complex molecules, e.g. molecules of life, can be created. The importance of the synthesis of carbon-carbon bonds is reflected by the fact that Nobel Prizes in Chemistry have previously been given to this area: The Grignard reaction (1912), the Diels-Alder reaction (1950), the Wittig reaction (1979) and very recently the olefin metathesis (2005).

## Transition metals in synthetic organic chemistry

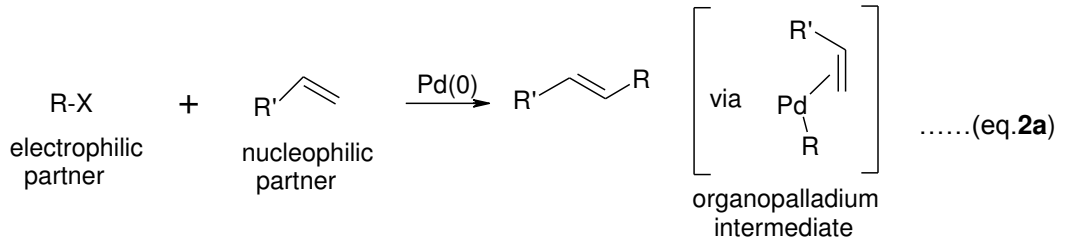
During the second half of the 20th century, transition metals have come to play an important role in organic chemistry and this has led to the development of a large number of transition metal-catalyzed reactions for creating organic molecules. Transition metals have a unique ability to activate various organic compounds and through this activation they can catalyze the formation of new bonds. One metal that was used early on for catalytic organic transformations was palladium. One event that stimulated research into the use of palladium in organic chemistry was the discovery that ethylene is oxidized to acetaldehyde by air in a palladium-catalyzed reaction and this became the industrially important Wacker process.[38] Subsequent research on palladium-catalyzed carbonylation led to new reactions for the formation of carbon-carbon bonds. In general, transition metals, and in particular palladium, have been of importance for the development of reactions involving the formation of a new carbon-carbon bond.

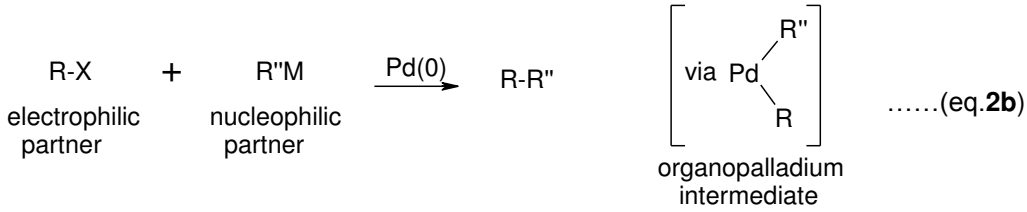
## Palladium-catalyzed carbon-carbon bond formation via cross coupling

The principle of palladium-catalyzed cross couplings involves:

1. Two molecules are assembled on the metal *via* the formation of metal-carbon bonds. In this way the carbon atoms bound to palladium are brought very close to one another.
2. In the next step they couple to one another and this leads to the formation of a new carbon-carbon single bond.

There are two types of cross-coupling reactions according to this principle that have become important in organic synthesis. These two types of reactions are shown in **Equations 2a** and **2b**.



