2-Furyl Phosphines as Ligands for Transition-Metal-Mediated Organic Synthesis

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I. Introduction

The construction of carbon−carbon and carbon−heteroatom bonds by transition-metal-mediated organic processes has become fundamental to the science of synthetic organic chemistry over the past three decades. In recent years there have been a multitude of new synthetic methods, catalysts, and reagents developed to aid in the construction of an overwhelming variety of chemical structures. In particular, the search for catalysts which exhibit higher reactivity or greater efficiency has become an extremely active area of chemical research. It has long been recognized that judicious placement of ancillary ligands in the coordination sphere of a metal

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Neil G. Andersen was born in Calgary, Alberta, Canada, in 1972. After obtaining his B.Sc. degree from the University of Calgary in 1995, Neil continued on under the direction of Professor Brian A. Keay and received his Ph.D. degree in December of 2000. His graduate research centered around the development of new axially stereogenic 2-furylphosphine ligands for asymmetric catalysis. Neil is currently an Alberta Heritage Foundation for Medical Research (AHFMR) postdoctoral fellow at Stanford University under the direction of Professor Barry M. Trost.

Brian A. Keay was born in 1955 and received his Ph.D. degree in 1983 from the University of Waterloo (Canada) working with Professor R. Rodrigo. After a Natural Sciences and Engineering Research Council of Canada (NSERC) postdoctoral fellowship with Professor E. Piers (University of British Columbia, Canada), he joined the faculty at the University of Windsor (Canada) as an Assistant Professor. In 1989, he moved to the University of Calgary, where he is now a Professor. In 1996, he was awarded the Merck Frosst Centre for Therapeutic Research lecture Award by the Canadian Society for Chemistry. His research interests include the design and synthesis of asymmetric ligands for use as catalysts or substrate-bound chiral auxiliaries with Lewis acids and transition metals, palladium-catalyzed polyene cyclizations, asymmetric intramolecular Diels–Alder reactions, and the synthesis of natural products.

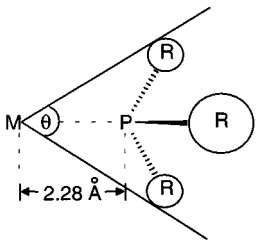
can govern the steric, electronic, and physical properties of a coordinated species, thereby effecting the system's catalytic activity. Of the ligands employed for this purpose, perhaps no general classification is more ubiquitous to organic chemistry than tertiary phosphines. However, the choice of which phosphorus(III) ligand to employ for a given synthetic transformation is indeed a topic of great complexity. Several efforts have been made to classify phosphorus ligands according to steric size and electron-donor ability, and although these parameters have been successfully correlated to observed chemical reactivity, a priori prediction of which phosphine will be best for a given purpose is still not a reality. Moreover, the selection of the right catalytic system is often complicated by other factors such as choice of solvent, reaction temperature, the use of additives, and the identity of the catalyst precursor. Hence, to determine which phosphine is best suited for a particular reaction, it is often necessary to rely on a trial and error type screening process. For example, in the late 1980s, Farina and co-workers reasoned that electron-poor ligands may be beneficial for the palladium(0)-catalyzed Stille cross-coupling reaction.[1] Experimental screening of a variety of weakly donating ligands subsequently confirmed the hypothesis, and tri-2-furylphosphine (TFP) was thus identified as an exceptional Stille ligand. On the basis of this landmark discovery, numerous other workers have since screened TFP in a variety of transition-metal-catalyzed reactions. This review begins with a brief look at the steric and electronic properties of phosphorus(III) ligands with special attention being paid to phosphines bearing the 2-furyl group. Following this discussion, the use of TFP as a ligand for transition-metal-mediated synthesis is exhaustively reviewed.[2] The development of new 2-furyl phosphorus ligands is the topic of the final section.

A. Quantification of the Steric and Electronic Properties of Phosphorus Ligands

Clearly, the steric and electronic properties of a tertiary phosphine can dramatically influence the reactivity of a metal center and lead to marked changes in chemical reactivity. The steric bulk and electron-donor ability of a ligand are difficult properties to quantify, and indeed, the two properties are closely related. For example, as the steric bulk of the R groups in a tertiary phosphine of type PR_3 are increased, it is expected that the intervalence angles about the phosphorus atom will increase. Such a structural change would thereby reduce the s-character of the phosphorus lone pair orbital, making the ligand more Lewis basic. Therefore, it is often difficult to separate steric and electronic effects with respect to phosphorus donor ligands since the two factors are so intimately related.

Tolman suggested, using a geometrical parameter known as the cone angle,[3] classifying phosphorus ligands according to size. For phosphines of type PR_3, the cone angle is defined as the apex of a cylindrical cone, centered 2.28 Å from the center of the phosphorus atom, which radiates out toward the R groups and just touches the van der Waals radii of the outermost atoms[4] (Chart 1). In cases where the R

Chart 1. The Tolman Cone Angle



groups contain internal degrees of freedom, the Tolman cone is taken to be the minimum angle which satisfies the condition that all of the R groups are completely contained within the geometrical con-

Table 1. Tolman Cone Angle (θ^c) for a Variety of Phosphines and Phosphinites[3]

ligand	cone angle (θ^c)	ligand	cone angle (θ^c)
PH_3	87°	P(*p*-Tol)$_3$	145°
P(OMe)$_3$	107°	P(*m*-Tol)$_3$	165°
PMe_3	118°	PCy_3	170°
P(OPh)$_3$	128°	P(O-*t*-Bu)$_3$	172°
PEt_3	132°	P(*t*-Bu)$_3$	182°
TFP	133°	P(C_6F_5)$_3$	184°
P(CF_3)$_3$	137°	P(*o*-Tol)$_3$	194°
PPh_3	145°	P(mesityl)$_3$	212°

Table 2. Electronic Parameter ν for a Variety of Phosphines and Phosphinites[8]

ligand	ν (cm^{-1})	ligand	ν (cm^{-1})
PF_3	2110.8	P(*p*-Tol)$_3$	2066.7
P(C_6F_5)$_3$	2090.9	P(*o*-Tol)$_3$	2066.6
P(OPh)$_3$	2085.3	PMe_3	2064.1
PH_3	2083.2	PEt_3	2061.7
P(OMe)$_3$	2079.5	PBu_3	2060.3
PPh_3	2068.9	PCy_3	2056.4
P(*m*-Tol)$_3$	2067.2	P(*t*-Bu)$_3$	2056.1

struct. For unsymmetrical phosphines or chelating diphosphines, the concept of cone angle is not as clear, however. Tolman proposed how an effective cone angle for such ligands could be defined.[3] Although the cone angle definition seems to be rather arbitrary, the values obtained by Tolman (Table 1) have been successfully correlated to the physical and spectroscopic properties as well as the chemical reactivity of a variety of coordination compounds.[3] However, based on Tolman's definition, it is hard to justify the large discrepancy between the PPh_3 cone angle (145°) and the P(C_6F_5)$_3$ cone angle (184°) given that the H and F atoms are similar in size.[5] As would be expected from the size of a 2-furyl group relative to a phenyl substituent, the cone angle of 133° measured for TFP[6] is slightly smaller than the triphenylphosphine cone angle.

To quantify the electron-donor ability of phosphine ligands, Strohmeier[7] and Tolman[8] proposed that the CO stretching frequencies of monosubstituted transition-metal carbonyls could be used as a measure (Table 2). Ligands of high donor ability cause a greater degree of back-bonding from the metal center into the CO π^* orbitals and hence give rise to a decreased CO bond order. Conversely, weakly donating ligands result in decreased M−CO back-bonding, which in turn gives rise to higher CO stretching frequencies. As a standard measure, the A_1 carbonyl mode of Ni(CO)$_3$L complexes, where L is the monodentate phosphine ligand, can readily be determined with an accuracy of ± 0.3 cm^{-1}. Such complexes are conveniently prepared upon mixing Ni(CO)$_4$ and the phosphine ligand in a 1:1 molar ratio at room temperature. Unfortunately, the electronic parameter ν for tri-2-furylphosphine (TFP) has not been reported in the literature.

Alternatively, Allen and Taylor showed that the $^1J(^{31}P-^{77}Se)$ coupling constant of phosphorus selenides may be used as a measure of the parent phosphine basicity.[9] An increase in the magnitude of the $^{31}P-^{77}Se$ coupling constant in these compounds has been shown experimentally and theoretically to correspond to an increase in s-character of the phosphorus lone pair. In other words, the phosphorus selenides of poorly donating phosphines exhibit larger $^1J(^{31}P-^{77}Se)$ coupling constants than the corresponding phosphorus selenides of electron-rich phosphines (Table 3). In light of the close relationship which exists between the steric bulk of the phosphine R groups and the s-character of the phosphorus lone pair, the $^{31}P-^{77}Se$ coupling constant method gives a remarkably reliable measure of phosphine basicity. Fortunately, the magnitude of the $^1J(^{31}P-^{77}Se)$ coupling constant seems to be predominantly controlled by the electronic properties of the R groups rather than the overall steric size of the phosphine. For example, the $^1J(^{31}P-^{77}Se)$ coupling constants for $Ph_3P{=}Se$ and Ph_2(*o*-Tol)P═Se shown in Table 3 are very similar even though the Tolman cone angles for these two phosphines are 145° and 161°, respectively. From the data in Table 3, it can be seen that an additive effect is observed in the $^{31}P-^{77}Se$ coupling constant upon the systematic replacement of phenyl groups in PPh_3 with 2-furyl or 2-thienyl groups. Moreover, these two heteroaryl groups are electron withdrawing relative to the phenyl substituent. As a result, 2-furyl and 2-thienyl phosphines are poorer σ-donor ligands. In the absence of synergic bonding, these ligands would then be expected to more easily dissociate from a metal center. However, the σ withdrawal of electrons away from the phosphorus atom by the heteroaryl groups causes the system to compensate by transferring electron density from the filled metal d orbitals into the π^*-antibonding orbitals of the ligand. In other words, 2-furyl[10] and 2-thienyl[11] phosphines can act as a π-acids. Clearly, this effect would be more pronounced for late transition metals in low oxidation states.[12]

Table 3. $^{31}P-^{77}Se$ Coupling Constants for Various Phosphine Selenides ($R_3P{=}Se$)[9]

PR_3	^1J (Hz)	PR_3	^1J (Hz)
P(*p*-$MeOC_6H_4$)$_3$	708	PPh_2(2-furyl)	754
PPh_2(*o*-Tol)	730	P(2-thienyl)$_3$	757
PPh_3	732	PPh_2(*m*-$CF_3C_6H_4$)	766
PPh_2(2-thienyl)	743	PPh(2-furyl)$_2$	774
PPh(2-thienyl)$_2$	752	P(2-furyl)$_3$	793

Numerous alternative methods have been devised for assessing phosphine basicity, including ^{31}P NMR shift correlation,[13] $^1J[^{31}P-^{195}Pt]$ coupling constant magnitude,[14] lone pair ionization potential,[15] and gas-phase basicity.[16] Unfortunately, these methods have not been applied to TFP or other 2-furylphosphine ligands.

In 1988, several years after the first synthesis[17,18] and characterization[19] of the TFP ligand, Farina and co-workers tested this phosphine in a Stille cross-coupling[1] with the hope that TFP's low electron-donating ability toward palladium(II) would accelerate the rate of reaction. This pioneering study, which constituted the first time TFP had been used in a metal-catalyzed reaction, subsequently led to the widespread use of tri-2-furylphosphine as a Stille ligand and further investigations in other metal-catalyzed processes.

B. Coordination Chemistry of Tri-2-furylphosphine (TFP)

The in situ generation of TFP catalyst systems has been studied in considerable detail by Amatore and Jutand.[20] These workers demonstrated that mixtures of $Pd(dba)_2$ and *n*TFP in DMF and THF lead to the formation of $Pd(dba)(TFP)_2$ as the major complex, which exists in equilibrium with the solvated adducts $SPd(TFP)_3$ and $SPd(TFP)_2$. Moreover, the less ligated complex $SPd(TFP)_2$ has been shown to be the reactive species in the oxidative addition with phenyl iodide. In DMF and THF, the mechanism of catalyst formation and oxidative addition is governed by the equations shown in Chart 2. The overall reactivity of

Chart 2. Equations Describing Complexation of TFP with $Pd(dba)_2$

$$Pd(dba)_2 + 2TFP \longrightarrow Pd(dba)(TFP)_2 + dba \quad (1)$$

$$Pd(dba)(TFP)_2 + S \rightleftharpoons SPd(TFP)_2 + dba$$

$$K_1 = \frac{[SPd(TFP)_2][dba]}{[Pd(dba)(TFP)_2]} \quad (2)$$

$$Pd(dba)(TFP)_2 + TFP \rightleftharpoons SPd(TFP)_3 + dba$$

$$K_0 = \frac{[SPd(TFP)_3][dba]}{[Pd(dba)(TFP)_2][TFP]} \quad (3)$$

$$SPd(TFP)_3 \rightleftharpoons SPd(TFP)_2 + TFP$$

$$K_2 = \frac{[SPd(TFP)_2][TFP]}{[SPd(TFP)_3]} = K_1/K_0 \quad (4)$$

$$SPd(TFP)_2 + ArX \longrightarrow ArPdX(TFP)_2 + S \quad k \quad (5)$$

{$Pd(dba)_2$ + *n*TFP} in the oxidative addition of phenyl iodide depends on both the intrinsic rate constant *k* of oxidative addition and the concentration of the reactive species $SPd(TFP)_2$. The value of *k* increases with phosphine basicity, but the concentration of $SPd(TFP)_2$ depends on the values of the two equilibrium constants K_1 and K_0. The two controlling factors can indeed be antagonist, thereby leading to a nonlinear correlation between ligand donor ability and catalyst reactivity. Employing ^{31}P NMR analysis, UV spectroscopic studies, and electrochemical experiments, Amatore and Jutand showed that in DMF, {$Pd(dba)_2$ + *n*TFP} is always more reactive than {$Pd(dba)_2$ + *n*PPh_3} for $n \geq 2$. However, in THF, {$Pd(dba)_2$ + *n*TFP} is only more reactive than {$Pd(dba)_2$ + *n*PPh_3} when $n > 6$. Clearly, factors such as solvent composition and molar ratio of Pd:L can have a significant impact upon the overall kinetics of a TFP-mediated catalytic cycle.

