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Rational Development of Practical Catalysts for Aromatic Carbon−Nitrogen Bond Formation

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During the past four years we have made considerable inroads toward our goal of developing general, reliable, and practical catalysts for the formation of aromatic carbon−nitrogen bonds by the cross-coupling of amines and aryl (and heteroaryl) bromides and triflates.[1] This Account details our progress and identifies the key features of the different catalyst systems which we have developed. John Hartwig and his group at Yale have also made substantial contributions to the area of metal-catalyzed aromatic carbon−heteroatom bond formation. As their work has recently been reviewed,[2] it will be mentioned only in the context of our own work.

Aromatic amines play a key role in a number of fields. These include pharmaceuticals,[3a] agrochemicals,[3b] photography,[3c] xeroxography,[3d] pigments[3e] and electronic materials.[3f] One of the most revealing facts is that in 1994's list of the twenty top-selling pharmaceuticals, a significant number contained aromatic carbon−nitrogen bonds.[4] The obvious importance of arylamines and the dearth of general methods for their synthesis (vide infra) enticed us to devise catalytic techniques for their synthesis.

The historical importance of aromatic amines, which is also reflected in their industrial relevance, spurred interest in developing methods for their production. Over the years a number of cleverly designed and extremely useful methods for aryl C−N bond formation have been reported.[5] None of these, however, are without their drawbacks in terms of harshness of the reaction conditions employed, generality, dependability, and cost. Among the most important developments in organic synthesis in the last 20 years has been the advent of palladium- and nickel-catalyzed cross-coupling procedures. This work, typified by methods developed by Kumada,[6] Stille,[7] Suzuki,[8] Negishi,[9] and others,[10] has had a major impact on aromatic carbon−carbon bond formation in academics and in industry. It was our goal to develop catalyst systems for aromatic carbon−heteroatom bond formation with the following characteristics: (1) They should be efficient and experimentally simple and operate under mild conditions. In particular we wished to avoid any requirement for the use of a glovebox. (2) They should be general for both electron-rich and electron-deficient aromatic systems. (3) They should be able to handle a wide variety of amine substrates. (4) They should demonstrate high levels of functional group compatibility. (5) They should be commercially available at a reasonable cost. (6) They should be able to operate with small quantities of catalyst and ligand. (7) They should handle Cl, Br, I, and OTf (and other sulfonate substrates). (8) The chemistry should be employable, hopefully by the same or similar procedures, on a very small (academics, medicinal chemists) or a very large scale (pilot plant, manufacturing). (9) In addition, we hoped that this chemistry would be readily adaptable for combinatorial chemistry applications.

Our chemistry built on the publication of Migita and co-workers in which they reported that *N*,*N*-diethylanilines could be prepared through the reaction of (*N*,*N*-diethylamino) tri-*n*-butylstannane with aryl bromides.[11] At the time our work began, we performed a Science Citation Index Search and found that, after 10 years, this paper had never been referenced in the primary literature! After some experimentation, we were able to completely reproduce the results described in the original Migita paper. We found in order to achieve high yields it was necessary to distill the (*N*,*N*-diethylamino) tri-*n*-butyl-

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Chart 1

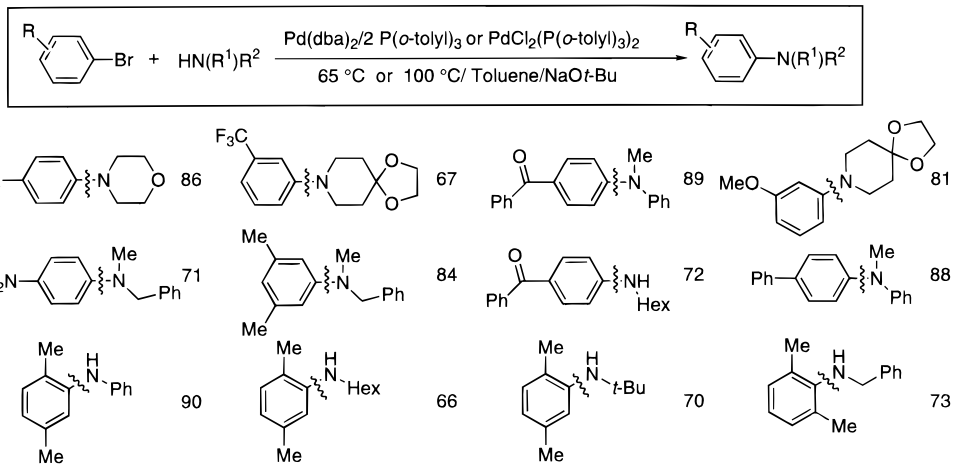
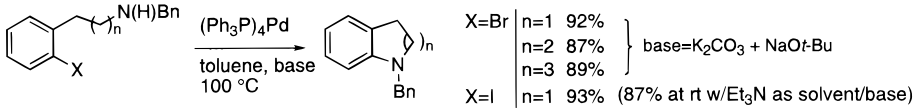
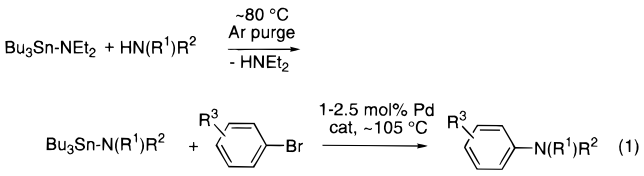


Chart 2



stannane and to handle it under anhydrous conditions, due to its moisture sensitivity.[12] That aminostannanes rapidly equilibrated with added amines[13] allowed us to employ distilled (*N*,*N*-diethylamino)tri-*n*-butylstannane as a general precursor to aminostannanes derived from a wide variety of secondary amines and primary and secondary anilines as is shown below. This was combined with the Migita protocol to provide the first general Pd-catalyzed cross-coupling methodology for the formation of aniline derivatives (eq 1).[1a]



While we were pleased with our initial results, there were significant limitations to the procedure which we had developed. In particular, the use of primary amines was problematic, and of course, the necessity to employ a stoichiometric quantity of tin reagent precluded its use on anything but a small scale. During the next few months we investigated the use of a variety of alternate main group complexes as surrogates for *n*-Bu_3Sn. While we had some success using aminoboron derivatives,[1b,12] all of these had limitations. Finally, we determined that the reaction could be carried out in the absence of a main group component when NaO*t*-Bu was employed as a base.[1b] The appropriate control experiments showed that in the absence of Pd catalyst no product was formed under the reaction conditions.

Some of the results which we were able to obtain are shown in Chart 1. As can be seen, the chemistry works for both electron-rich and electron-deficient aryl bromides. Primary amines work moderately well for electron-deficient and/or ortho-substituted substrates. Using this ligand system, however, the coupling of primary amines with other types of aryl bromides was inefficient.

It was also possible to extend this technique to heterocycles via cyclizations of amino bromides (Chart 2).[1b,e] While there were many similarities between the inter- and intramolecular processes, there were a few differences. First, $(Ph_3P)_4Pd$, which was ineffective for intermolecular processes, was an efficient catalyst for the intramolecular processes. Moreover, iodides were superior to bromides as substrates, in contrast to the intermolecular processes.