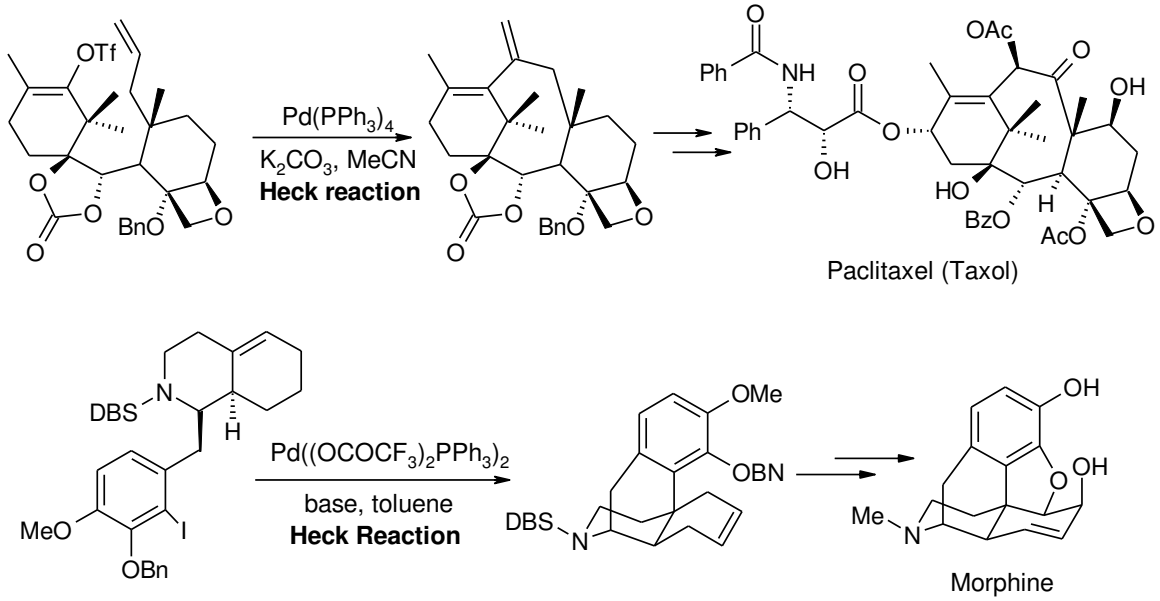




Both reactions are catalyzed by zero valent palladium and both reactions employ an organohalide RX (or analogous compound) as the electrophilic coupling partner. However, the nucleophilic coupling partner differs in the two reactions. In the first type it is an olefin (**Eq. 2a**) whereas in the second type it is an organometallic compound R"M (**Eq. 2b**). In this way the palladium-catalyzed cross-coupling reactions, both the cases, complement one another as regards the nucleophilic coupling partner. A common feature of the two types of cross couplings is that the organic groups from the reagents are assembled on palladium. Furthermore, both reactions begin by generating an organopalladium complex RPdX from the reaction of the organic halide with Pd(0). The organopalladium species RPdX will subsequently react with the nucleophilic coupling partner. The reactions are very mild since they utilize organic halides (or analogous compounds) and olefins or organometallic compounds R''M of low reactivity, where M is typically zinc, boron or tin.

## Application of Palladium-catalyzed cross couplings

The palladium-catalyzed carbon-carbon bond forming reactions (for eg. Heck, Negishi Suzuki and Sonogashira) have had a significant impact on synthetic organic chemistry and have found many applications in target oriented synthesis. Their widespread application in organic synthesis is due to the mild conditions associated with the reactions together with their tolerance of a wide range of functional groups. These cross-coupling reactions have been applied to the synthesis of a large number of natural products and biologically active compounds of complex molecular structures. They have also found applications in the fine chemical and pharmaceutical industries. Select examples of the use of these reactions in natural product synthesis and industrial applications are given below.

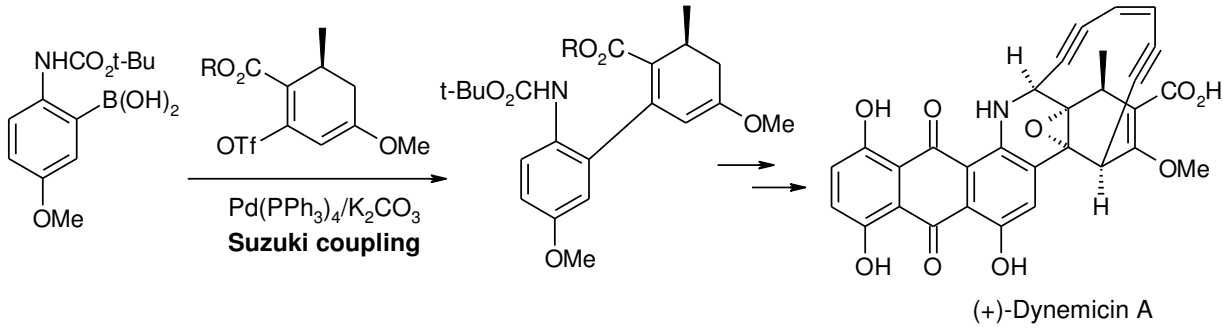
The Heck reaction has been used in more than 100 different syntheses of natural products and biologically active compounds. Two examples are given in **Scheme 33**. The first example is for the synthesis of Taxol,® where the Heck reaction was employed for creating the eight-member ring.[39a] The ring closure to complete the rigid tricyclic system is not trivial. In the other example an intramolecular Heck-type coupling provides the morphine skeleton and the product is transformed to morphine in a few steps.[39b]




**Scheme 33**: Examples of the use of the Heck reaction in natural product synthesis

The Heck reaction has also been used as an important carbon-carbon bond-forming step in the synthesis of other complex organic molecules such as steroids,[40a] strychnine,[40b] and the diterpenoid scopadulcic acid B[40c,d] with cytotoxic and antitumor activity.

An efficient synthesis of the potent natural antitumor agent (+)-dynemicin A involved a Suzuki coupling in one of the key carbon-carbon bond forming steps (**Scheme 34**).[41a] There are a number of natural product syntheses reported in the literature that rely on the Suzuki couplings for carbon-carbon bond formation.