C. Catalyst Preparation

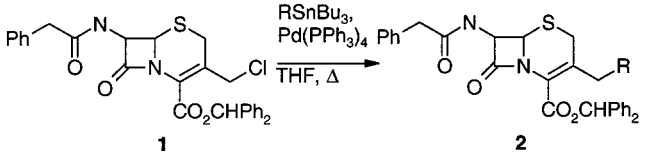
Although $Pd(TFP)_2Cl_2$ has been isolated and characterized,[21] nearly all of the reactions reported employing the TFP ligand involve in situ catalyst generation. In the case of palladium-catalyzed reactions, standard Pd(0) sources such as $Pd(dba)_2$, $Pd_2(dba)_3$ and $Pd_2(dba)_3 \cdot CHCl_3$ are frequently used with Pd:L ratios in the range from 1:1.5 to 1:6. To our knowledge, no studies have been conducted which compare the use of preformed TFP catalysts to those generated in situ. Moreover, the thermal stability of TFP-derived catalysts relative to conventional PPh_3 systems remains to be studied. Although many authors have noted that Pd(0)/TFP catalysts seem to possess greater longevity than Pd(0)/$AsPh_3$ species, this observation has unfortunately not been studied quantitatively for any synthetic transformation.

II. Use of TFP as a Ligand in Metal-Catalyzed Reactions

A. Discovery of TFP as an Exceptional Ligand for the Stille Reaction

In 1988, during a research program directed toward the preparation of 3-substituted cephalasporin derivatives for antibiotic screening, workers at Bristol-Myers[1] sought to couple 3-chloromethylcephem **1** with various organostannanes using the Stille protocol[22] (Scheme 1). Using the standard $Pd(PPh_3)_4$

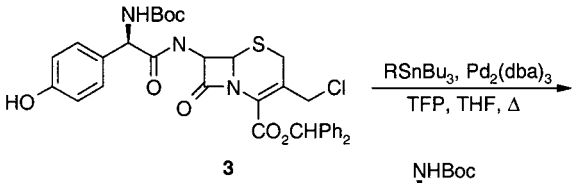
Scheme 1



1 **2**

catalyst system in refluxing THF gave poor yields of the desired cross-coupled products **2** and very slow reaction rates.[1] Changing the cross-coupling conditions to include higher boiling, more polar solvents or additives[23] failed to improve the reaction yield. Faced with these results, Farina postulated that the use of less coordinating, poorer donating phosphine ligands should render the Pd(II)−allyl intermediate more electrophilic and hence more reactive in the rate-determining[24] transmetalation step. On the basis of Allen's study of tri-2-furylphosphine,[9,25] Farina and co-workers decided to test the TFP ligand in the Stille reaction. To their delight, use of a $Pd_2(dba)_3$/TFP catalyst system with **3** in refluxing THF efficiently afforded the desired cross-coupled products **4**−**8** (Scheme 2). Moreover, a 45-fold rate enhancement was observed when lactam **3** was coupled with

Scheme 2



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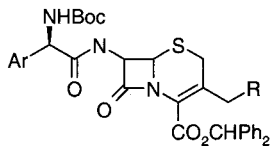


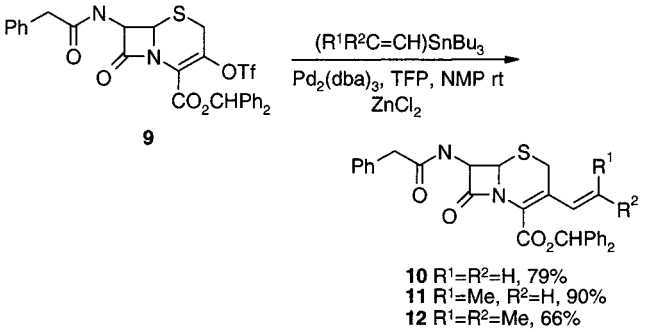
4-8

R	Time (h)	Yield (%)	Product
vinyl	3	82	**4**
Z-propenyl	16	78	**5**
2-methylpropenyl	72	60	**6**
1,2,2-trifluorovinyl	72	65	**7**
1-ethoxyvinyl	2	71	**8**

vinyltributylstannane in the presence of the tri-2-furylphosphine catalyst system.[1]

In a related study[26] aimed at developing an efficient synthesis of antibiotic BMY-28100,[27] Farina showed that the beneficial effects observed upon substitution of TFP for PPh_3 in the Stille reaction may be of general scope. Treatment of vinyl triflate **9** with a variety of organostannanes at room temperature in NMP using $ZnCl_2$ and the TFP catalyst system smoothly afforded the desired cross-coupled products **10**−**12** in moderate to excellent yields[28] (Scheme 3).

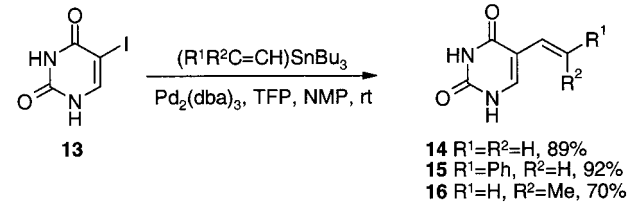
Scheme 3



Performing the reaction with triphenylphosphine required elevated reaction temperatures and resulted in extensive decomposition of the starting triflate. Using TFP as the palladium ligand afforded a ca. 17-fold rate enhancement and allowed for a much milder set of conditions to be employed. The synthetic power of the Stille cross-coupling reaction, in conjunction with the TFP rate enhancement, makes this methodology the first general, economically viable route to 3-substituted cephalosporin antibiotics.

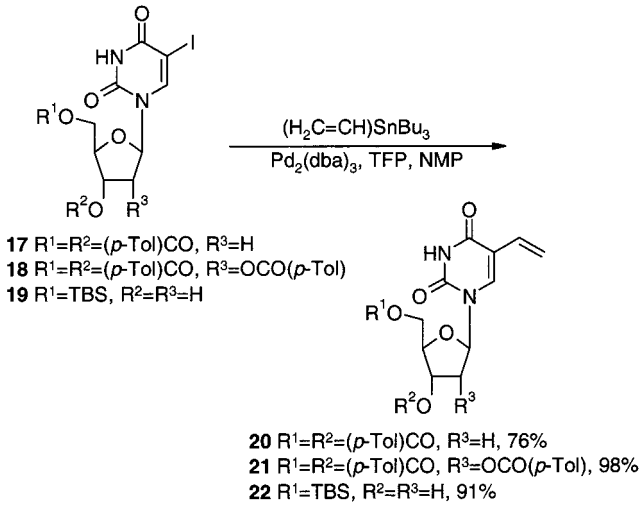
The favorable effects of using TFP in the Stille coupling of organoiodides was later demonstrated by Farina in a project aimed at the synthesis of thymidylate synthetase inhibitors for cancer chemotherapy.[29,30] Treatment of 5-iodouracil (**13**) with a variety of stannanes and the TFP catalyst system at room temperature smoothly furnished the desired coupled products **14**−**16** in moderate to excellent yields (Scheme 4). Literature conditions for coupling

Scheme 4



vinyliodides and stannanes[31] were found to be unsatisfactory in the present case. Farina subsequently determined that the TFP catalyst system could be effectively employed for the derivatization of 5-iodouridine and deoxyuridine precursors **17**−**19** (Scheme 5). The coupling conditions were tolerant toward ester and silyl ether protecting groups on the sugar moiety as well as an unprotected hydroxyl group. Use of mild reaction conditions in conjunction with the

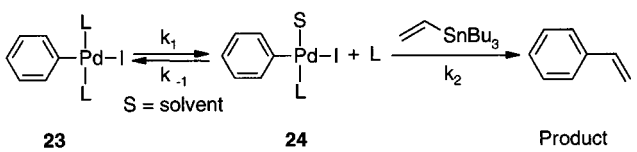
Scheme 5



TFP catalyst system was required for obtaining coupled products **20**−**22** in synthetically useful yields.

After these findings, Farina systematically studied the use of poor donating ligands such as TFP and triphenylarsine in a diverse range of Stille cross-coupling reactions.[10,32] This vigorous kinetic study conclusively showed that large rate enhancements, typically 10^2−10^3 over triphenylphosphine-based catalysts, are observed with TFP and Ph_3As (Table 4). While observed ligand effects in the Stille reaction had previously been attributed to steric origin,[22] Farina's results clearly demonstrate that no correlation exists between the relative rates of coupling and the Tolman cone angle. In addition, the results confirm that ligands of low donor ability generally afford less stable catalyst systems. For example, the $P(C_6F_5)_3$ ligand (entry 5) gives a catalyst which completely decomposes under the conditions of the reaction within 2 min but affords a 13.2% yield of the desired product as determined by HPLC analysis.[10] Although triphenylarsine (entry 6) generally yielded the fastest coupling rates, Farina noted that the Ph_3As catalyst was found to be less stable than the TFP-derived species. Hence, ligands of intermediate electronic availability, which strike a compromise between increased reactivity and decreased stability, are likely to serve as the best cross-coupling catalysts. Farina further showed that free ligand inhibits the Stille reaction and that the degree of inhibition was greater for ligands of high donor ability (Table 4). To account for this observation, it was postulated that a preequilibrium exists between the fully coordinated species **23** and a coordinatively unsaturated intermediate **24** (Scheme 6).[10,33] Ligands of high electron-

Scheme 6



donating ability therefore impede the reaction by lowering the concentration of the reactive species **24**. As can be seen from the data in Table 4, ligands

Table 4. Relative Rates of Stille Coupling between Iodobenzene and Vinyltributyltin with Various $Pd_2(dba)_3$/Ligand Catalysts at 50 °C in THF[10]

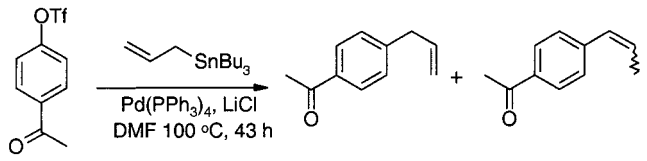
	ligand[a]	cone angle	relative rate[b]	inhibition factor[c]	yield (%)[d]
1	PPh_3	145°	1	19	15.2
2	$(p\text{-Tol})_3P$	145°	<0.07	>100	<2
3	$(o\text{-Tol})_3P$	194°	35.2	3.4	19
4	TFP	133°	105	3.7	>95
5	$P(C_6F_5)_3$	184°	e	- -	13.2
6	Ph_3As	142°	1100	1.3	>95

[a] Pd:L ratio = 1:4. [b] For PPh_3, $k = 4.6 \times 10^{-5}$ min^{-1}. [c] Ratio of PdL_2 catalyst rate to PdL_4 catalyst rate. [d] HPLC yield after 72 h, [e] Catalyst decomposition was instantaneous (<2 min).

which give high rates of coupling are generally associated with low inhibition factors while sluggish catalysts are comprised of ligands with large inhibition factors.