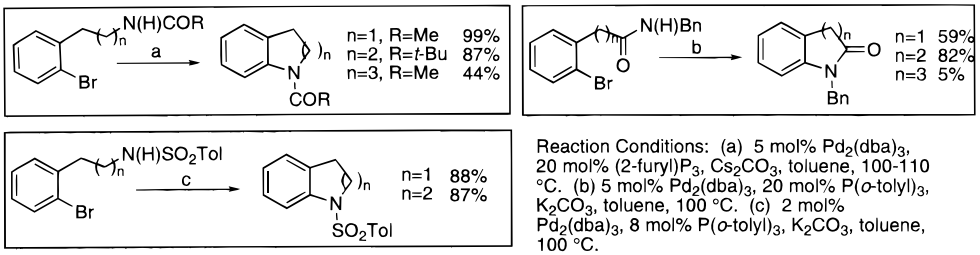
The reaction worked well for the formation of five-, six-, and seven-membered rings, but our few attempts to form eight-membered cyclic amines were fruitless. Interestingly, the cyclization of secondary amides and sulfonamides could be accomplished in moderate to good yield (Scheme 1), while we were unable to effect the analogous intermolecular processes.

Applications to the Synthesis of Indoles

We were interested in the application of this methodology to the synthesis of naturally occurring indoles. We felt that a combination of the aryl amination methodology with the zirconocene−benzyne chemistry previously reported from our laboratories[14] would be useful for the preparation of a variety of indoles.

First, we decided to look at intramolecular aryl amination processes as a means to form tricyclic indoles. Our general plan of attack is shown in Scheme 2.[1i,t] In route 1, zirconocene−benzyne chemistry was used to build the five-membered ring, and the six-membered ring was then formed using the aryl amination reaction. In route 2, the tack was reversed. The six-membered ring came from the zirconocene chemistry and was formed first. Subsequently, aryl amination was used to construct the five-membered ring.

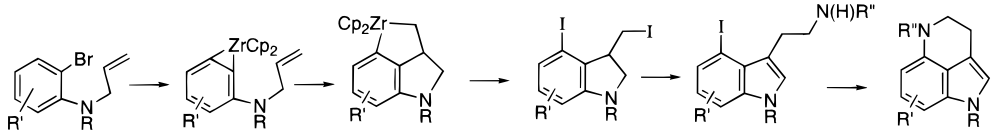
Scheme 1



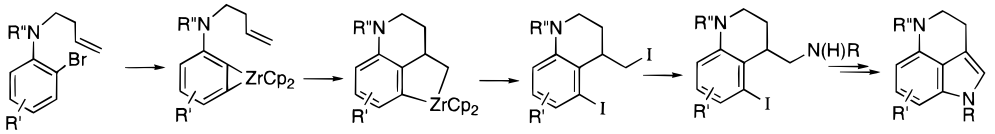
Reaction Conditions: (a) 5 mol% $Pd_2(dba)_3$, 20 mol% (2-furyl)P_3, Cs_2CO_3, toluene, 100-110 °C. (b) 5 mol% $Pd_2(dba)_3$, 20 mol% P(*o*-tolyl)$_3$, K_2CO_3, toluene, 100 °C. (c) 2 mol% $Pd_2(dba)_3$, 8 mol% P(*o*-tolyl)$_3$, K_2CO_3, toluene, 100 °C.

Scheme 2

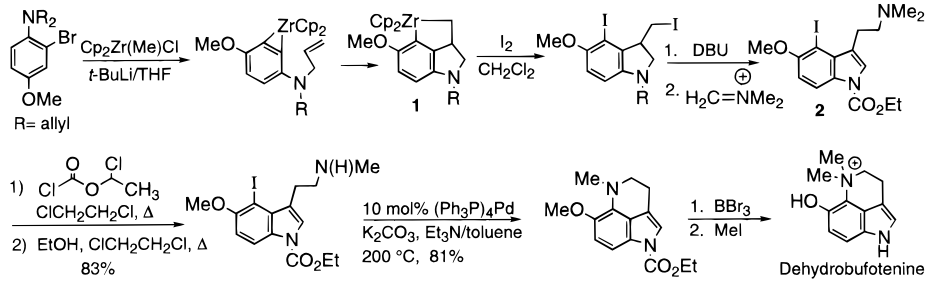
Route 1: The indoline ring is formed using Zr chemistry and the 6-membered ring is formed using Pd chemistry.



Route 2: The six-membered ring is formed using Zr chemistry and the indoline ring is formed using Pd chemistry.



Scheme 3

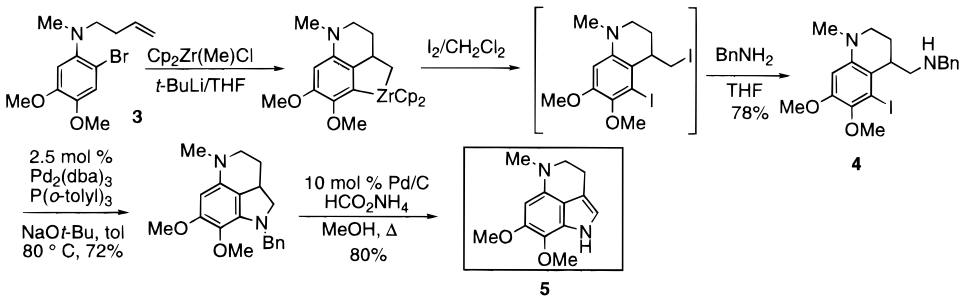


Our first target molecule, to be constructed according to route 1, was dehydrobufotenine, a toxin from a South American toad which has been shown to possess several interesting biological properties.[15] Beginning with 2-bromoanisidine, the requisite iodoindole derivative **2** could be constructed via zirconacycle **1** as shown in Scheme 3. Cleavage of one of the methyl groups from the *N*,*N*-dimethylamino moiety was accomplished using Olofson's reagent[16] to provide the substrate necessary for aryl amination. The formation of the tricyclic indole was accomplished using 10 mol % $(Ph_3P)_4Pd$ in the presence of K_2CO_3 in Et_3N/toluene at 200 °C. The high temperatures were required because the use of a stronger base (e.g., NaO*t*-Bu) caused cleavage of the carbamate protecting group. Nonetheless, the desired product was formed in 81% yield. Subsequent demethylation of the aryl ether with concomitant cleavage of the carbamate followed by quaternization of the 4-amino group provided the natural product.

We next wanted to demonstrate the viability of using route 2 and did so by constructing the tricyclic indole **5** (Scheme 4). The requisite aryl bromide **3** was prepared in three steps from 3,4-dimethoxyaniline. Application of our zirconocene−benzyne protocol followed by quenching the intermediate zirconacycle with iodine gave the diiodotetrahydroquinoline as shown. The crude diiodide was treated with benzylamine in THF at room temperature to afford the (aminomethyl)tetrahydroquinoline **4** in 78% overall yield from **3**. When **4** was subjected to the aromatic amination conditions, cyclization to the tricyclic indoline took place in 72% yield. Debenzylation with concomitant dehydrogenation gave the tricyclic indole **5** in 80% yield. Since **5** had previously been converted to the natural products makaluvamine C and damirone A and B,[17] this constituted a formal total synthesis of these natural products.