**Scheme 34**: An efficient Suzuki coupling in the synthesis of (+)-Dynemicin A

The Suzuki reaction was used for preparing the antiviral bromoindole alkaloid dragmacidin F.[41b]

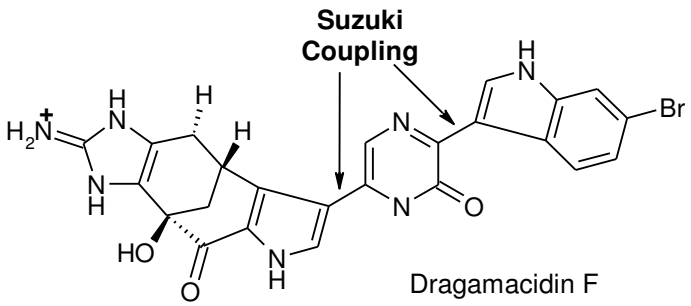
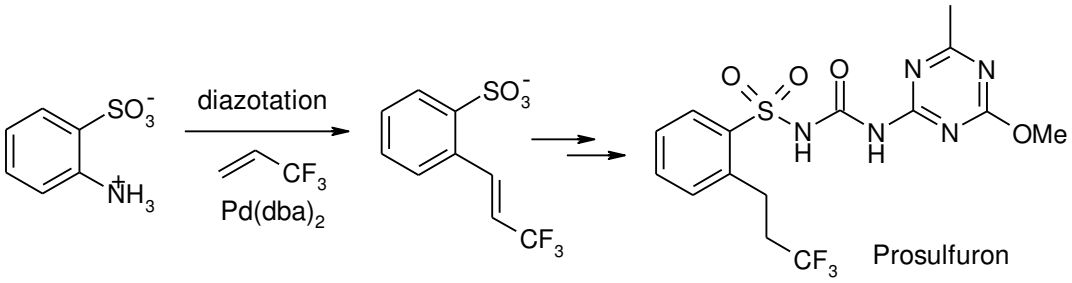


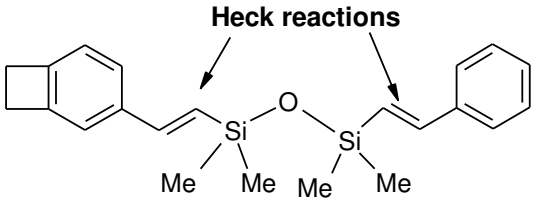

**Figure 5**: Synthesis of Dragamacidin F

At the cross coupling stage there were several sensitive functional groups present, and therefore mild reagents such as an organoboron or organozinc reagent is required.

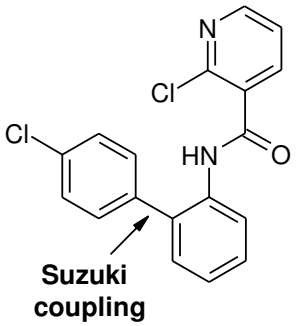
The palladium-catalyzed cross-coupling reactions are suitable for carrying out on a large scale and the Heck reaction has been used for a number of large scale industrial applications. Several of these processes are run on a multi-ton scale per year. The sulfonyl urea herbicide Prosulforon® is produced on a large scale with a process developed by Ciba-Geigy (**Scheme 35**). The key step is a Heck reaction, where a diazonium salt generates an arylpalldium intermediate, which couples with the olefin.



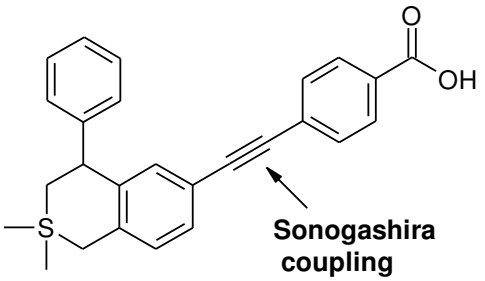

**Scheme 35**: An industrial process for the synthesis of Prosulfuron[42]



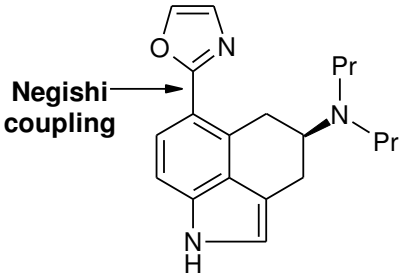

DVS-bis-BCB
(Monomer for high performance electronic resins (cyclotene)) (Dow chemical 1989)




Boscalid (Fungiside) BASF,1997




AGN-194310 RAR Antagonist




5-HT1A Agonist Eli Lilly 1997

**Figure 6**: Palladium-catalyzed cross-coupling reactions in industrial preparation of fine chemicals: DVS-bis-BCB[43a], Boscalid[43c,d,e], AGN-194310 RAR[43f] Antagonist and 5-HT1A Agonist[43b]

The anti-inflammatory drug Naproxen (Albermarle, Hoechst AG, 1994) and the asthma drug Singulair (Merck, 1993) are other examples of industrial manufacturing of pharmaceuticals *via* the Heck reaction. Some examples of the use of the Heck, Negishi, and Suzuki reactions in the industrial preparation of fine chemicals are given in **Figure 6**.