The utilization of tri-2-furylphosphine in the Stille cross-coupling, which often allows the reaction to proceed at ambient temperature, may be extremely advantageous when unwanted thermally controlled side reactions are possible. Under classical Stille conditions, aryl triflate **25** and allyltributyltin give a mixture of double-bond isomers, compounds **26** and **27** (Scheme 7). The major product of the reaction is

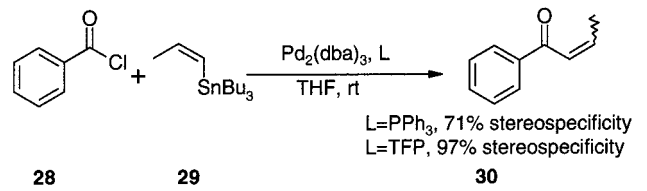
Scheme 7



Catalyst	% Yield 26	% Yield 27
$Pd(PPh_3)_4$	18	54
Pd_2dba_3 + 8TFP	78.5	0

a result of double-bond migration into conjugation with the aromatic ring.[34] Using TFP as the Stille ligand at room temperature furnishes the desired olefin **26** in 78.5% yield, free from any traces of the conjugated isomer.[10] Similarly, the palladium-catalyzed coupling of acyl chlorides with vinyltins often results in products with a significant amount of *E*/*Z* double-bond isomerism even under relatively mild conditions (Scheme 8).[35] However, the coupling of

Scheme 8



benzoyl chloride (**28**) with (*Z*)-1-propenyltributyltin (**29**) using TFP as the palladium ligand affords the desired product **30** with remarkable stereospecificty (97%).[10] Clearly, ligands of poor Lewis basicity offer a major synthetic advantage when the starting materials and/or products of a process contain sensitive or labile functional groups. As a result, TFP and Ph_3As have become the ligands of choice for the Stille reaction.

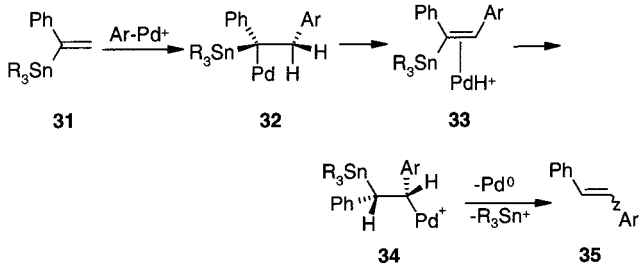
Farina's recent review[36] comprehensively detailed the Stille cross-coupling reaction through 1994, and the section that follows supplements this review by covering the recent use of tri-2-furylphosphine as a Stille ligand. In some cases, authors have reported the use of TFP in the Stille reaction without comparison to either PPh_3 or Ph_3As catalyst systems. These accounts are included for completeness; however, special attention will be paid to the literature reports which either demonstrate a clear advantage to using the TFP catalyst system or compare the use of different ligands under otherwise identical conditions.

B. Use of TFP in the Stille Reaction since 1994

1. Investigations of Stille Byproduct Formation Using TFP

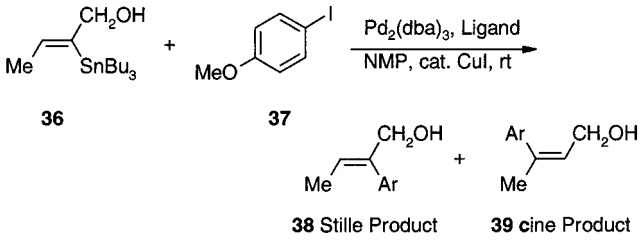
A number of unwanted side reactions have been observed in the Stille coupling[36] including homocoupling, alkyl group transfer, protodestannylation, phosphorus to palladium aryl migration, olefin geometry isomerization, and cine substitution. Many of these processes may be attenuated through the use of additives[37] or by lowering the reaction temperature.[36] Since TFP often allows the Stille reaction to proceed at room temperature, use of this ligand can be advantageous for limiting these undesired side reactions.[38] The cine substitution product **35**, formed from **31** through intermediates **32**−**34** (Scheme 9),

Scheme 9



has traditionally been attributed to steric hindrance at the a carbon of the migratory group on tin.[39] While initial studies on the TFP catalyst system, relative to the PPh_3 catalyst, have shown small increases in the amount of cine product obtained,[40] Flohr recently demonstrated that judicious choice of electrophile, ligand, and coupling conditions may be used to control the ratio of Stille/cine products.[41] Treatment of vinyl stannane **36** with *p*-methoxyiodobenzene **37** under the modified TFP Stille conditions afforded a 4:1 mixture of the Stille **38** and cine **39** products,

Scheme 10

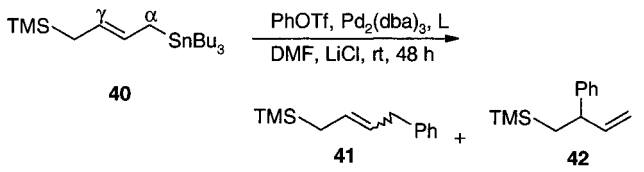


Ligand	Time (h)	Conversion (%)	Stille:cine
TFP	90	30	4 : 1
Ph_3As	160	>90	2 : 1

respectively (Scheme 10). Although the yield was increased upon using the weaker donating ligand Ph_3-As, the relative proportion of cine-substituted product was also found to increase. Flohr[41] also noted that addition of CuI to the reaction inhibited the decomposition of the TFP catalyst system. The results of this study clearly show that electronic effects in the electrophile may influence product distribution, and hence, the choice of catalyst ligand is an important factor governing the reaction pathway.

As noted previously, double-bond isomerism is often a significant side reaction to the Stille cross-coupling.[36] When substituted allylic stannanes are employed in the Stille reaction, extensive allylic rearrangement has been observed.[42] The less desirable γ-product, which results from allylic rearrangement, is normally the major component of the reaction mixture. Recently, Tsuji showed that the use of poor donor ligands such as TFP and Ph_3As increase the ratio of **41**:**42** in favor the formation of the more synthetically useful α-product **41** (Scheme 11).[43]

Scheme 11

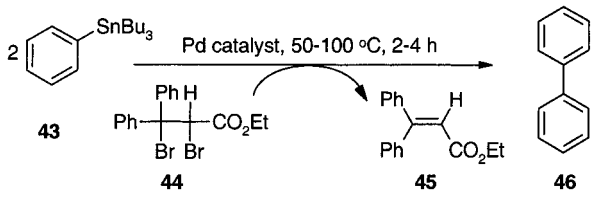


Ligand (L)	Yield (%)	41 (% E isomer)	α : γ
PPh_3	66	15	61 : 39
TFP	83	57	83 : 17
Ph_3As	87	84	91 : 9

Hence, treatment of tributyl[(*E*)-4-(trimethylsilyl)-2-butenyl]stannane (**40**) with phenyl triflate and a Ph_3-As-derived catalyst afforded the highest yield and regioselectivity. Moreover, the double-bond stereochemistry of the α-product was found to increase in favor of the trans isomer as the ligand electron-donating ability was decreased.

Homocoupling of stannanes is one of the most common side reactions observed in Stille coupling and in some instances has been shown to be synthetically useful.[36] Tamao and co-workers recently developed a catalytic homocoupling of arylstannanes **43** using an acrylate dibromide derivative **44** as the stoichiometric oxidant, which is converted into ester **45**[44] (Scheme 12). In this study, the highest yields of homocoupled product **46** were obtained when using highly basic, bidentate ligands such as 1,3-bis(di-

Scheme 12



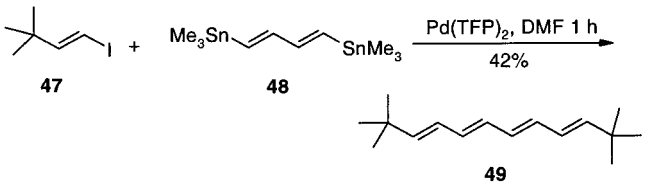
Catalyst	Yield (%)
$PdCl_2(MeCN)_2$/TFP	64
$PdCl_2(MeCN)_2/PPh_3$/CuI	54
$PdCl_2(MeCN)_2$/dppp	83

phenylphosphino)propane (dppp). However, since the catalytic cycle involves an oxidative addition step, it is unclear from this study whether the efficacy of homocoupling decreases with the use of more poorly donating phosphine ligands.

2. Small Molecule Synthesis Using TFP-Modified Stille Reactions

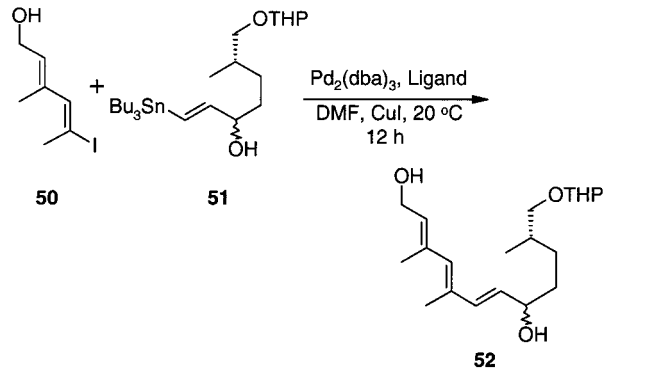
a. Alkenyl Iodide Precursors. Since Farina's review of the Stille reaction,[36] several workers have applied the TFP-modified Stille conditions in a wide range of small molecule syntheses. For example, Müllen and co-workers[45] prepared a variety of linear polyenes such as **49** via cross-coupling of bis-stannane **48** with 2 equiv of vinyl iodide **47** (Scheme 13).

Scheme 13



Although a $PdCl_2(MeCN)_2$ catalyst system was found to afford the desired polyene **49** in comparable yield, the TFP catalyst was more stable under the reaction conditions. Pancrazi and co-workers[46] also utilized the modified Stille protocol for the synthesis of polyene systems (Scheme 14). Treatment of vinyl iodide **50** and stannane **51** with a $Pd_2(dba)_3/PPh_3$

Scheme 14

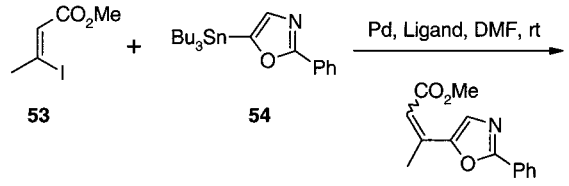


Ligand	Yield (%)
PPh_3	34
TFP	26
$AsPh_3$	44

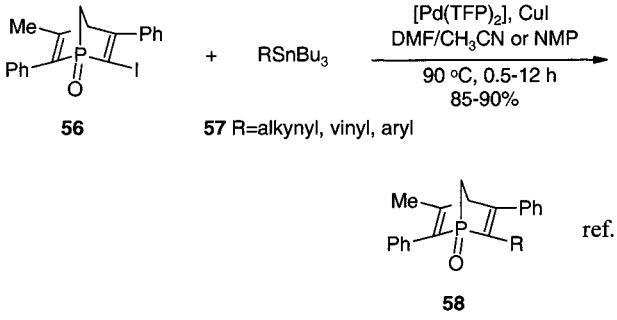
catalyst system furnished triene **52** in 34% isolated yield, while the TFP-derived catalyst afforded only 26% of the desired product. Employment of a triphenylarsine catalyst for this coupling improved the yield to 44% but unfortunately led to the production of unwanted side products.

Vedejs and Monahan[47] recently reported the derivatization of 5-(tributylstannyl)-2-phenyloxazole (**54**) with methyl (*Z*)-3-iodocrotonate (**53**) (Scheme 15). Using the TFP catalyst system in place of $PdCl_2$-

Scheme 15



Catalyst	Yield (%)	*Z* : *E*
$PdCl_2(MeCN)_2$	50	20 : 1
$Pd_2(dba)_3$/TFP	70	10 : 1

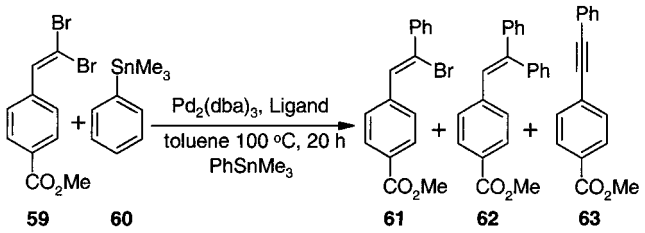


$(MeCN)_2$ was found to increase the cross-coupling yield albeit with decreased retention of double-bond geometry in **55**. Mathey and co-workers[48] reported the functionalization of vinyl iodide **56** using various alkynyl-, vinyl-, and aryltributylstannanes **57** (Scheme 15). The resulting substituted phosphanorbornadienes **58** can be obtained in excellent yields giving access to a wide variety of new ligands for homogeneous catalysis.

b. Alkenyl Bromide Precursors. Numerous examples of Stille cross-coupling between vinyl bromides and organotin species, using the TFP-modified protocol, have recently been reported in the literature. For example, treatment of geminal dibromide **59** and tributylphenyltin (**60**) with a $Pd_2(dba)_3$/TFP catalyst in toluene at 100 °C for 20 h gives predominantly the trans-functionalized product **61** along with 8% of **62** (Scheme 16).[49] Moreover, the high yield and regioselectivity observed using tri-2-furylphosphine catalyst system was found to be general for a wide variety of 1,1-dibromo-1-alkenes and stannanes. Interestingly, performing the reaction at 80 °C in DMF with 1.5 equiv of DIPEA gives the alkynyl product **63** exclusively in 91% isolated yield. This reaction was found to be of general scope with the desired substituted acetylenes being formed in good yields from a wide variety of geminal dibromides and organostannanes.[49]