While the chemistry described above is a means to construct polycyclic indoles, we sought a simple means to form a more structurally diverse set of indoles. In this instance we focused on the use of titanocene−benzyne complexes as intermediates (Scheme 5).[18] These could be generated by successive addition of an aryl Grignard reagent and MeMgBr to titanocene dichloride. The olefin was added, and the reaction mixture was heated to produce the titanacycle. Bromination was accomplished, following a solvent exchange to CH_2Cl_2, to give 1,4-dibromides as is shown. These could be converted into indole derivatives by either of two methods. In most instances, simple application of standard catalyzed amination methodology gave the desired indolines. When the

Scheme 4



Scheme 5

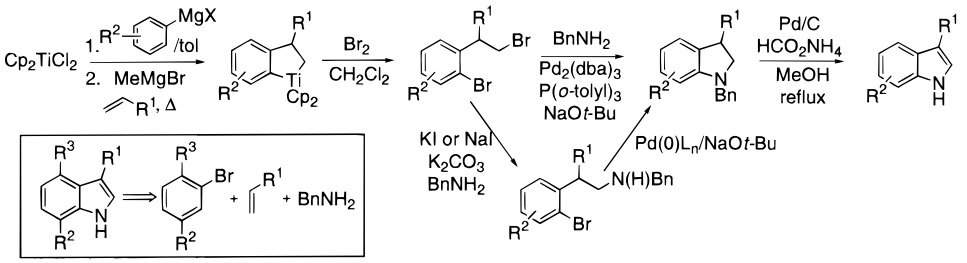
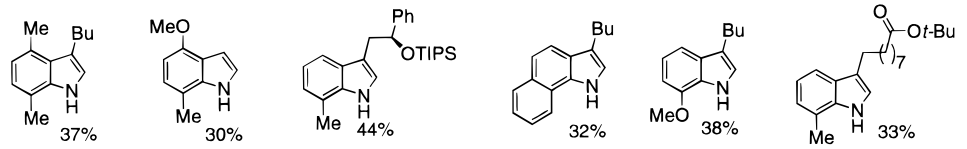


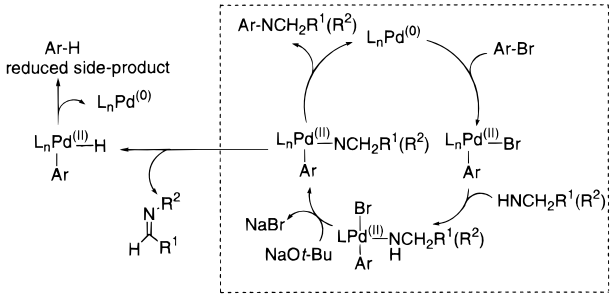
Chart 3



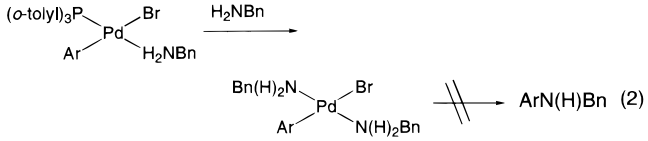
olefin employed was ethylene or in a few other cases, it was necessary to use an alternate strategy. The dibromide was converted to the amino bromide under Finkelstein-type conditions.[19] Subsequent Pd-catalyzed cyclization produced the indoline which could be converted to the final indole product as before. As is shown below, the overall transformation is the combination of an aryl bromide, a simple olefin, and benzylamine (as an ammonia surrogate) to form the indoles. Since a large number of the latter two components are commercially available, this method is applicable to the ready synthesis of a large variety of indoles; a representative sample is shown in Chart 3.[1s]

While the chemistry using *o*-tol$_3$P as the supporting ligand was a good starting point, there were some severe limitations. These included problems in many instances with reactions of primary amines and with several types of acyclic secondary amines (vide infra), an inability to utilize halopyridines or aryl triflates, and problems with aryl iodides. In addition, many of the reactions were slower than desirable and/or required higher quantities of catalyst than was desirable. An oversimplified reaction scheme for the Pd-catalyzed amination of aryl bromides is shown in Scheme 6. A plausible catalytic cycle, which is very similar to that postulated for other cross-coupling processes,[10b] is outlined in the dotted box. Oxidative addition of the aryl bromide to L$_n$Pd(0) complex gives the intermediate Pd(II) complex as shown.[20c] Metathesis of amine for bromide gives the key aryl amido intermediate.[1f,g,2] This can reductively eliminate to produce

Scheme 6



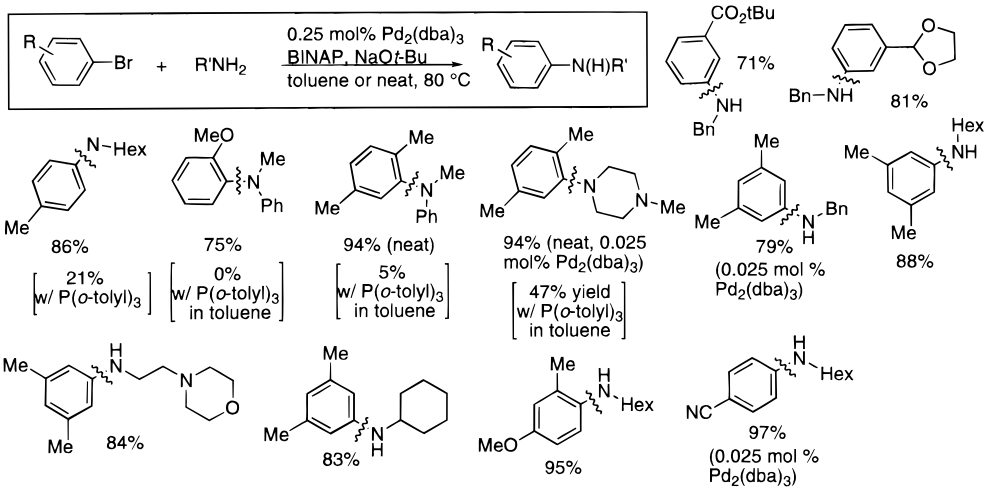
the desired aniline derivative and regenerate the Pd(0) catalyst.[21] Alternatively, in some instances, β-hydride elimination generates the imine, which can be identified by GC/MS, and the Pd(aryl) hydride complex. The latter reductively eliminates to produce reduced arene side product and regenerate the Pd(0) catalyst.[1b,22] In addition to β-hydride elimination, there appear to be several other deleterious side reactions which diminish the efficiency of the aryl amination process. In particular, our model studies suggest that the low yields realized in many reactions of primary amines with aryl bromides may result from the formation of bis-amine complexes (eq 2).[1c,h] An



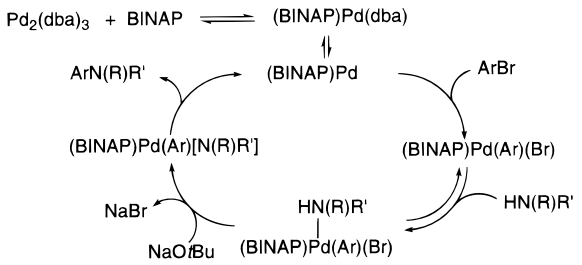
(2)

additional problem is that aryl iodides are not very good

Chart 4



Scheme 7



6

substrates in processes which utilize *o*-tol$_3$P.[1d] Thus, we wished to develop a process which could rectify these three problems but would still utilize readily available components.