## Replacement of Phosphine Ligands

These cross coupling reactions were usually performed with 1 to 5 mol% of Pd catalyst along with phosphine ligands, which sometimes creates practical problems because orgonophosphines tend to be expensive, poisonous and air sensitive.[44] Accordingly, a current challenge is to develop Pd catalyst that can utilize inexpensive

phosphine free ligands. In this regard a number of ligands including N-Heterocyclic carbenes (NHC),[45] oxazolines,[46] amines,[47] Schiff bases,[48] pyridines,[49] hydrazones,[50] guanidines,[51] pyrazoles,[52] tetrazoles,[53] quinolines,[54] carbazones,[55] imidazoles,[56] thioureas[57] and 1,3-dicarbonyl compounds[58] have been examined for Pd catalysis recently. Note that not all of these phosphine-free ligands (eg NHC) are less expensive than phosphines or are easier to prepare. In this chapter we present some of the examples of phosphine-free ligands used for Pd catalyzed cross coupling reactions.

**(A) <u>N,N-Bidentate ligand</u>**

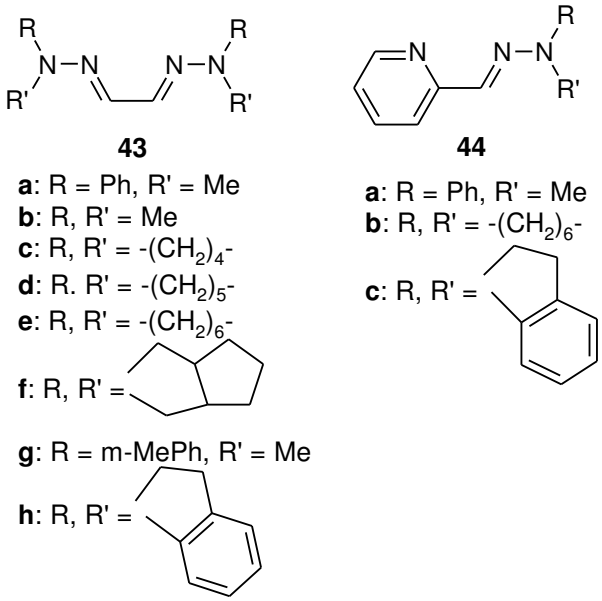
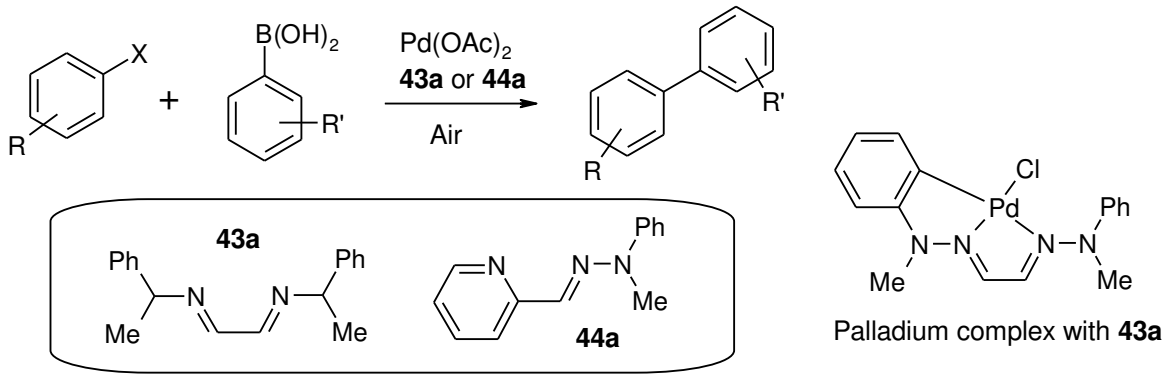



**Figure 7**: List of N, N-bidentate ligands used for Pd catalyzed cross-coupling reactions

The synthesis and properties of palladium complexes with hydrazone ligands have been previously reported[59] and hence Mino et al expected hydrazone ligands to have advantage over phosphine ligands due to their ease of synthesis and air stability. Hence, they have reported the Suzuki-Miyaura cross coupling reactions using glyoxal bis (N-methyl-N-phenyl-hydrazone) **43a** as a ligand of catalyst precursor.[60]

Glyoxal bis (N-methyl-N- phenyl-hydrazone) **43a** and its related compounds such as 2-pyridine-carboxaldehyde N-methyl-N-phenylhydrazone **44** were prepared and examined as ligands for the Suzuki-Miyaura cross-coupling reaction of aryl