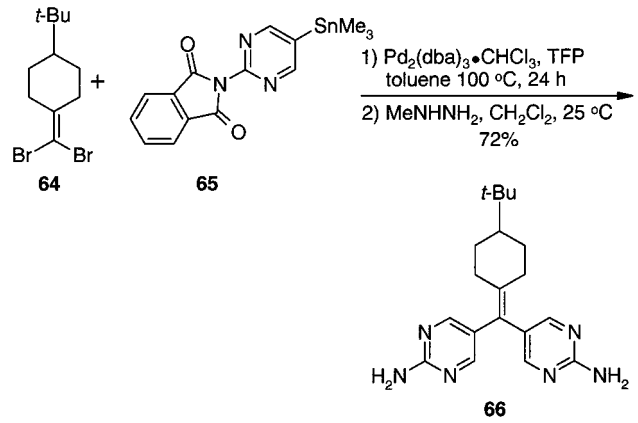
Lehn and co-workers[50] recently used TFP-modified Stille conditions to functionalize geminal dibromide

Scheme 16



		Yield (%)		
Ligand	Conv. (%)	61	62	63
PPh_3	23	4	1	18
TFP	100	92	8	0
$AsPh_3$	69	37	32	0

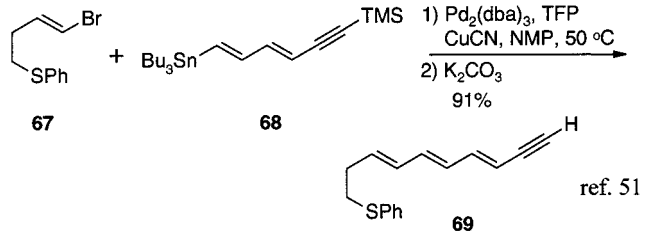
Scheme 17

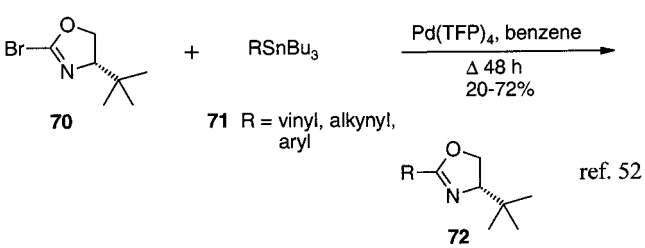


64 with 2 equiv of stannane **65** (Scheme 17). The desired cycloalkylidene product **66** was obtained in only 5% yield after 3 days when $Pd(PPh_3)_4$ was used as the catalyst. Utilization of $Pd_2(dba)_3$ in conjunction with the TFP ligand led to a dramatic increase in the rate of coupling providing compound **66** in 72% isolated yield.

Lipshutz and co-workers[51] recently prepared polyene **69** via a TFP-mediated Stille cross-coupling of vinyl bromide **67** and stannylated dieneyne **68** (Scheme 18). It has been demonstrated that subsequent hydrozirconation of terminal acetylene **69** with Schwartz's reagent provides a powerful method for

Scheme 18

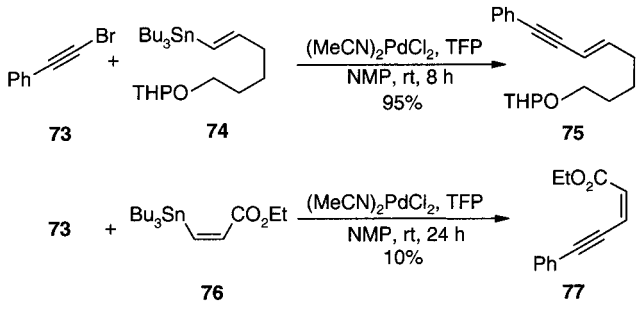




the bidirectional construction of all-*E* polyenes. Meyers[52] recently showed that 2-bromooxazoline derivative **70** can be functionalized with a variety of vinyl-, alkynyl-, and aryltributylstannanes **71** under mild TFP-mediated Stille conditions. In this study, both TFP- and PPh_3-derived catalysts were found to provide the desired substituted oxazolines **72** in moderate to excellent yield.

c. Alkynyl Halide Precursors. Alkynyl halides have been used far less frequently in the TFP-modified Stille reaction. Zapata and Rondón[53] recently reported the room temperature cross-coupling of acetylenic bromides with alkenyltins to furnish highly conjugated enynes (Scheme 19). Treatment of

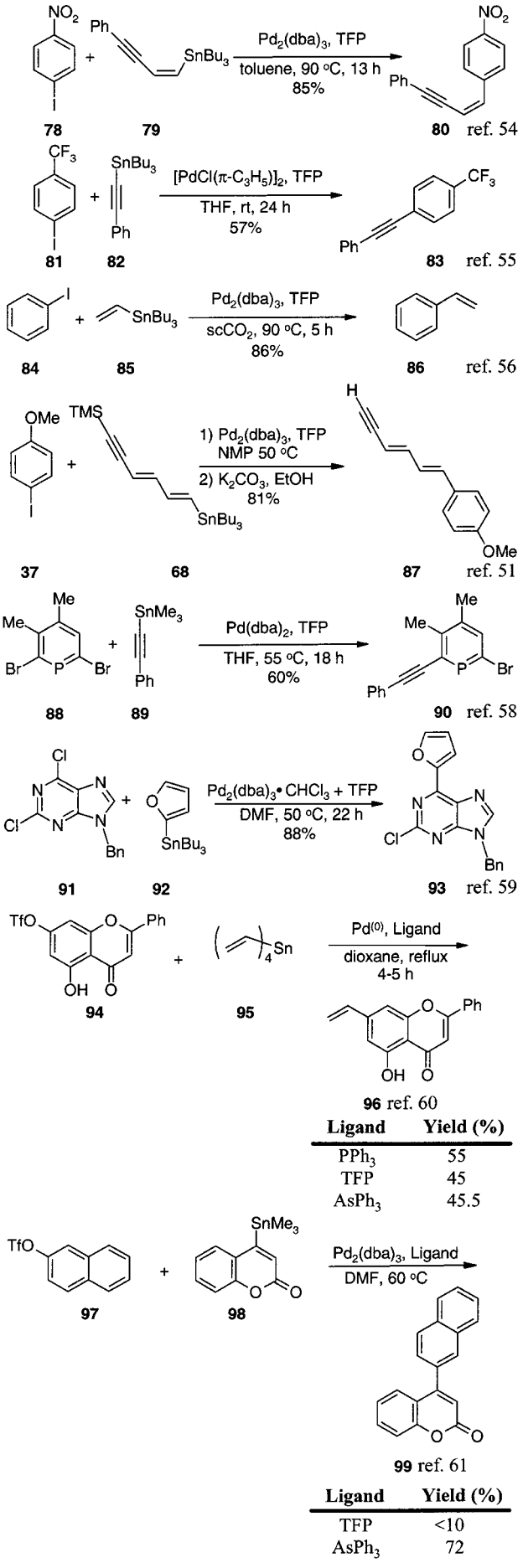
Scheme 19



bromide **73** with functionalized alkenyl stannanes **74** and **76** with a $PdCl_2(MeCN)_2$/TFP catalyst system in NMP at room temperature for 8 h afforded coupled products **75** and **77** in 95% and 10% yield, respectively. Moderate to excellent yields have been obtained using this procedure with a variety of coupling partners, although the reaction does seem to be limited by the presence of an electron-withdrawing group in the cis position of the alkenyltin species (Scheme 19).

d. Aryl Halide and Sulfonate Precursors. The TFP-modified Stille coupling reaction has been used extensively in recent years on aryl iodide, bromide, chloride, and triflate starting materials (Scheme 20). For example, the treatment of **78** and **81** with vinyl stannane **79**[54] and alkynyl stannane **82**[55] in the presence of the TFP catalyst system gave **80** and **83**, respectively. In the latter case, performing the reaction with the PPh_3 ligand under otherwise identical conditions gave only 1% of the desired aryl acetylene **83**. Workers at Los Alamos National Laboratories recently reported the Stille cross-coupling of iodobenzene (**84**) and vinyltributyltin (**85**)[56] with tri-2-furylphosphine in supercritical carbon dioxide (Scheme 20). The only phosphine ligand to out perform TFP in this study was tris[3,5-bis(trifluoromethyl)phenyl]-phosphine, which gave styrene (**86**) in near quantitative yield. While the latter phosphine does constitute a poorly donating ligand, Tumas and co-workers[56] noted that the increase in yield is likely due to the enhanced solubility of the catalyst in $scCO_2$.[57] Arylation of stannylated dienyne **68** with *p*-iodoanisole (**37**) in NMP at 50 °C using a $Pd_2(dba)_3$/TFP catalyst furnished arene **87** in 81% yield after removal of the TMS protecting group.[51] Mathey and co-workers[58] reported a regioselective functionalization of dibromoarene **88** with alkynyl stannane **89** under TFP-

Scheme 20



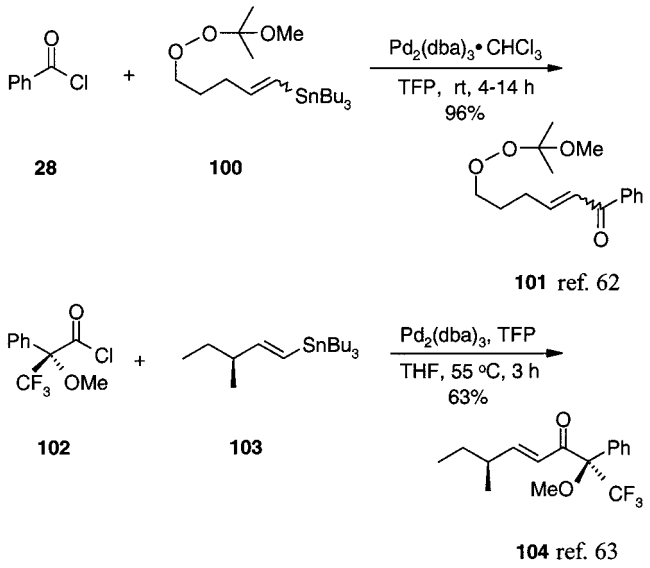
Ligand	Yield (%)
PPh_3	55
TFP	45
$AsPh_3$	45.5

Ligand	Yield (%)
TFP	<10
$AsPh_3$	72

modified Stille conditions. The resulting substituted phosphabenzene **90** was thus obtained in 60% isolated yield as a single regioisomer (Scheme 20). Treatment of 2,6-dichloropurine derivative **91** with 2-(tributylstannyl)furan (**92**) under classical Stille conditions afforded a 5:2 mixture of 6-substituted and 2-substituted products, respectively, in moderate yield. However, use of a TFP-based catalyst system allowed the reaction to be performed at a lower temperature, providing the desired 6-substituted product **93** exclusively in 88% isolated yield.[59] Treatment of aryl triflate **94** and tetravinyltin (**95**) with a variety of palladium(0) catalysts was found to give 7-vinylflavone **96** in moderate yield.[60] In this study, the best yield of the desired vinylated product **96** was realized using the traditional $Pd(PPh_3)_4$ catalyst system. Finally, Ortar and co-workers[61] reported that the coupling of 2-naphthyl triflate (**97**) and 4-trimethylstannylcoumarin (**98**) with a $Pd_2(dba)_3$/TFP catalyst system failed to produce any appreciable amount of product **99**. Interestingly, in this case an $AsPh_3$ catalyst afforded the best results and additives such as LiCl and CuI were found to significantly retard the rate of cross-coupling.

e. Acyl Chloride Precursors. A remarkable example of the synthetic versatility gained through the use of TFP in the Stille reaction was recently reported by Dussault, whereby benzoyl chloride (**28**) was coupled with peroxide **100** to furnish enone **101** in excellent yield[62] (Scheme 21). Clearly, the advan-