During our studies of the coupling of enantiomerically pure amines with aryl bromides (vide infra), we found that BINAP[23] (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) was a particularly effective supporting ligand for the Pd-catalyzed aryl amination processes.[1c] This was somewhat surprising for two reasons. First, we had previously tried to utilize simple chelating phosphines such as DPPE (1,2-bis(diphenylphosphino)ethane), and these attempts were unsuccessful.[12] Second, kinetic studies of the reaction employing *o*-tol$_3$P indicated that it was desirable to have only one phosphine bound to the Pd center at any given time.[20] With the finding that this was not necessarily the case, we undertook a somewhat detailed survey of substrate combinations which were not tenable substrates in processes which used *o*-tol$_3$P.

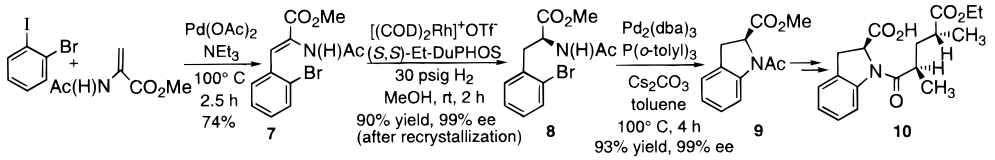
Shown below are several examples of products derived from the Pd-catalyzed coupling of primary amines with aryl bromides utilizing BINAP as a supporting ligand (Chart 4).[1c] As can be seen, in several cases there is a dramatic improvement in the yield. In particular, primary amines can be utilized in many instances in which their coupling reactions were inefficient using *o*-tol$_3$P.

Our view of the reaction scheme when BINAP is employed as a ligand is shown in Scheme 7. Of importance is that, in contrast to chemistry seen when *o*-tol$_3$P is used as the ligand, all of the key intermediates have two phosphines bound to the Pd and are hence either four- or five-coordinate. For example, we believe that the substitution of the amine for the bromide proceeds via the five-coordinate intermediate **6** shown. A strong base is required to deprotonate the coordinated amine and drive the reaction to completion. That the results with BINAP are so different than those found with *o*-tol$_3$P warns against mechanistic generalizations.

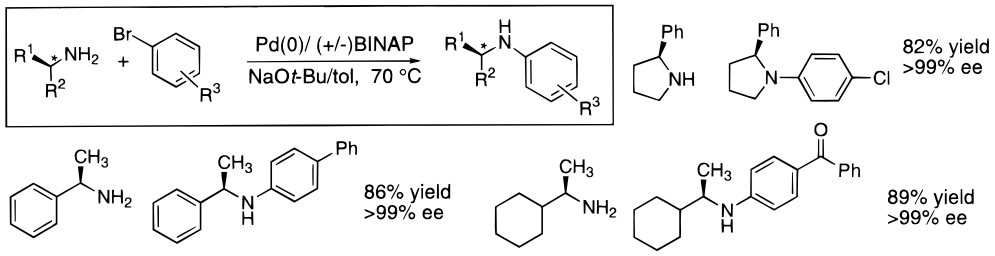
Contributing to the efficacy of BINAP are that (1) the rate of β-hydride elimination of the aryl amido intermediate is slow compared to reductive elimination to form arylamine,[24] (2) its use minimizes the formation of Pd(amine)$_2$(Ar)X complexes[1h] and bridging halide complexes, thereby directing a greater proportion of the Pd to catalytically active intermediates which lead to the desired product, and (3) BINAP is an exceptional ligand for Pd, $\leq$1.5:1 ratio of ligand:Pd is usually employed. In many cases this ratio can be close to 1:1. In contrast, other chelating phosphines are often used at ratios as high as 4:1.[25] Moreover, the catalyst loading needed by the BINAP system is usually much lower than that employing other ligands. This greatly aids in the isolation of the desired amine product. For many substrate combinations, procedures employing BINAP are significantly more effective than those employing other ligands. While optically active BINAP is expensive, the finding that ($\pm$)-BINAP is usually a suitable surrogate has led to its commercial availability.[26]

As part of our work on the intramolecular carbon−nitrogen bond formation processes, we thought it would be interesting to examine the cyclization of an enantiomerically pure substrate.[1j] We chose to do this in the context of preparing **9**, which had previously been used as an intermediate in the synthesis of the ACE inhibitor **10**.[27] For reasons of ease of synthesis, we chose the acetamide **8** as our substrate for cyclization. This was readily prepared in enantiomerically pure form as shown in Scheme 8. A diastereoselective Heck arylation[28] produced enamide **7**[29] which could be asymmetrically hydrogenated using Burk's DuPhos methodology.[30] Cyclization was accomplished in 93% yield, with no erosion of

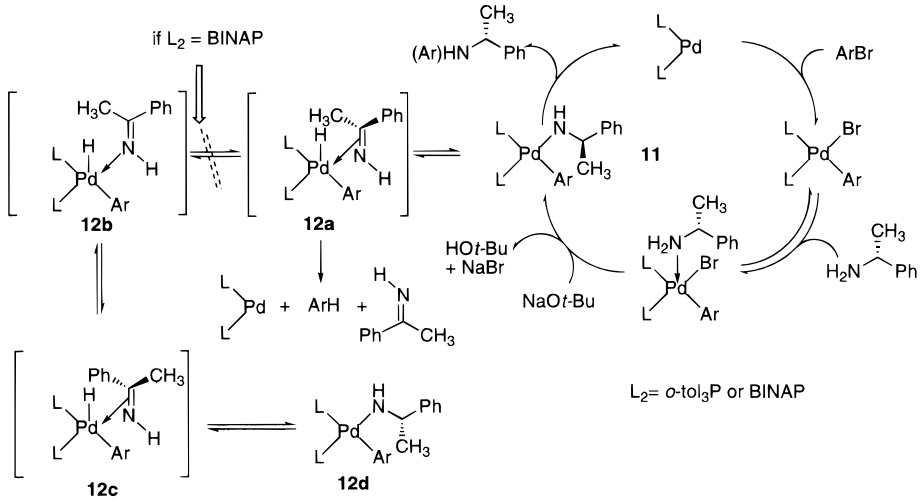
Scheme 8



Scheme 9

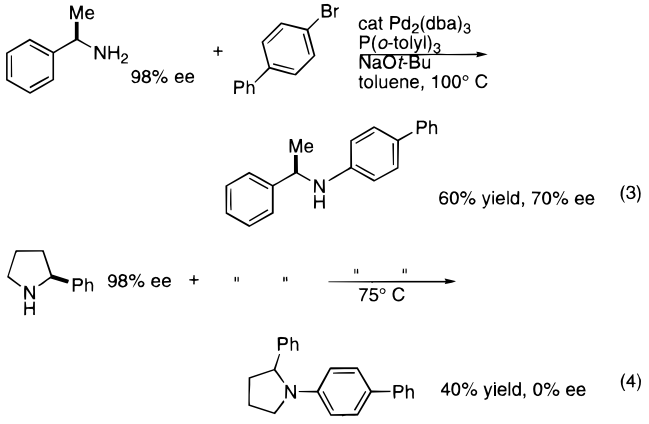


Scheme 10



enantiomeric purity using the conditions shown below (Scheme 8).[1j] Thus, this constituted a formal total synthesis of **10**.