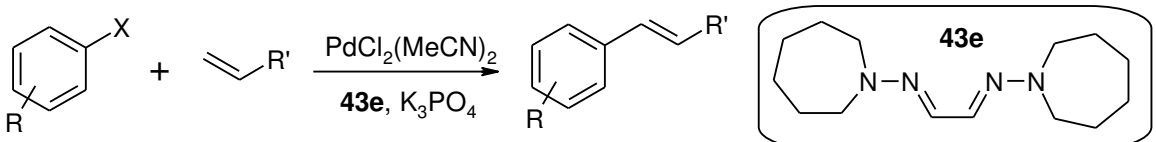
halides and aryl boronic acid under mild phosphine-free conditions with cesium carbonate in the DMF-water system under an aerobic atmosphere at room temperature.[61a]




**Scheme 36**: Suzuki reaction

Under low catalyst loading conditions, ligand **43b** gave a high turnover number and a high turnover frequency. $Pd(OAc)_2$/hydrazone **43** also showed a reactivity of the Suzuki-Miyaura reaction with aryl chloride such as that with 4-chloroacetophenone at 100°C.

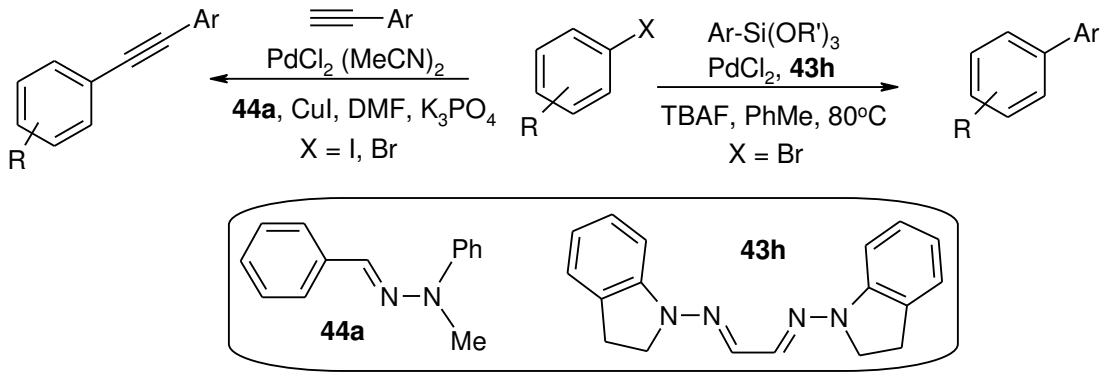
They have also reported Mizoroki-Heck cross-coupling reaction of aryl halides and olefins under phosphine-free conditions,[61b] based on $PdCl_2(MeCN)_2$/hydrazone **43f**. Under the condition of low catalyst loading ligand **43f** gave a high turnover number and turnover frequency. This palladium catalyst system shows the reactivity of the coupling reaction with 4-iodotoluene at room temperature and the reaction with electron-deficient aryl chlorides at 120°C.




X = I, DMF, 80°C
X = Br, Cl, NMP, TBAB, 120°C

**Scheme 37**: Heck reaction

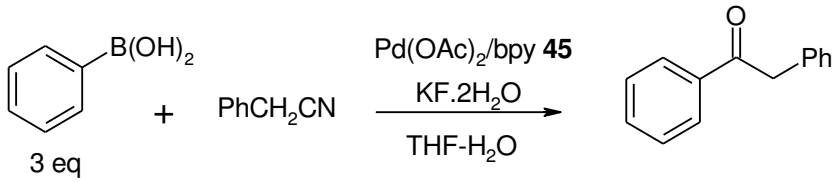
Moreover, palladium/copper catalyzed Sonogashira cross-coupling reaction of aryl halides with a variety of terminal alkynes under amine-free conditions in dimethylformamide at 80°C gave internal arylated alkynes using $PdCl_2(MeCN)_2$ with phosphine-free hydrazone **44a** as a ligand and CuI as the co-catalyst in good yields.[61c]