Scheme 21



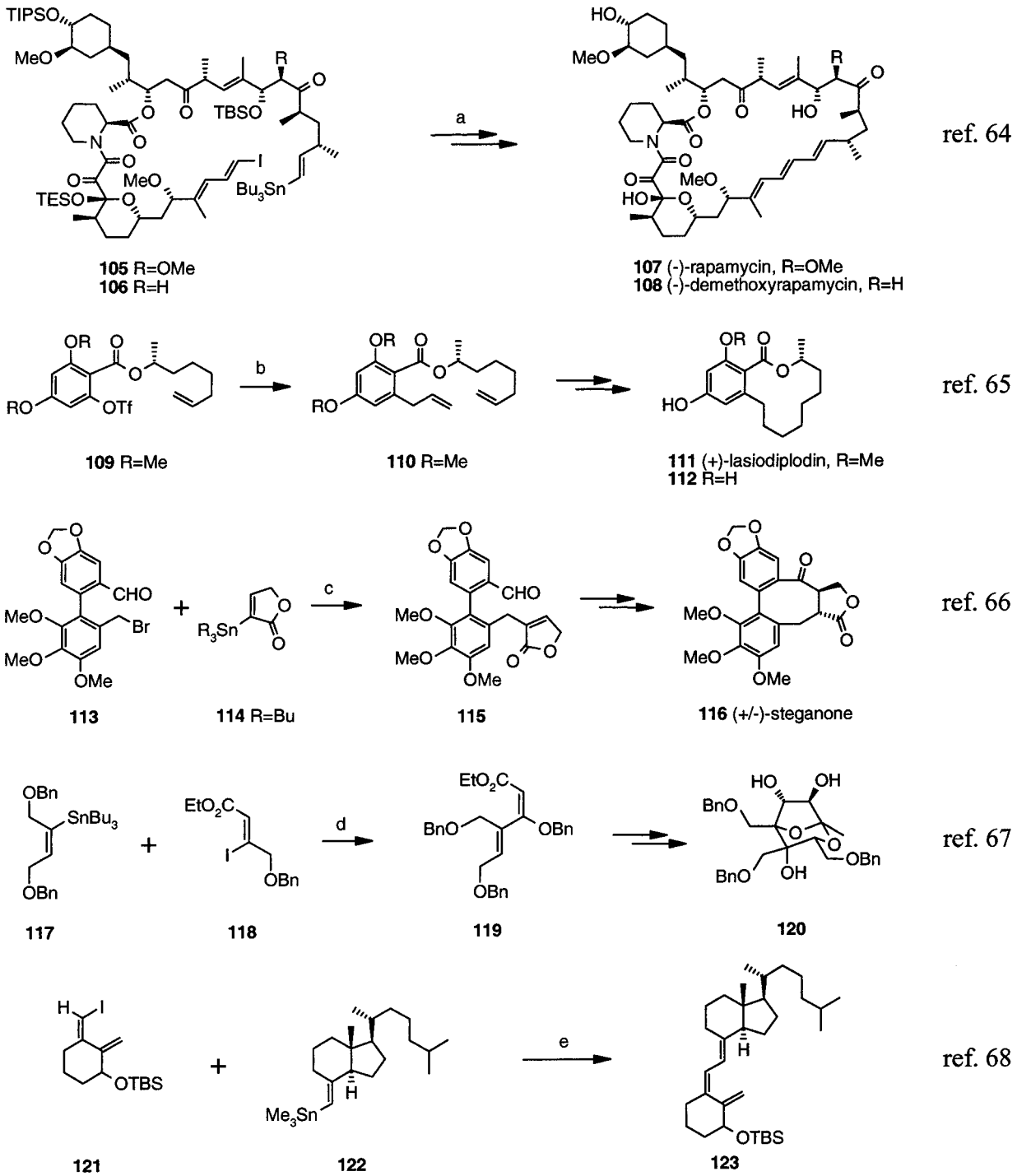
tageous use of a poorly donating ligand, which allows the reaction to be performed at ambient temperature, is essential for the successful coupling of such a thermally labile functional group. Hodgson and co-workers[63] recently reported that enantiopure (*S*)-MTPA-Cl (**102**) may be cross-coupled with chiral stannane **103** under TFP-modified conditions to furnish enone **104**. Subsequent stereochemical analysis of product **104** serves as a method for determining the enantiomeric purity of the starting organostannane **103**.

3. Approaches toward and Total Syntheses of Natural Products Involving TFP-Modified Stille Reactions

The TFP-modified Stille conditions have recently been used in a variety of contexts for the total syntheses of complex natural products and advanced intermediates. In a particularly striking example, Amos B. Smith III and co-workers[64] successfully prepared (−)-rapamycin (**107**) and its naturally occurring cogener (−)-27-demethoxyrapamycin (**108**) using a TFP-modified Stille macrocyclization as the key synthetic transformation (Scheme 22). Hence, treatment of vinyl iodide **105** and **106** with a $PdCl_2(TFP)_2$ catalyst in a mixture of DIPEA, DMF, and THF at room temperature, under conditions of high dilution, furnished the desired macrocycle in 74% isolated yield. Subsequent removal of the silyl protecting groups gave the desired natural product **107** identical in all respects to the natural material. Fürstner and co-workers[65] reported the total synthesis of (*R*)-(−)-lasiodiplodin (**111**) and its de-*O*-methyl cogener **112** using a TFP-modified Stille allylation procedure. Treatment of aryl triflate **109** and allyltributyltin with a $Pd_2(dba)_3$/TFP catalyst in NMP at 40 °C smoothly provided terminal diene **110** in 93% yield. Molander and co-workers[66] recently synthesized (±)-steganone (**116**) via **115** using a TFP-modified Stille coupling between benzyl bromide **113** and 3-tributylstannyl-(5*H*)-furan-2-one (**114**). Treatment of vinylstannane **117** and iodide **118** with a TFP catalyst system at 50 °C for 4.5 days was found to give diene **119** in 86% isolated yield. Subsequent Sharpless asymmetric dihydroxylation of diene **119** has been shown by Armstrong and Barsanti[67] to be an efficient strategy for the synthesis of the 2,8-dioxabicyclo[3.2.1]octane ring system found in the zaragozic acid family **120** (Scheme 22). A mild, convergent approach to the vitamin D skeleton has recently been reported by Mancareñas and Mouriño[68] using TFP-modified Pd(0) catalysis. Thus, treatment of iododiene **121** and vinylstannane **122** with a $Pd_2(dba)_3$/TFP catalyst system in DMF at room temperature for 4 days gave a 33% yield of conjugated triene **123**.

Snieckus and co-worker[69] recently reported the synthesis of defucogilvocarcin V (**126**) via **125** using a TFP-modified Stille coupling between aryl triflate **124** and tributylvinyltin (**85**) (Scheme 23). The total synthesis of (±)-licarin B[70] (**129**) has been achieved via Stille coupling of aryl iodide **127** with (*E*)-propenyltributyltin (**128**). Eupomatenoids-1 and -12, two closely related natural products (not shown), have also been synthesized by Engler[70] using the same Stille functionalization as the final step. Hirama and co-workers[71] recently synthesized the marine antibiotic korormicin (**133**) using a Stille cross-coupling. Treatment of vinyl iodide **130** and epoxy stannane **131** with a TFP-derived Pd(0) catalyst in NMP at room temperature for 6 days furnished key intermediate **132** in 34% yield. A total synthesis of (−)-pateamine A (**137**) has recently been developed[72] whereby macrocyclic bromide **134** is coupled with stannyl diene **135** under TFP-modified conditions to

Scheme 22[a]



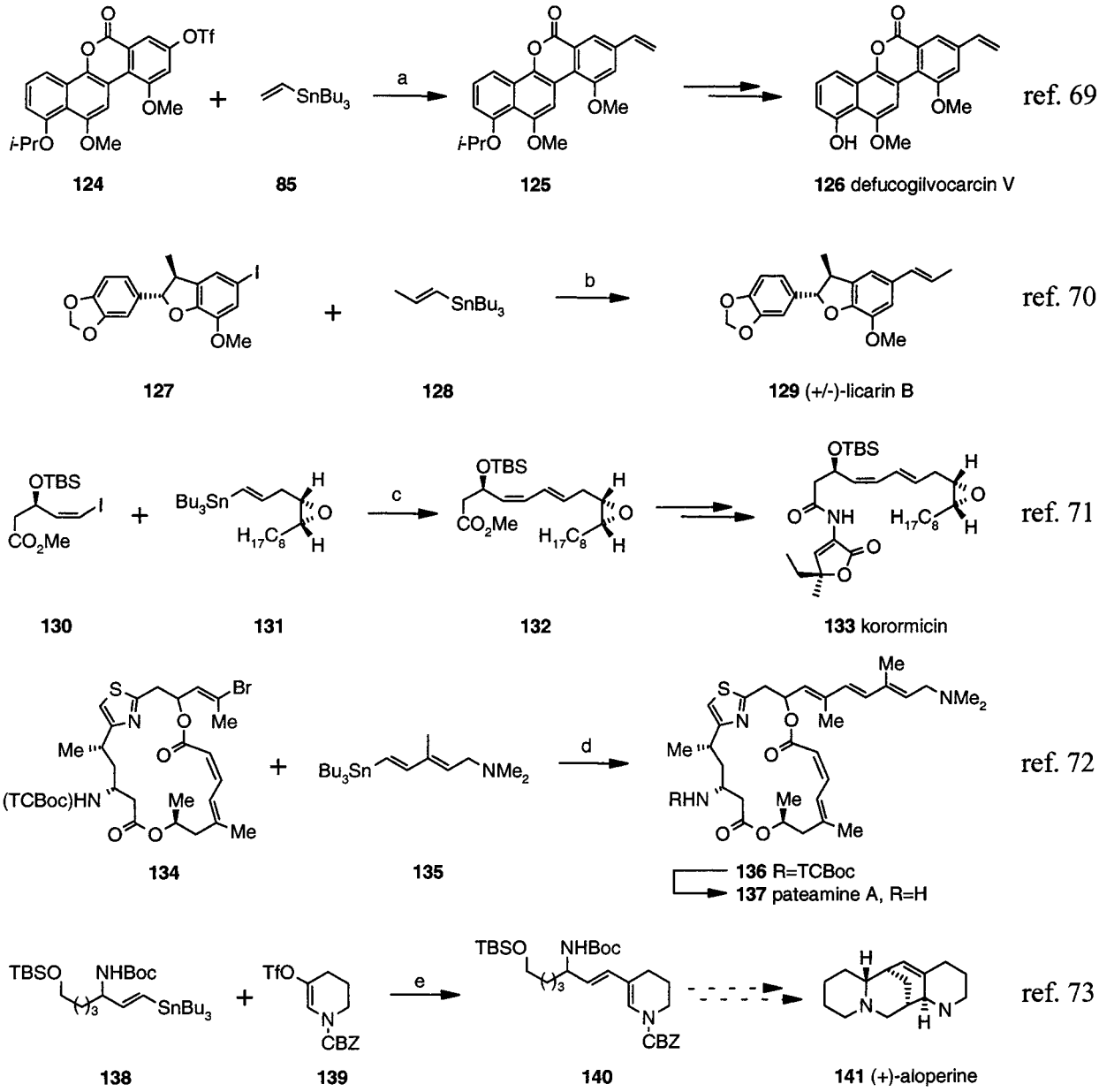
[a] Conditions: (a) $(TFP)_2PdCl_2$, *N*,*N*-diisopropylethylamine (DIPEA), DMF, THF, rt, 74% R = OMe; 65% R = H. (b) allyltributylstannane, LiCl, $Pd_2(dba)_3$, TFP, 1-methyl-2-pyrrolidinone (NMP), 40 °C, 93%. (c) $Pd_2(dba)_3$, TFP, *N*,*N*-dimethylacetamide (DMA), 80 °C, 83%. (d) $Pd_2(dba)_3$, TFP, $ZnCl_2$, DMF, 50 °C, 4.5 days, 86%. (e) $Pd_2(dba)_3$, TFP, CuI, DMF, 25 °C, 4 days, 33%.

give **136**. In this study, stopping the Stille reaction prior to completion and recycling the unreacted bromide **134** proved beneficial due to competitive formation of a palladium π-allyl species. Overman and co-workers[73] recently succeeded in the total synthesis of the C_{15} alkaloid (+)-aloperine (**141**) using Diels−Alder chemistry. In an initial approach, which later had to be abandoned, diene **140** was prepared in 93% isolated yield using a TFP-mediated Stille reaction between functionalized stannane **138** and enol triflate **139** (Scheme 23). Subsequent [4+2] cycloaddition of diene **140** with methyl acrylate unfortunately failed to provide the required cycloadduct.

4. TFP-Modified Stille Reactions Involving Organometallic Substrates

The Stille cross-coupling of various organometallic species using tri-2-furylphosphine-based catalysts has recently been studied. For example, treatment

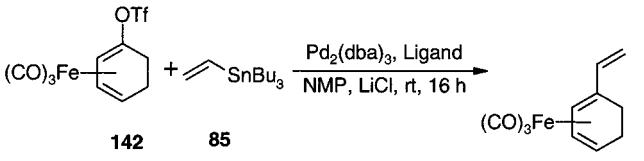
Scheme 23[a]



[a] Conditions: (a) $Pd_2(dba)_3$, TFP, NMP, rt, 5 h, 69%. (b) $Pd_2(dba)_3$, TFP, LiCl, DMF, 120−130 °C, 84−86%. (c) $Pd_2(dba)_3$·$CHCl_3$, TFP, NMP, rt, 6 days, 34%. (d) $Pd_2(dba)_3$, TFP, NMP, 25 °C, 27% (57% based on recovered starting material); TCBoc = 1,1-dimethyl-2,2,2-trichloroethoxycarbonyl. (e) $Pd_2(dba)_3$, TFP, LiCl, NMP, rt, 1.5 days, 93%.

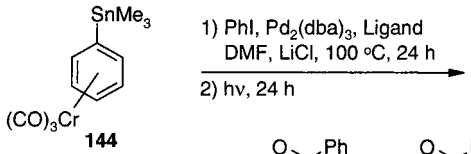
of cyclohexadienyl triflate iron π-complex **142** and vinyltributyltin (**85**) with $Pd(PPh_3)_4$ in NMP at room temperature for 16 h gave coupled product **143** in 38% yield[74] (Scheme 24). However, utilization of the TFP-derived catalyst system for this coupling increases the yield of the reaction to 50%. In either case, the η^4-bound tricarbonyliron moiety is cleanly retained under the cross-coupling conditions. In contrast to this finding, Johansson and co-workers[75] reported that the Stille coupling of (η^6-arene)$Cr(CO)_3$ complex **144** with iodobenzene affords a mixture of products **145**, **146**, and **46** (Scheme 25). Photolysis of the reaction mixture and subsequent analysis of the products conclusively showed that CO transfer had taken place under the reaction conditions. Moreover, unwanted methyl group transfer had competed with the desired arylation process. Using a TFP-based catalyst gave lower overall conversion but an increased ratio of carbonylated products. In either case, the desired Stille product, biphenyl (**46**), was the minor component of the reaction mixture.