A logical extension was to prepare enantiomerically pure *N*-arylamines by an intermolecular coupling protocol.[1j] We were quite surprised when we found in our original attempts, shown in eqs 3 and 4, that the *N*-arylated



products which were formed had lower levels of enantiomeric purity than the starting amines. Fortunately, we found that substitution of (*rac*)-BINAP for *o*-tol$_3$P gave a process which was both higher yielding and completely stereospecific (Scheme 9). A detailed mechanistic study of the coupling of enantiomerically pure amines with aryl bromides was carried out.[1j]

The findings from this study indicated that racemization was occurring by a β-hydride elimination−facial isomerization−reinsertion sequence (Scheme 10, **11** → **12a** → **12d**). When BINAP was used as the supporting ligand, this process was shut down. We speculate that this is due to an inability of the π-bound imine **12a** to facially equilibrate to **12c**.[31] The rearrangement **12a** → **12b** → **12c** requires that the methyl group rotate past the very bulky diphenylphosphino moiety of BINAP and is thus disfavored.

A second class of substrates for which (*o*-tol)$_3$P is unsuitable as the supporting ligand are halopyridines. Pyridine has previously been shown to form catalytically inactive *trans*-bis(pyridyl)palladium complexes when this ligand is used.[20a,32] We found that by employing chelating bisphosphines, bromopyridines can be efficiently converted to their amino derivatives.[1k] The success of these

Chart 5

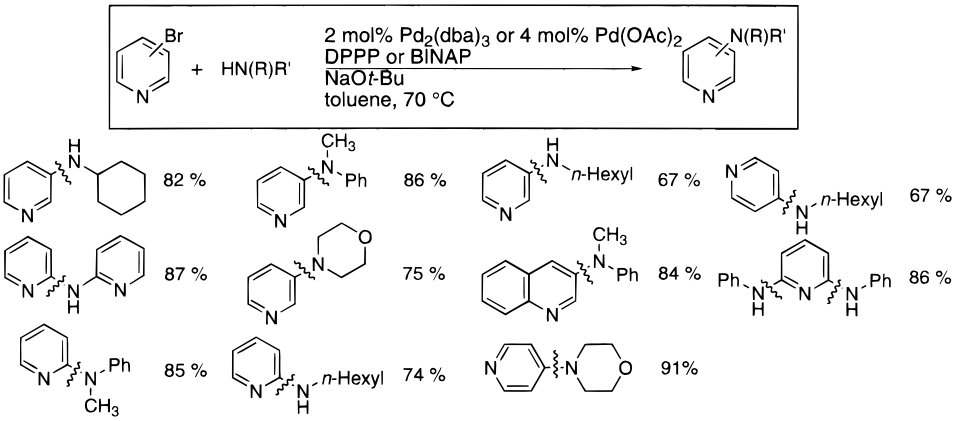
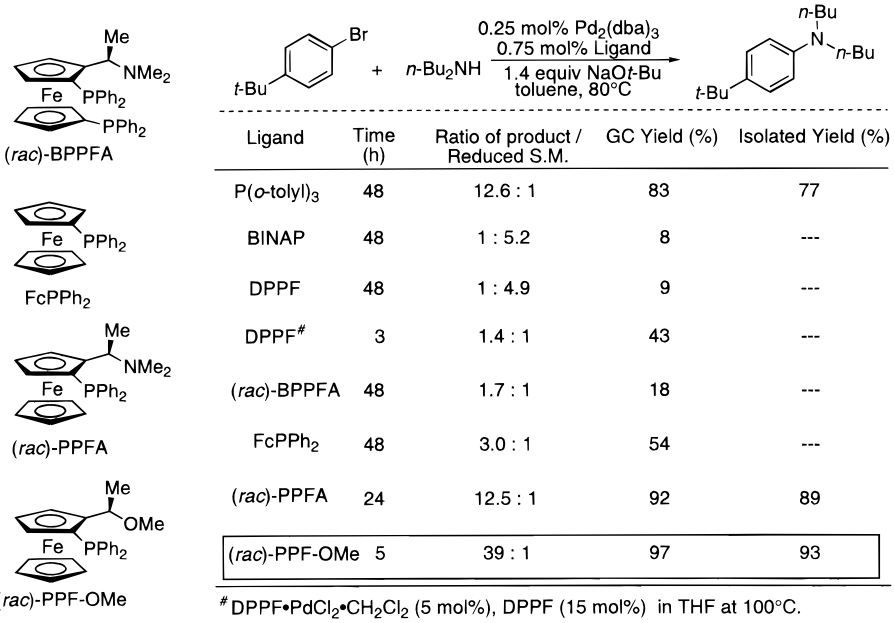


Chart 6



Ligand	Time (h)	Ratio of product / Reduced S.M.	GC Yield (%)	Isolated Yield (%)
P(*o*-tolyl)$_3$	48	12.6 : 1	83	77
BINAP	48	1 : 5.2	8	---
DPPF	48	1 : 4.9	9	---
DPPF[#]	3	1.4 : 1	43	---
(*rac*)-BPPFA	48	1.7 : 1	18	---
$FcPPh_2$	48	3.0 : 1	54	---
(*rac*)-PPFA	24	12.5 : 1	92	89
(*rac*)-PPF-OMe	5	39 : 1	97	93

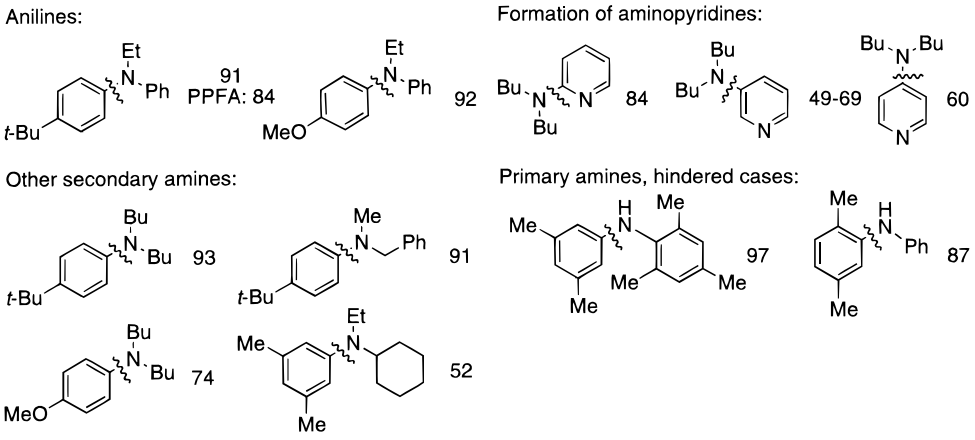
[#] $DPPF•PdCl_2•CH_2Cl_2$ (5 mol%), DPPF (15 mol%) in THF at 100°C.

ligands is due to their resistance to ligand substitution by pyridine. Shown in Chart 5 are representative examples of aminopyridines prepared using this methodology. Of importance is that these processes work for 2-, 3-, and 4-bromopyridines with anilines as well as primary and secondary amines. The simple chelating bisphosphine DPPP (1,3-bis(diphenylphosphino)propane) could be employed in some instances. BINAP, however, proved to be a more generally satisfactory ligand.