**Scheme 38**: Sonogashira and Hiyama reactions.

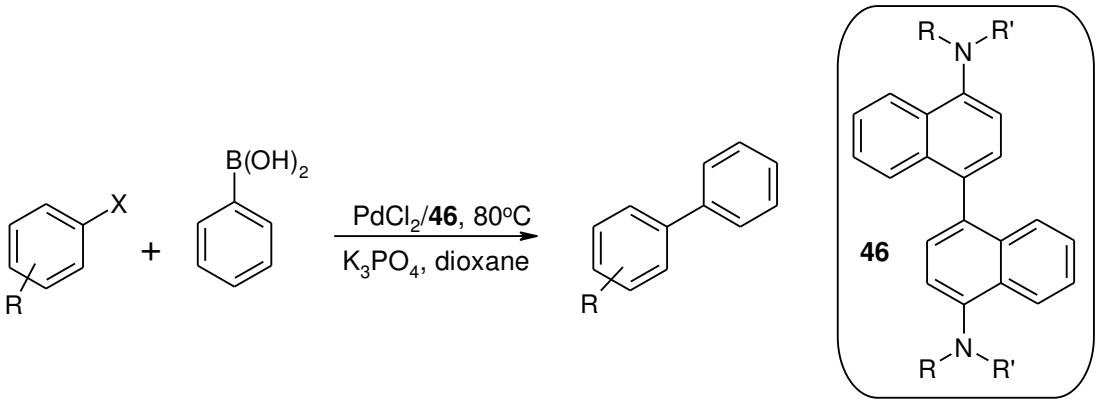
They have also found $PdCl_2$/hydrazone ligand **43h** in PhMe at 80°C was a phosphine-free efficient catalyst system for a Hiyama cross-coupling reaction of aryl bromides with aryl(trialkoxy)silanes in good yield (**Scheme 38**).[61c]

Lu et al. developed a Pd (II)-catalyzed addition of arylboronic acids to C-N bond in the presence of 2,2'-bipyridine as a ligand to yield aryl ketones with moderate to excellent yield.[62] The use of 2,2'-bipyridine, which may switch the arylpalladium species from more electrophilic to more nucleophilic, was crucial in this reaction (**Schem 39**).




**Scheme 39**: Palladium(II)-bipyridine **45** catalyzed addition of phenylboronic acid to phenylacetonitrile

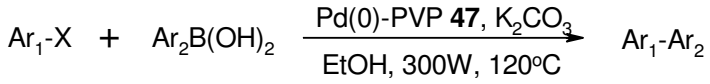
Transition-metal nanoparticles have attracted a great deal of attention in the last few years; their preparation, structure determination and applications are topic of current interest.[63] An important field of application for nanoparticles is that of catalysis due to their large surface area. Desmarets et al. have developed a novel and efficient catalyst system for the Suzuki- Miyaura reaction by using napthidine di(radicalcation)s-stabilized palladium nanoparticles as catalyst and $K_3PO_4$ as base in dioxane.[63] Stable Pd(0) nanoparticles were prepared at room temperature in 1,4-dioxane from $PdCl_2$ using N,N'-bis(4-methoxyphenyl)-(1,1'-binapthyl)-4,4'-diamine(napthidine) as reducing and stabilizing agent.




**Scheme 40**: Naphthidine di(radical cation)s-stabilized Palladium nanoparticles catalyzed Suzuki-Miyaura reaction

This procedure resulted in Pd(0) particles possessing an average diameter of ca 25nm stabilized against aggregation due to a barrier of the naphthidine di(radical cation) Napht.$^{2.2+}$ The organic/inorganic material thus produced was found air- and moisture stable allowing the reactions to be conducted under aerobic conditions. These particles were evaluated for their capacity to act as catalyst in Suzuki-Miyaura coupling reaction. This catalyst provides a general and convenient method to prepare biaryls from aryl bromides or iodides and aryl boronic acids with a broad range of functional groups in 1,4dioxane at 80$^{o}$C and under aerobic conditions.

Martins et al. have carried out microwave-assisted Suzuki cross-coupling reaction in ethanol utilizing a palladium colloidal solution stabilized by polyvinylpyrrolidone (PVP).[64] High isolated yields (75-97%) and high turnover numbers (up to $10^4$ to $10^5$/ h in 12 min x 750/h in 40min) were obtained using different bases, aryl halides and aryl boronic acids with a small loading of the palladium catalyst Pd(0)-PVP nanoparticles with 3-6 nm of medium diameter were prepared from $Pd(OAc)_2$ in the presence of the stabilizer PVP using methanol as the reducing agent.




**Scheme 41**: Pd(0)-PVP **47**-catalyzed Suzuki-Miyaura reaction

**(B) N,O-Bidentate ligand**

Yao et al. reported in 2003,[65a] that $Pd(OAc)_2$, albeit being very simple, could also efficiently catalyze the Heck reaction where the acetate anion was proposed to function as ligand. This interesting finding was consistent with the theory of Amatore and Jutand[65b] who claimed that coordination by anionic carboxylates could enhance the activity of Pd toward oxidative addition.