Scheme 24



Ligand	Yield (%)
PPh_3	38
TFP	50

Scheme 25

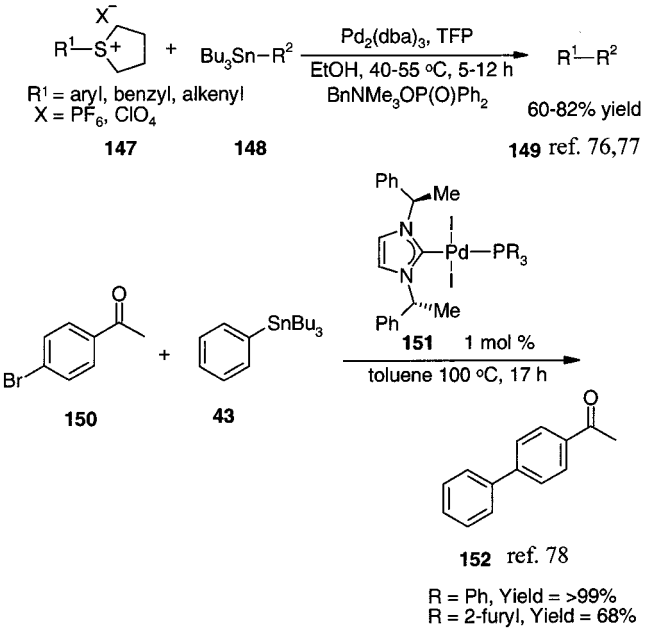


Ligand	Yield (%) 145	146	46
PPh_3	44	24	13
TFP	36	25	2

5. New Frontiers in Stille Coupling Using TFP-Modified Conditions

Until recently, the Stille reaction has been limited to the coupling of organostannanes with organo halides and sulfonates. Liebeskind and co-workers[76] reported the efficient cross-coupling of organotins **148** with various aryl-, heteroaryl-, alkenyl-, benzyl-, and heterobenzylic[77] sulfonium salts **147** using the TFP-derived catalyst system (Scheme 26). In this study,

Scheme 26

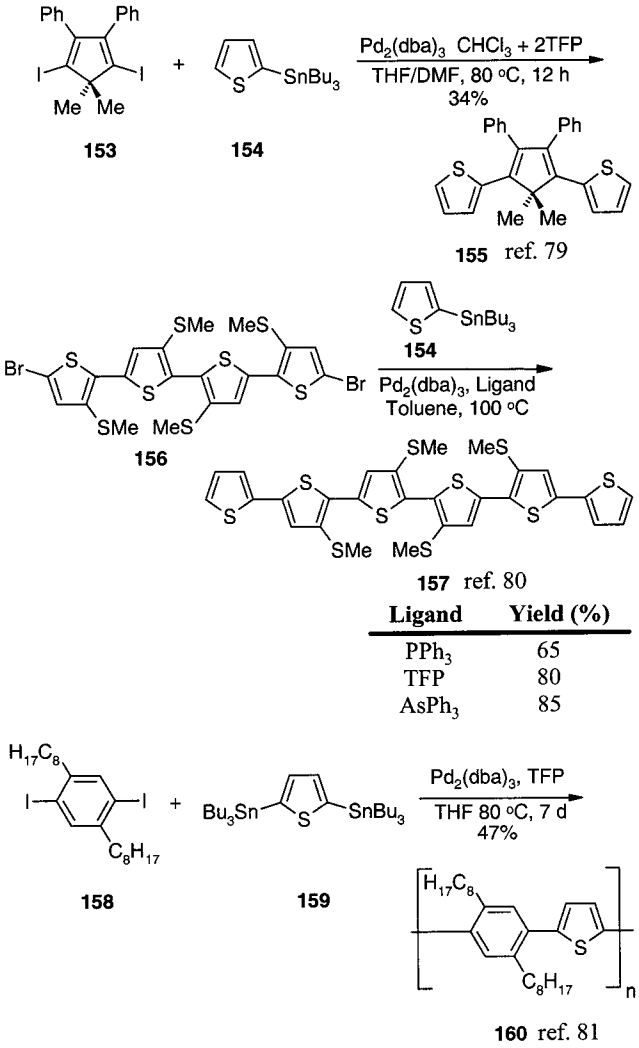


very low levels of palladium catalyst (0.01−0.5 mol %) could be employed to obtain a variety of cross-coupled products **149** in moderate to excellent yield. Recent advances in the Stille coupling procedure have not been limited, however, to the use of novel oxidative insertion precursors. Herrmann[78] reported a new *N*-heterocyclic carbene catalyst system **151** for the Stille process between **150** and **43** (Scheme 26). In contrast to Farina's findings,[10] the use of poorly donating ligands such as TFP in conjunction with the imidazolin-2-ylidene catalyst system did not lead to increased yields or reaction rates. Unfortunately, palladium catalyst **151** was not compared to either the $Pd(PPh_3)_4$ or $Pd_2(dba)_3$/TFP catalyst systems. While the *N*-heterocyclic carbene moiety presumably imparts increased thermal stability to the Pd species, the overall efficiency of catalyst **151** relative to traditional bis(phosphine) Stille catalysts remains to be studied.

6. TFP-Modified Stille Reactions for the Preparation of Oligomers and Polymers

Tri-2-furylphosphine has recently been employed as a Stille ligand for the preparation of various polymers and oligomers. Cyclopentadiene derivative **155** was synthesized by Tamao and co-workers[79] through the cross-coupling of diiodide **153** with 2 equiv of 2-(tributylstannyl)thiophene (**154**) (Scheme 27). The interesting physical and electronic properties

Scheme 27



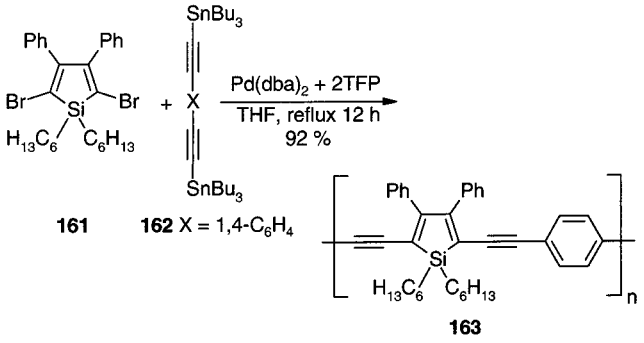
Ligand	Yield (%)
PPh_3	65
TFP	80
$AsPh_3$	85

of conjugated thienyl systems, such as compound **155**, has generated considerable interest in polythiophene materials. Functionalized sexithiophene **157** has recently been prepared via Stille coupling of dibromide **156** with 2-(tributylstannyl)thiophene[80] (**154**). Use of poorly coordinating ligands was found to be highly beneficial to the obtention of oligomer **157** in high yield. Poly(phenylenethiophene) polymers such as **160** have been prepared through Stille cross-coupling reactions. For example, polymerization of 2,5-dioctyl-1,4-diiodobenzene (**158**) with 1,4-bis(tri-

butylstannyl)-thiophene (**159**) has been reported with the TFP-modified catalyst system[81] giving a 47% yield of the desired polymer **160** with moderate molecular weight (40 000 amu). When the polymerization was carried out with PPh_3 as the ligand, the yield and molecular weight of the polymer decreased to 34% and 24 000 amu, respectively. Conversely, using a ligand of lower electron-releasing ability such as Ph_3As gave **160** in 57% yield with an average molecular weight of 56 000 amu. Although the triphenylarsine catalyst was found to increase the yield and molecular weight of the desired polymer, the catalyst lifetime was found to be significantly shorter than the corresponding TFP-derived system.

Silole−acetylene polymers such as **163** exhibit interesting physical properties such as narrow band gaps and have been applied as efficient electron-transporting emissive materials in organic electroluminescent devices[82] (Scheme 28). TFP-mediated Stille

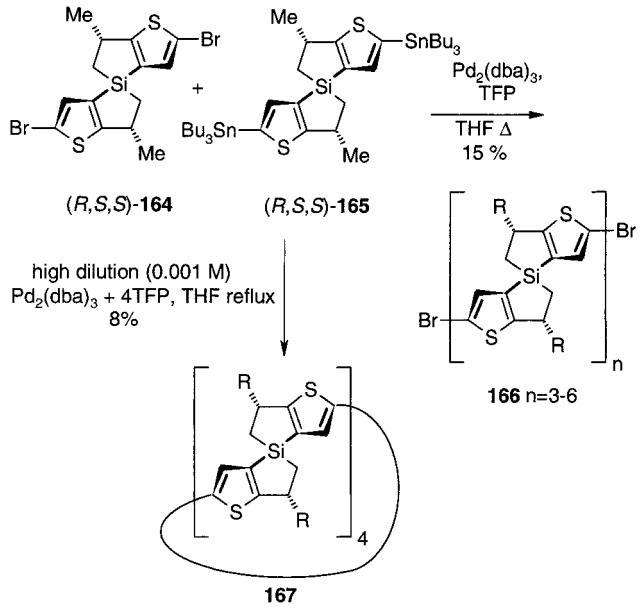
Scheme 28



coupling of dibromosilole derivative **161** with bis-(stannylethynyl)arene **162** in refluxing THF smoothly furnished the desired polymer **163** in excellent yield.[83]

The Stille coupling of enantiopure spirosilane monomers **164** and **165** to give the corresponding oligomers **166** has been reported[84] (Scheme 29). Using high dilution techniques, Tamao and co-workers successfully prepared the cyclic tetramer **167**

Scheme 29

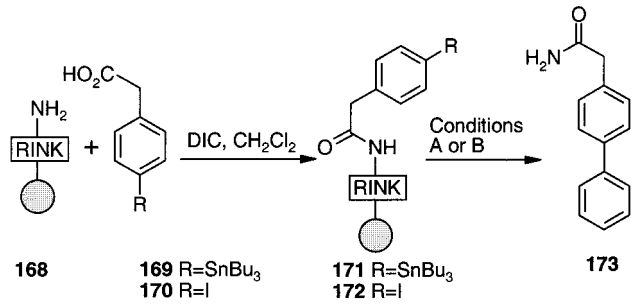


in 8% yield.[84] This compound, which has an estimated pore size of 9.4 Å, should prove very interesting in the construction of self-assemblies having chiral network structures.

7. Resin-Bound TFP-Mediated Stille Cross-Coupling

Carbon−carbon bond-forming reactions on solid support[85] can be a powerful, automatable tool for combinatorial drug discovery efforts. The solid-phase synthesis of biaryls via the Stille reaction has been investigated by Sucholeiki and co-workers[86] (Scheme 30). Treatment of the Rink amide resin **168** and

Scheme 30[a]



[a] Conditions A: (i) 3 equiv of iodobenzene (**84**), 10 mol % $Pd_2(dba)_3$, 10 mol % TFP, 2 equiv of LiCl, NMP, 25 °C, 12 h; (ii) 5% TFA−CH_2Cl_2, 15% yield (2 steps). Conditions B: (i) 3 equiv of trimethylphenyltin, 10 mol % $Pd_2(dba)_3$, 10 mol % TFP, 2 equiv of LiCl, NMP, 25 °C, 12 h; (ii) 5% TFA−CH_2Cl_2, 33% yield (2 steps).