One class of substrates for which this process was ineffective was acyclic secondary amines. The failure to successfully handle this important class of amine substrates, it turned out, plagued all of the known catalyst systems which employed chelating bisphosphine ligands.

We began our search for a ligand which would handle acyclic secondary amines by investigating the use of Hayashi-type ferrocenyl ligands.[33] That this was a logical starting point was predicated on their ease of preparation and the ready availability of many structural variations. Our test reaction, shown in Chart 6, was the combination of 4-*tert*-butylbromobenzene and di-*n*-butylamine. We decided to use a moderate catalyst level (0.5 mol % Pd, 0.75 mol % ligand) so that any success realized could be immediately transformed into a useful procedure. It was interesting that the use of *o*-tol$_3$P gave better results than did BINAP or DPPF. Another interesting feature was that while the use of DPPF and BINAP gave nearly identical results under our standard conditions, by employing the conditions used by Hartwig (5 mol % Pd, 20 mol % DPPF),[25] the yield increased significantly, although it was still about half of that realized when *o*-tol$_3$P was employed. The use of Hayashi's BPPFA[33] also gave disappointing results. The simple ferrocenyl(diphenyl)phosphine was substantially better. BPPFA functions similarly to DPPF, and we felt that better results might be obtained using a different type of chelating ligand. To this end we examined the use of the ferrocenylamine PPFA.[33] To our delight, use of this ligand gave results superior to those which we had previously realized.[1q] Use of the related ferrocenyl ether PPF−OMe[33] led to the shortest reaction times and highest yields of all the ligands investigated. Some representative results for couplings of acyclic secondary amines with aryl bromides using PPF−OMe are shown in Chart 7. Of particular note are the couplings

Chart 7



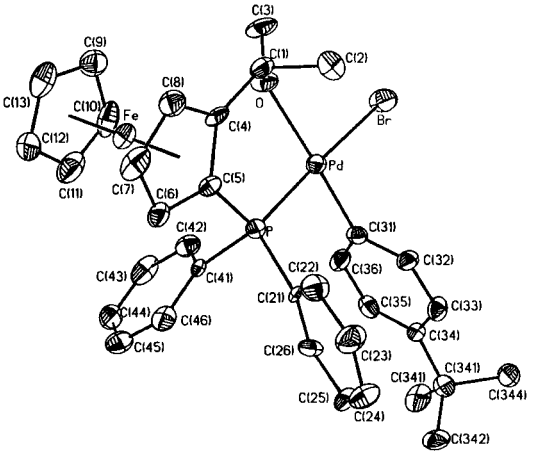
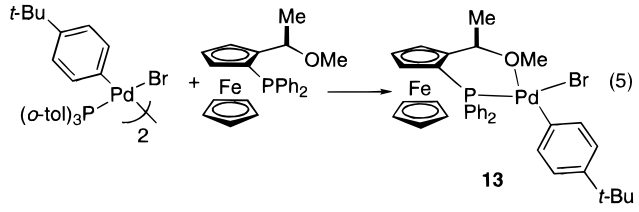


FIGURE 1. X-ray structure of **13**.

of di-*n*-butylamine with 4-bromoanisole and 4-*tert*-butylbromobenzene which take place in good to excellent yield.

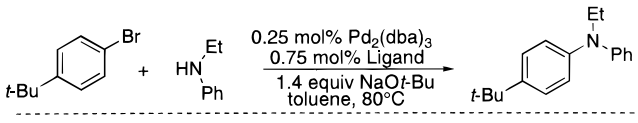
To probe the structural effects which contribute to the enhanced efficiency of PFF−OMe, we first chose to examine the structure of the Pd complex **13**, which was prepared as shown in eq 5. A single-crystal X-ray structure

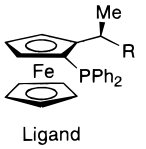


revealed that the O−Pd bond distance was 2.215 Å, indicative of a very strong dative interaction (Figure 1).[34] In the ^{1}H NMR of **13** in $CDCl_3$ the −OMe signal was shifted downfield by ∼1 ppm relative to the corresponding signal in the ^{1}H NMR spectrum of the free ligand. This provided a strong indication that PPF−OMe is a chelating ligand in solution as well as in the solid state. The difference between PPF−OMe and, e.g., BINAP or DPPF is that only one of the two donor groups of the chelating ligand is a phosphine.

In an attempt to understand the reason behind the efficacy of PPFA and PPF−OMe, we investigated the effect

Chart 8





R	Reaction Time (h)	Yield (%)
OMe	5	91
NMe_2	12	84
PPh_2	20	50 (GC)

of changing R for the coupling reaction shown in Chart 8. As R was changed from Ph_2P− to Me_2N− to MeO−, a monotonic increase in the yield of the reaction and rate of the reaction was seen.[35] These results correlate with the σ-donating capability of R, which decreases in the same order: Ph_2P− > Me_2N− > MeO−. In the product-forming step, reductive elimination to form the aniline, the Pd center changes from the formal oxidation state of +2 to 0. Thus, electron-donating substituents should disfavor this process. This sort of effect on the relative rates of reductive elimination is well-known.[36]

While PPF−OMe is an excellent ligand for amination reactions using acyclic secondary amines, it is not generally useful for other types of amines. As an example, reactions with primary amines are particularly inefficient. This result is not entirely unexpected; since the ether oxygen is loosely bound to the Pd center, it is readily displaced by sterically unencumbered primary amines. As a result, catalytically inactive bisamine complexes are formed.[1h] In accord with this notion is that the reaction of aniline with 3,5-dimethylbromobenzene proceeds in low yield, while the same process with the very hindered 2,4,6-trimethylaniline proceeds in near quantitative yield. We presume that the steric bulk of 2,4,6-trimethylaniline precludes the formation of bisamine complexes.

One desirable goal was the development of a catalytic aryl amination protocol which could be conducted at room temperature. This would render this chemistry more easily adaptable to rapid throughput screening methods or combinatorial chemistry. Moreover, we hoped that a greater degree of functional group compatibility would be realized. During mechanistic studies on these

Chart 9

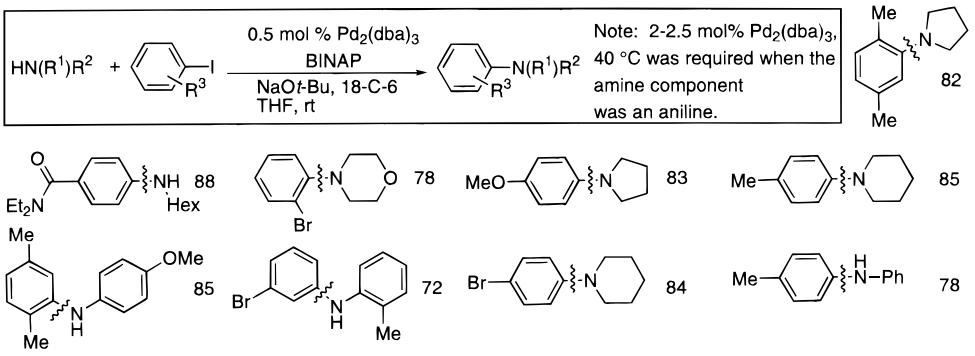
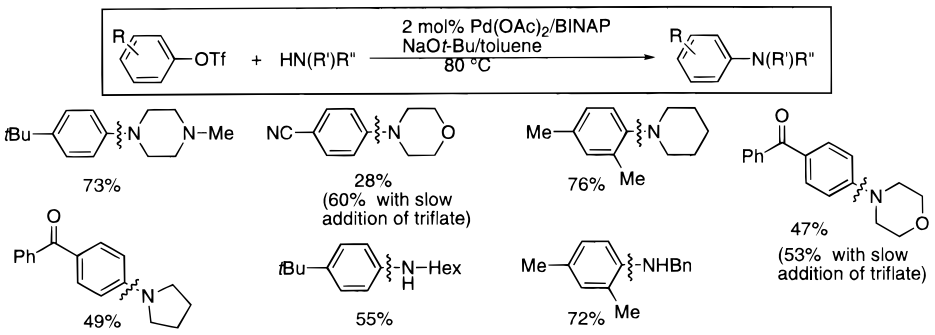