Prompted by Yao's pioneering discovery, Guo hypothesized that it was possible to design phosphine-free Pd catalysts more efficient, yet still low priced, than $Pd(OAc)_2$ by strategically incorporating an additional coordinating site into the acetate anion (**Figure 8**). This hypothesis was partly validated by their study on the use of amino acids as ligands for Pd-catalyzed Heck reactions[65c] and an earlier related study by Reetz et al.[65d]

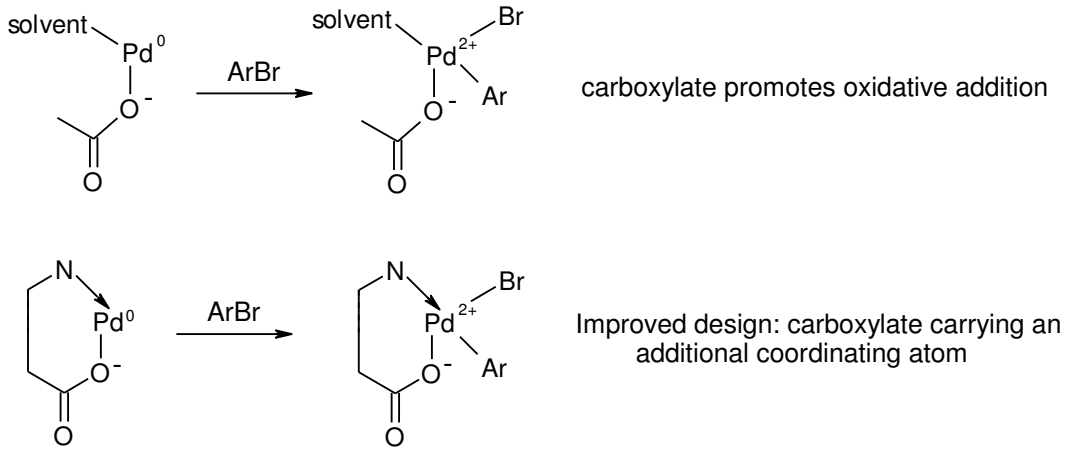
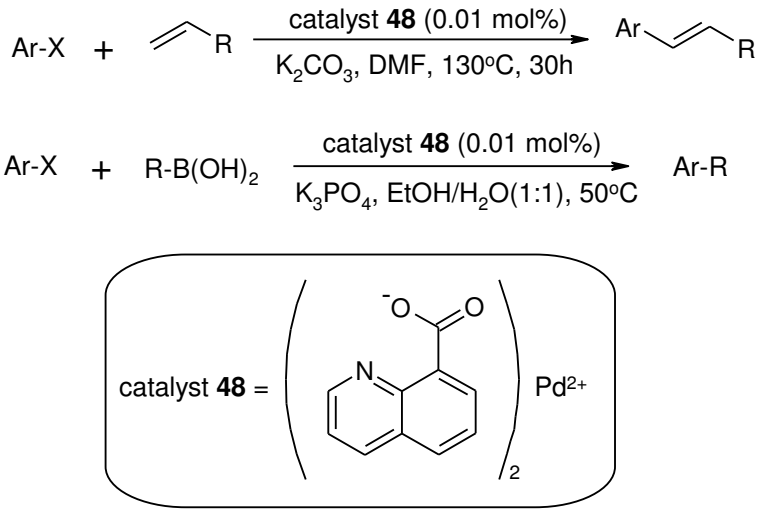


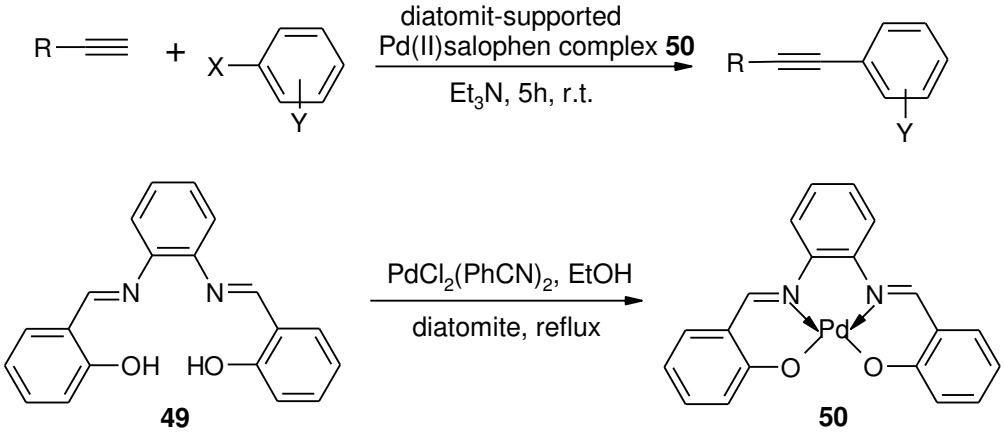

**Figure 8**: Improved Design of P-Free ligands for Pd catalysis by incorporating an additional coordinating atom

Therefore Guo et al. have extended search for more efficient phosphine-free ligands for Pd catalysis by systematically evaluating various N,O-bidentate compounds.[65e] Through detailed kinetic measurements they demonstrated the significant effect of incorporating as additional co-ordinating site into the acetate. They also found that Pd(quinoline-8-carboxylate)$_2$ **48** constituted one of the most efficient, yet low-priced, phosphine-free catalysts for the Heck and Suzuki reactions with fairly high turnover numbers up to ca 10,000 for unactivated aryl bromides.