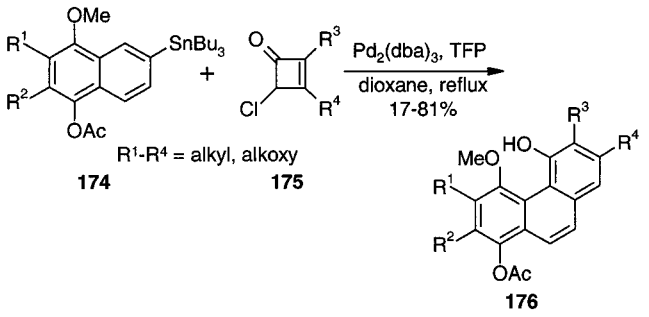
4-tributylstannylphenylacetic acid (**169**) with diisopropylcarbodiimide (DIC) in CH_2Cl_2 cleanly furnished resin-bound stannane **171**. Subsequent palladium-catalyzed Stille cross-coupling of amide **171** with iodobenzene (**84**) using the classic triphenylphosphine-based catalysts failed to produce the desired biaryl **173** under a variety of conditions. However, usage of the tri-2-furylphosphine-derived catalyst system provided compound **173** in 15% yield after cleavage from the solid support. Alternatively, aryl iodide **172**, prepared from **168** and **170**, could be coupled with trimethylphenyl tin under TFP-modified conditions to give phenylacetamide **173** in 33% overall yield. This methodology has also been studied with other polymer supports, but the yields of cross-coupled products are generally quite low.[86]

8. Tandem Processes Involving a TFP-Modified Stille Coupling Step

Since the Stille methodology is a powerful tool for carbon−carbon bond formation, which tolerates a wide range of functionalities, a variety of multistep transformations have been reported which include this cross-coupling reaction.[36] Liebeskind and co-workers reported a number of interesting methods for the construction of substituted aromatics based on the ring opening of cyclobutenones.[87] This methodology has recently been applied toward the synthesis of highly oxygenated, angularly fused polycyclic aromatic compounds. The functionalized cyclobutenones required for thermal rearrangement may conveniently be prepared via Stille cross-coupling. For example, treatment of naphthyl stannane **174** and chlorocyclobutenone **175** under the TFP-modified Stille protocol affords the desired 4-arylcyclobutenone

intermediate (not shown) which subsequently undergoes electrocyclic ring opening/closure in situ to give substituted phenanthrene **176**[88] (Scheme 31). Many

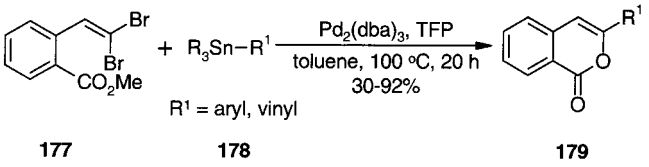
Scheme 31



biologically important polyketide natural products including pradimicin A, cervinomycin A_1, and simaomicin a contain a core phenanthrene structure similar to compound **176**.

The preparation of isocoumarins **179** via a two-step Stille coupling/palladium annulation procedure has recently been reported by Shen and co-workers[89] (Scheme 32). In this sequence, dibromide **177** is

Scheme 32

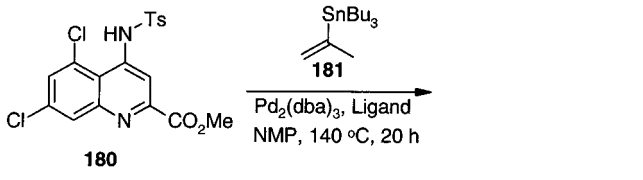


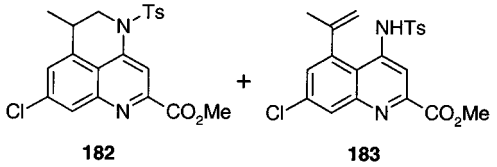
regioselectively functionalized at the trans position using a TFP-modified Stille reaction with aryl and vinyl stannanes **178**. Subsequent palladium-catalyzed annulation onto the ester function with loss of MeBr furnishes the desired isocoumarin **179** in moderate to excellent yield. Interestingly, these workers found that the TFP ligand performed very well when the migratory group on tin was an aryl group. However, if a vinylstannane was employed, better results were obtained using the traditional Pd$(PPh_3)_4$ catalyst system.

In an effort to develop therapeutic agents for neurodegenerative disorders such as Alzheimer's and Huntington's diseases, Nagata and Hume[90] sought to cross-couple substituted quinoline **180** with 2-propenyl(tributyl)tin (**181**) (Scheme 33). Unexpectedly, the product of the Stille coupling underwent a palladium-catalyzed oxidative cyclization under the reaction conditions to provide sulfonamide **182**. Using a $Pd_2(dba)_3$/TFP catalyst system, cyclized product **182** was obtained in higher yield along with 15% of the uncyclized adduct **183**. In both cases, cross-coupling was found to occur exclusively at the 5 position, giving the corresponding 7-chloro derivatives **182** and **183**.

A one-pot palladium-catalyzed hydrostannylation/Stille coupling has recently been developed by Maleczka[91] (Scheme 34). A variety of acetylenes **184**, including propargyl alcohols and amines, may be treated with either Bu_3SnH or $(Bu_3Sn)_2O$ and poly-

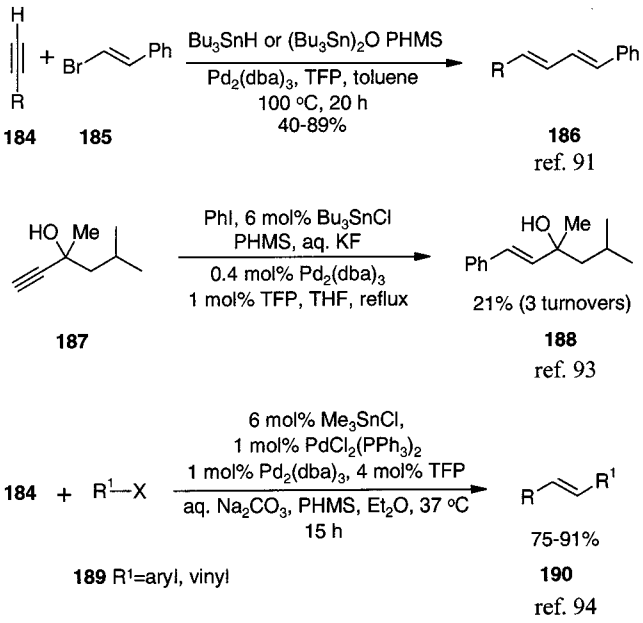
Scheme 33





Ligand	Yield (%) 182	183
PPh_3	18	0
TFP	38	15

Scheme 34



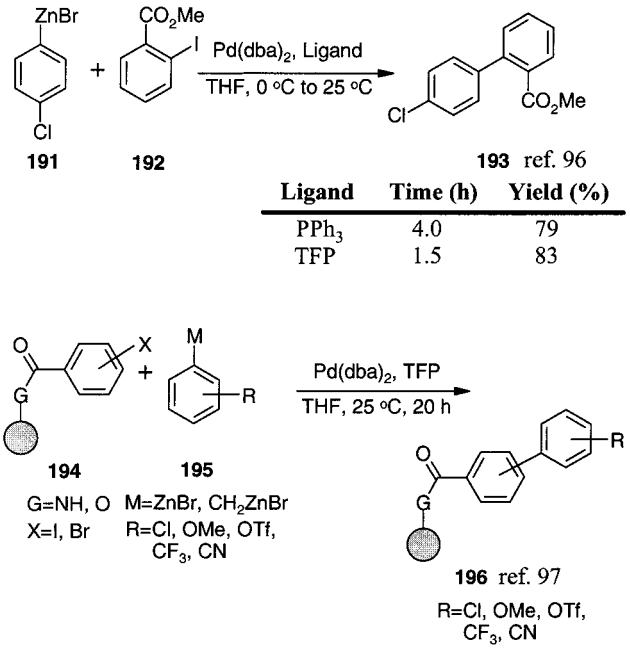
methylhydrosiloxane (PMHS)[92] to give an (*E*)-vinylstannane, which subsequently undergoes TFP-modified Stille coupling with vinyl bromide **185** to furnish diene **186**. Interestingly, the reaction can be modified in such a way that only catalytic tin is required; however, the yield of the desired diene (22−47%) is significantly reduced. Maleczka subsequently showed that a mixture of PHMS and aqueous KF can efficiently convert tin halides to tin hydrides.[93] Using this protocol, 3,5-dimethyl-1-hexyn-3-ol (**187**) and iodobenzene could be coupled with a TFP-derived catalyst to afford allylic alcohol **188** in 21% isolated yield. Although the catalyst turnover for this sequence is quite low, the experiment clearly demonstrates that the tin species is indeed recycled. By switching to the sterically less demanding trimethyltins, Maleczka and co-workers[94] dramatically increased the efficiency of the hydrostannylation−Stille sequence. Interestingly, an unprecedented mixed catalyst system consisting of 1 mol % $PdCl_2(PPh_3)_2$, 1 mol % $Pd_2(dba)_3$, and 4 mol % TFP provided the desired coupled products in 75−91% yield, representing an average of ∼15 tin turnovers (Scheme 34).

C. Tri-2-furylphosphine as a Ligand in Other Palladium-Catalyzed Organic Reactions

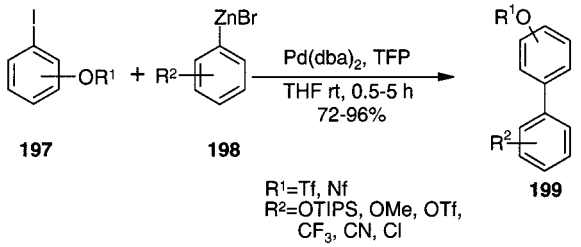
1. Palladium-Catalyzed Cross-Coupling of Organozinc Compounds

The palladium-catalyzed Negishi[95] cross-coupling reaction between aryl iodides and aryl zinc compounds is a powerful method for the formation of biaryl bonds which tolerates a wide variety of functionalities and employs quite mild reaction conditions. Knochel and co-workers recently applied the tri-2-furylphosphine ligand in a wide variety of Negishi cross-coupling reactions (Scheme 35). Treatment of aryl zinc **191** and methyl 2-iodobenzoate (**192**) with a $Pd(dba)_2/PPh_3$ catalyst in THF for 4 h smoothly furnished biaryl **193** in 79% isolated yield.[96] Similar to Farina's findings,[10] Knochel and co-workers observed a significant increase in cross-coupling rate upon employment of the TFP ligand, and product **193** was thus obtained in 83% yield after a 1.5 h reaction period. Knochel and Rottländer[97] subsequently applied the TFP-modified Negishi coupling to the solid-phase synthesis of polyfunctional biaryls, diphenylmethanes, and terphenyls. These workers elegantly showed that a variety of resin-bound aryl and heteroaryl halides **194** can be efficiently coupled under mild TFP-mediated conditions with functionalized aryl and benzylic zinc bromides **195** (Scheme 35). Cleavage of the cross-coupled products from the solid support using TFA in CH_2Cl_2 generally furnished the desired materials **196** in high yield and purity. The same workers also showed that aryl iodides which bear triflate[98] or nonaflate (perfluorobutanesulfonate)[99] moieties selectively couple through the halide functionality with aryl and benzylic[100] zinc reagents using TFP-based catalysts (Scheme 36). Hence, bifunctional iodides of type **197** were found to smoothly couple with substitued organozincs **198** to afford biaryl sulfonates **199** in excellent yield under mild reaction conditions. Moreover, subsequent palladium-catalyzed cross-coupling chemistry on biaryl products **199** with a variety of electrophiles provides a general, efficient synthesis of polyfunctional terphenyls.

Scheme 35



Scheme 36



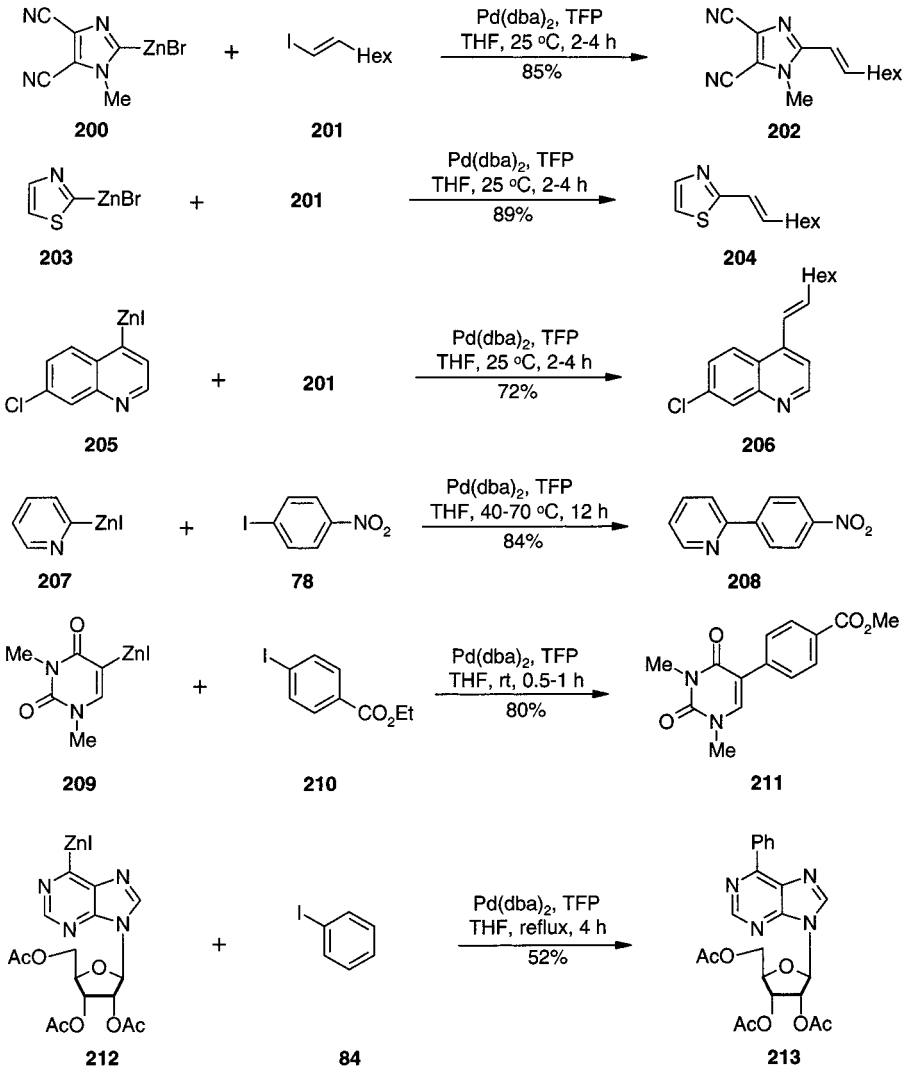
Knochel and co-workers demonstrated the tremendous versatility of the palladium-catalyzed Negishi cross-coupling reactions using a wide variety of zincated nitrogen-containing heterocycles including substituted imidazoles **200**, thiazoles **203**, quinolines **205**, pyridines **207**, purines **209**, pyrimidines, and nucleosides **212** (Scheme 37).[101] For these studies, in situ generation of the Pd catalyst from bis(dibenzylideneacetone)palladium(0) (1−2 mol %) and TFP (4−8 mol %) generally gave the best results affording the desired cross-coupled products in moderate to excellent yields.