Chart 10



amination reactions, we noticed that the addition of 18-crown-6 significantly increased the rate of the reaction.[32] Our supposition was that this additive was increasing the rate of formation of the Pd−N covalent bond. Therefore, we chose to study the reactions of aryl iodides, substrates for which the oxidative addition reaction is fast.[36] We undertook a study of the effect of crown ethers and polyether additives and solvents on the rate of formation of arylamines from aryl iodides. A variety of different additives were tested, and the use of a stoichiometric quantity of 18-crown-6 gave superior results. Using the conditions shown a number of aryl iodides could be efficiently transformed to anilines (Chart 9).[11] Among the examples were the first successful instances in which the selective substitution of a bromide in the presence of an iodide could be effected. The reactions of anilines, which are less nucleophilic than aliphatic amines, required a temperature of 40 °C and a higher catalyst loading (4−5 mol % Pd). This is consistent with our notion that Pd−N bond formation is rate-limiting for the reactions of aryl iodides under these conditions. To our great disappointment, however, this protocol did not exhibit a greater degree of functional group tolerance than those conducted at 80 °C.

It is interesting that the combination of NaO*t*-Bu and 18-crown-6 gave equal or better results than when the combination NaO*t*-Bu and 15-crown-5 or KO*t*-Bu and 18-crown-6 were used; at present we have no good explanation for this result.

The net conversion of a phenol to an aniline is a transformation of great importance. An obvious extension of our aryl amination methodology was to employ sulfonate substrates such as triflates. In papers published back-to-back last year, we[1m] and Hartwig's group[37] reported that the triflate to aniline transformation could be accomplished using conditions similar to those employed for aryl bromide substrates (Chart 10). What was disappointing, in our work, was that, in almost every instance, the yields for the reactions of the aryl triflates were lower than those realized for the corresponding aryl bromides. This was particularly true in the case of triflates derived from electron-deficient phenols. The major problem was the competitive cleavage of the triflate to the phenol by attack at sulfur by NaO-*t*-Bu. In some cases the yields could be improved by slow addition of the triflate to the reaction mixture, a protocol developed by the Hartwig group.[37] Unfortunately, this had little effect in most instances that we tried. This left the development of a truly general protocol for the amination of aryl triflates an open problem.

In our work on the amination using acyclic secondary amines we ascribed the greater efficacy of PPF−OMe to the decreased σ-donating capability of an ether oxygen relative to a triarylphospine. While considering this notion, we realized that this implied that the Pd(II) center in the intermediate shown below should be more strongly Lewis acidic than for an analogous bisphosphine complex and would therefore bind an amine more tightly (Figure 2) which, in turn, would acidifiy the hydrogen of the bound amine. Hence, we reasoned that in this case we might be able to successfully employ a milder base. In fact, we found that Cs_2CO_3 functioned as a suitable base when PPF−OMe was employed in the amination of aryl bromides.[1o] Subsequently we also found that Cs_2CO_3 could be used in procedures which employed BINAP in instances in which the aryl bromide was electron defi-

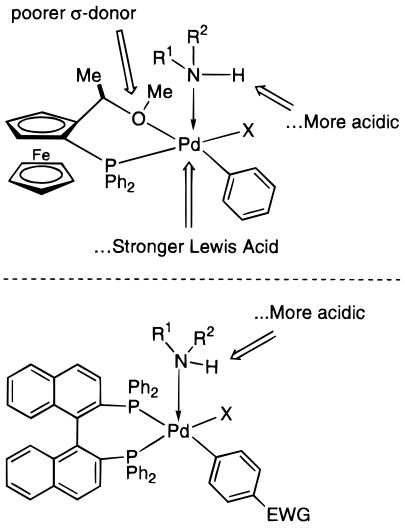


FIGURE 2. Rationalization for efficacy of Cs_2CO_3 in Pd-catalyzed amination procedures.

cient.[38] This led to the protocol shown in Chart 11. Of great importance was that this new protocol offered a much higher degree of functional group compatibility than had previously been possible for a Pd-catalyzed aryl amination. For example, methyl and ethyl esters, enolizable ketones (for aniline nucleophiles), and aromatic nitro groups, all previously incompatible functional groups, were now tolerated. Of interest in the latter case was that we could selectively substitute a *p*-bromide over an *o*-chloride, selectivity which is complementary to that normally observed for nucleophilic aromatic substitution processes.[5a]

We were very pleased when we determined that a procedure employing Cs_2CO_3 could also be employed for the amination of aryl triflates (Chart 12).[1r] This greatly improved protocol had two significant advantages. First, competitive cleavage of the aryl triflates was virtually eliminated in most instances. Thus, triflates derived from electron-deficient phenols now were among the best substrates; the yields were 2−3 times what we had been able to obtain using the procedure employing NaO*t*-Bu. Second, as in the case of aryl bromides, we saw a very large gain in the utility of the method due to increased functional group compatibility. Again, aryl triflates with methyl and ethyl esters were excellent substrates. Aryl triflates containing enolizable ketones could also be utilized in moderate yields with aliphatic amines and in good to excellent yields with anilines. The ability to utilize milder bases and the increased functional group toleration which was seen represents one of the most important practical advances in the aryl amination methodology.

It is interesting to point out that prior to the success described above, we had examined protocols using Cs_2CO_3 numerous times. Somehow, our empirical approach had missed what our more rational approach was able to find!

Aryl chlorides are another desirable class of aromatic substrates, due to their wide availability and low cost. After several attempts to utilize Pd catalysts for the amination of aryl chlorides, we investigated the use of low-valent nickel complexes (Chart 13).[1p] We found the combination of $Ni(COD)_2$ and DPPF comprised a catalyst which was able to effect the desired amination of aryl chlorides at 70−100 °C in toluene in the presence of NaO*t*-Bu. This procedure worked well for a number of important classes of aryl chlorides including *ortho*-substituted, electron-rich and -deficient, 3- and 4-chloropyridines. The high cost of DPPF along with its tendency to complicate workup procedures, gave us incentive to search for a better alternative. We found that 1,10-phenanthroline was a good surrogate. This was a major improvement as this nitrogen heterocycle is relatively inexpensive and can be easily removed from the products of the amination reaction. One drawback was that this procedure necessitated the use of pyridine as the solvent. We next sought to eliminate the need to use $Ni(COD)_2$. This complex, while commercially available, is expensive and air-sensitive. We found that we could use $(DPPF)NiCl_2$ in conjunction with MeMgBr,[39] although, of course, this reintroduced the problem of using an expensive phosphine. Finally, we were able to couple pyrrolidine with 4-chlorotoluene using $(1,10\text{-phenanthroline})NiCl_2$[40]/2MeMgBr as the catalyst (albeit in pyridine).