**Scheme 42**: Heck and Suzuki reaction catalyzed by Pd(quinoline-8-carboxylate)$_2$ **48**

Bahramian et al. presented a new supported catalyst in which the Pd(II) salophen complex[66] **50** was immobilized on widespread natural diatomite by a simple procedure. This catalyst showed high activity for copper-free and solvent-free Sonogashira coupling reaction of alkynes with halobenzens and it could be recovered easily and reused many times. This novel supported catalyst is air-stable and all the reactions can be conducted in air. All these virtues indicated that the diatomite-supported catalyst has potential applications.




Preparation of the diatomite-supported Pd(II) salophen complex **50**

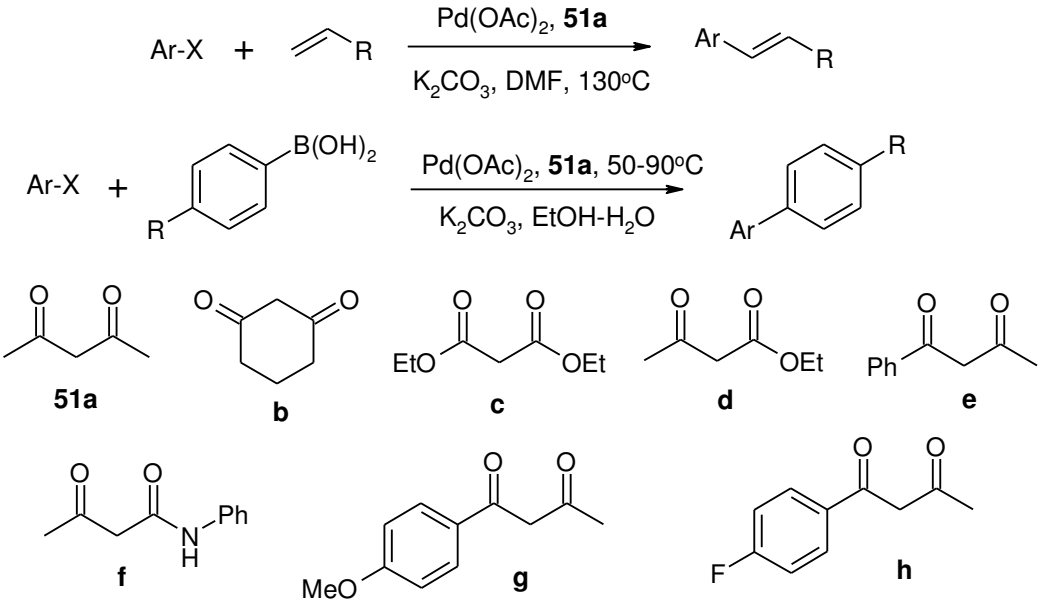
**Scheme 43**: Copper- and solvent-free heterogeneous Sonogashira reaction catalyzed by diatomite-supported palladium(II)salophen complex **50**

**(C) <u>O,O-Bidentate ligand</u>**

It is noteworthy to record that 1,3-dicarbonylcompounds were discovered in 2002 by Song and co-workers to be useful ligands for Cu-catalyzed Ullmann diaryl

ether synthesis.[67a] Soon Buchwald and Shafir discovered that a 1,3-dicarbonyl ligand could facilitate Cu-catalyzed C-N coupling reactions.[67b]

Despite these interesting reports, very little has been known about the effects of 1,3-dicarbonyl ligands in Pd-catalyzed transformations. Later on Guo et al. have found some 1,3-dicarbonyl compounds[67c] (such as pantane-2-4-dione and 3-oxo-N-phenybutanamide) to constitute highly efficient, yet low-priced and phosphine-free ligands for the Pd catalyzed Heck and Suzuki reactions of aryl bromides and iodides with very high turnover numbers ca ($10^3$-$10^4$). These systems provided clear evidence that 1,3-dicarbonyl ligands could assist Pd-catalyzed coupling reactions.




**Scheme 44**: 1,3-Dicarbonyl compounds **51** as phosphine-free ligands for Pd-catalyzed Heck and Suzuki reactions.

In summary, a 'library' of racemic and chiral non-racemic Betti bases is now readily available accessible and some of them are commercially available. The configurations of these bases is known and they offer us an handy tool for several occasions. Further the structure of the Betti bass can offer a building block that presents more than one stereogenic centre and can be obtained without any special effort. The catalytic activity of racemic Betti bases have been uncovered to a small extent. Here we present our efforts to explore some new applications of racemic and chiral non-racemic Betti bases.

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