Despite some effort, we were unable to develop a useful procedure for the direct preparation of primary anilines using the Pd-catalyzed methodology. During our work on the preparation of monodisperse oligoanilines, we found

Chart 11

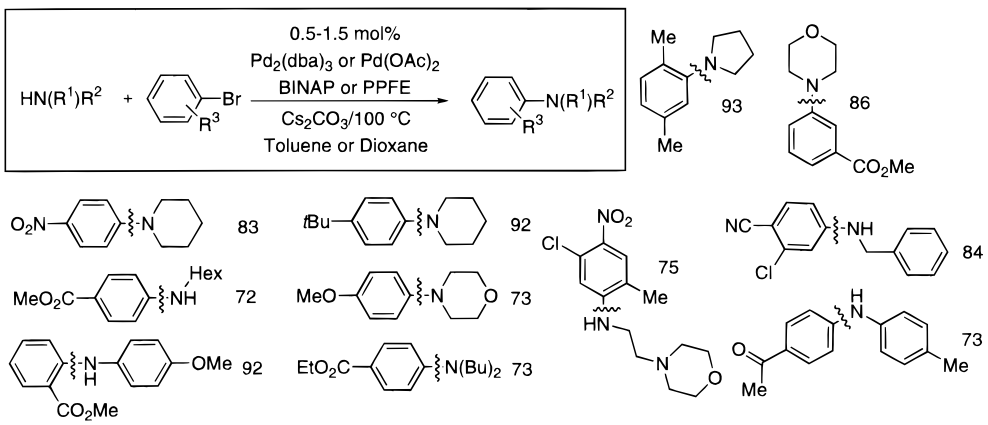


Chart 12

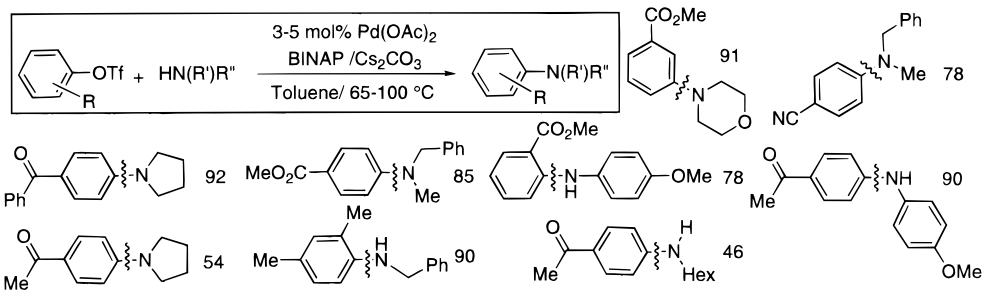


Chart 13

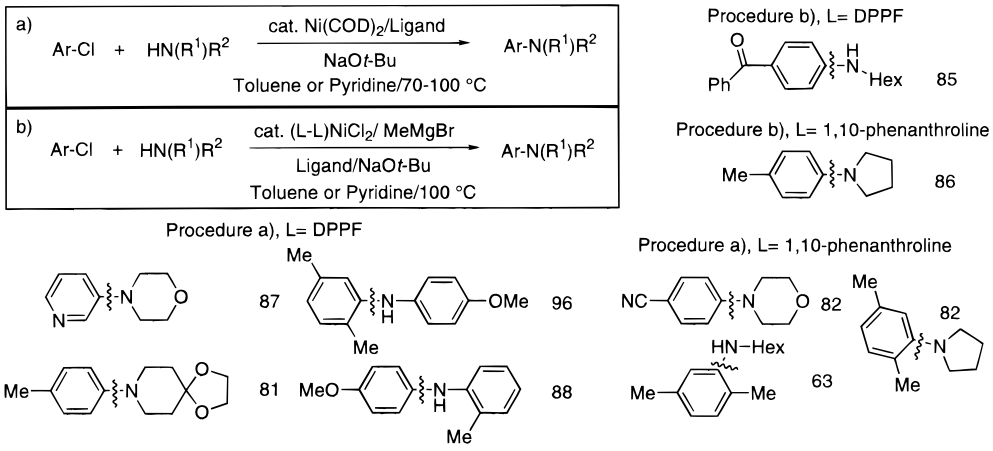
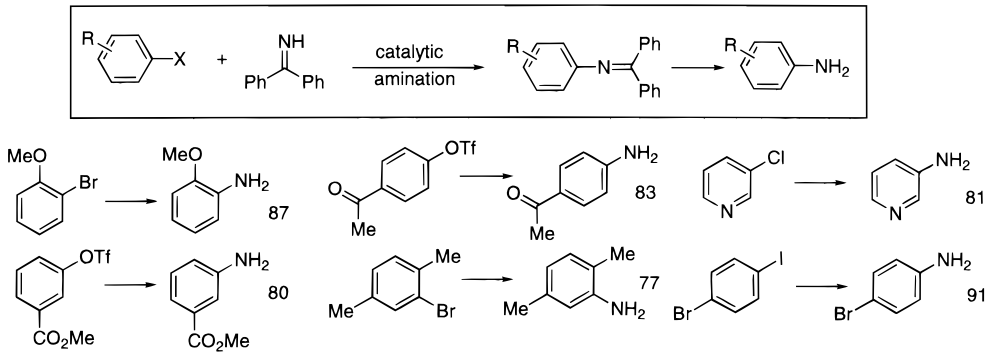


Chart 14



that the benzophenone imine group was a good surrogate for a primary amine.[41] We wondered whether we could directly construct this protected aniline derivative by cross-coupling the commercially available ammonia/benzophenone condensation product with an aryl halide or triflate substrate. Our initial experiments indicated that this idea was well founded (Chart 14).[1n] In fact, as is indicated in the examples shown below, this coupling is among the most general and high yielding that we have uncovered (Chart 14). In order for the coupling procedure to be of any use, it is necessary to have simple, reliable methods for the liberation of the primary aniline. We found that we could do this by three orthogonal techniques: (1) Pd-catalyzed transfer hydrogenation using ammonium formate,[42a] (2) treatment with hydroxylamine under mildly acidic conditions,[42b] or (3) hydrolysis with aqueous acid.[42c] As can be seen, these procedures worked well with bromides, chlorides, iodides, and triflates and were compatible with a very wide range of functional groups. Alternately, the intermediate *N*-aryl benzophenone imine products may be easily isolated by recrystallization from methanol.

In summary we have developed a series of catalyst systems which are highly efficient for the synthesis of aniline derivatives by cross-coupling of amines and aryl bromides, chlorides, iodides, and sulfonates. The substrate scope with respect to the amine as well as the aromatic component is quite broad. The title this Account was chosen because the work has involved the combination of design, empirical discovery, and mechanistic studies almost always necessary for important discoveries to be made and converted to useful processes. Moreover, it represents another example where attention to concepts and the practical realities of both organic synthesis and organometallic chemistry is required to achieve optimum results.

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