Knochel and co-workers[102] recently showed that zincated thymine derivatives may be coupled with aryl and vinyl iodides under TFP-modified conditions (Scheme 38). This methodology, which is amenable to solid-phase synthesis, constitutes the first report of a heterocyclic benzylic zinc reagent used in a cross-coupling reaction. Using the TFP-based catalyst system, organozinc **214** was cross-coupled with a variety of substituted aryl iodides **215** at room temperature for 12 h to furnish the desired coupled products **216** in 62−95% isolated yield. Using Rink- or Wang-resin-bound aryl iodides **217** with organozinc **214** gave, after cleavage from the solid support, the expected cross-coupled products **218** in 89−93% purity as indicated by HPLC analysis.

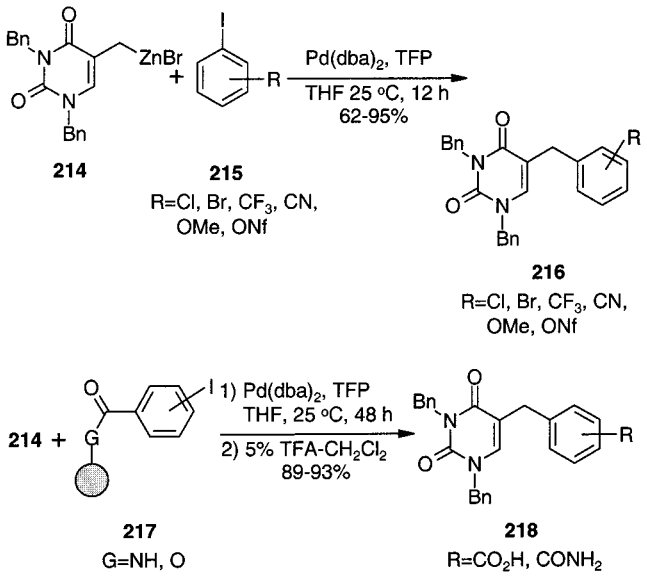
The antitumor drug *Z*-tamoxifen (**221**) has recently been prepared by Knochel and co-workers through a TFP-mediated Negishi coupling of vinyl iodide **220** and aryl zinc **219** (Scheme 39).[103] The required iodide **220**, which can be obtained in high stereochemical purity via carbonickelation of a suitably functionalized alkyne and subsequent iodolysis, couples with the organozinc reagent **219** with complete retention of the double-bond geometry giving the desired product in 77% isolated yield.

Kagan recently employed the TFP-modified Negishi reaction in the diastereoselective ortho functionalization of enantiopure ferrocenyl sulfoxides[104] (Scheme 40). Directed ortho lithiation of *S*-sulfoxide **222** with LDA in THF at −78 °C and subsequent transmetalation of the resulting lithio ferrocene with $ZnCl_2$ afforded (R_{Fc},S_S)-**223** with 98% diastereoselectivity. TFP-modified Negishi cross-coupling of **223** with *p*-(dimethylamino)iodobenzene (**224**) according to Knochel's conditions[96] afforded α-aryl sulfoxide (S_{Fc}, S_S)-**225** in 37% isolated yield.

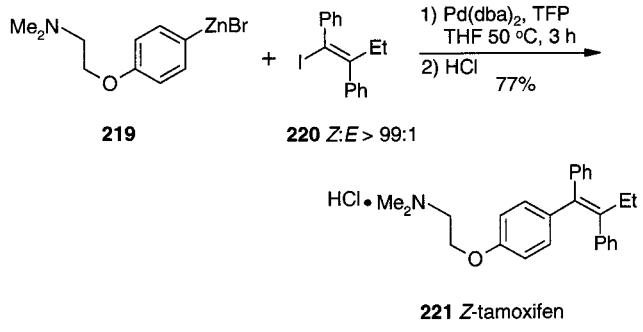
Scheme 37



Scheme 38

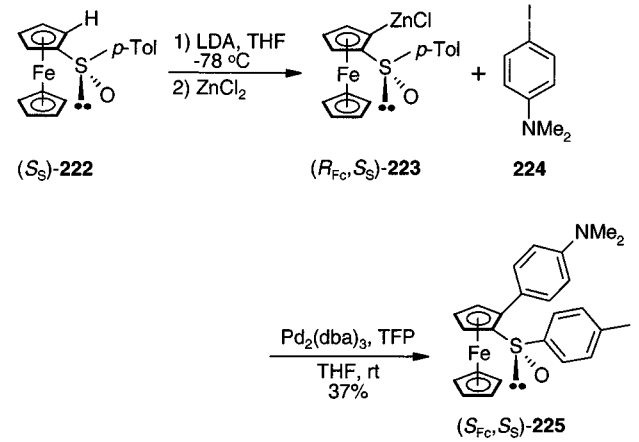


Scheme 39

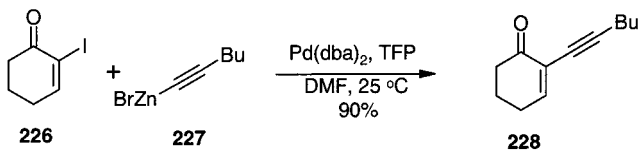


The palladium-catalyzed cross-coupling of organozinc reagents with α,β-unsaturated carbonyl derivatives bearing an α-iodide function has been studied by Negishi and co-workers. For example, treatment of iodide **226** with alkynyl zinc reagent **227** in DMF with a $Pd(dba)_2$/TFP catalyst furnished enyne **228** in excellent yield (Scheme 41).[105] Similarly, α-iodoeneone **229** was found to cross-couple with vinyl zinc **230** under TFP-modified conditions to afford diene **231** in 72% yield (Scheme 42).[106] Unfortunately, this coupling procedure could not successfully be extended to the functionalized α-iodoeneone **232**. All attempts to couple this halide with alkenyl zinc reagent **230** failed to provide >5% yield of the desired diene **233**. To alleviate this problem, Negishi and co-workers sought to couple TMS-protected allylic alcohol **234** with zincated olefin **230** (Scheme 43). The desired diene **235**, which was required for a formal synthesis

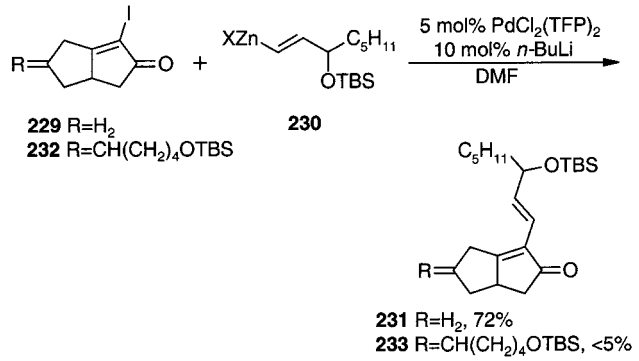
Scheme 40



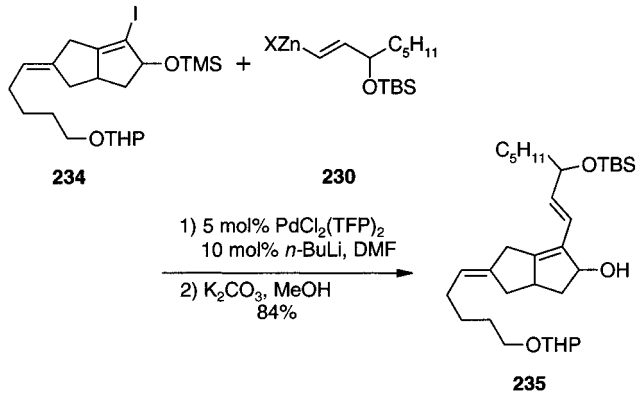
Scheme 41



Scheme 42



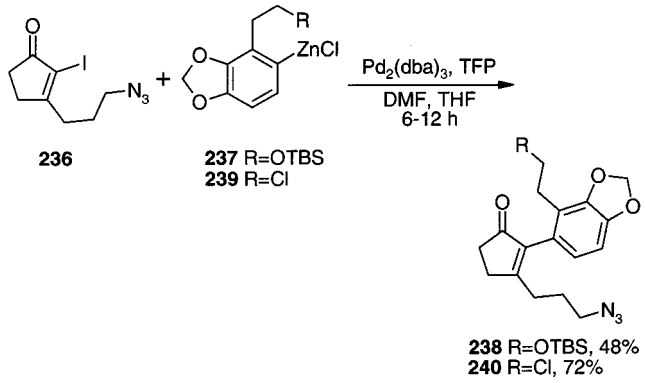
Scheme 43



of (±)-carbacyclin, was thus obtained in 84% isolated yield after selective cleavage of the TMS ether functionality.[106]

Negishi's conditions for the cross-coupling of α-iodoenones with zinc reagents have recently been employed by Molander and co-workers in a synthetic approach toward the alkaloid natural product cephalotaxine.[107] Treatment of azido halide **236** with aryl zinc **237** in DMF at room temperature with a $Pd_2(dba)_3$/TFP catalyst system furnished coupled product

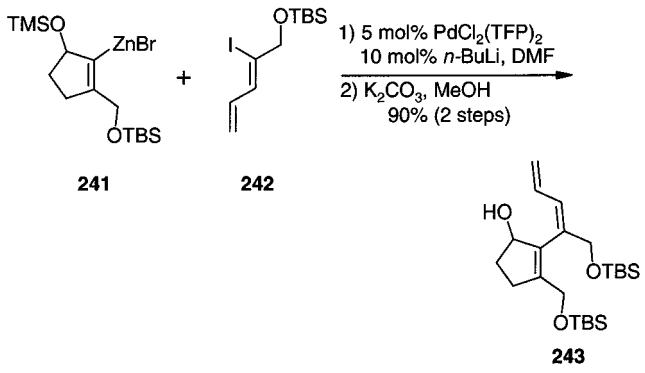
Scheme 44



238 in 48% yield (Scheme 44). Under otherwise identical conditions, α-iodoenone **236** could be coupled with aryl zinc **239** to give **240** in 72% yield after a 12 h reaction period. In both cases, thermal decomposition of the azide functionality was avoided by use of the mild TFP-mediated cross-coupling conditions. Moreover, as noted by Carboni and co-workers,[108] use of the less nucleophilic TFP ligand in place of PPh_3 with azido substrates may serve to eliminate competitive phosphinimine formation.

The total synthesis of nakienone A, a polyene natural product of marine origin, has recently been reported by Negishi and co-workers.[105,109] The key synthetic step, which was performed using a TFP-derived catalyst, involved the palladium(0) cross-coupling of vinyl zinc **241** with iodo diene **242** (Scheme 45). After selective cleavage of the TMS

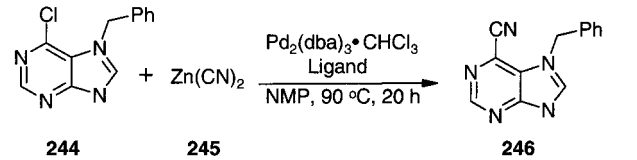
Scheme 45



protecting group, the desired product **243** was obtained in 90% yield with full control of the alkene geometry.

The synthesis of purinecarbonitriles via palladium(0)-catalyzed cross-coupling of halopurines with zinc cyanide has been reported by Gundersen.[110] In this study, $Pd_2(dba)_3 \cdot CHCl_3$ + 8TFP was found to be the catalyst of choice giving high yields of the desired nitriles. For example, treatment of chloropurine **244** and $Zn(CN)_2$ (**245**) with $Pd(PPh_3)_4$ in NMP at 90 °C gave cyanopurine **246** in 52% isolated yield (Scheme 46). Alternatively, use of the TFP-derived catalyst gave the desired product in 75% yield while the $Pd_2(dba)_3 \cdot CHCl_3$ + 8$AsPh_3$ completely failed to catalyze the reaction. Moreover, Gundersen showed this trend to be quite general for a variety of 2-, 6-, and

Scheme 46



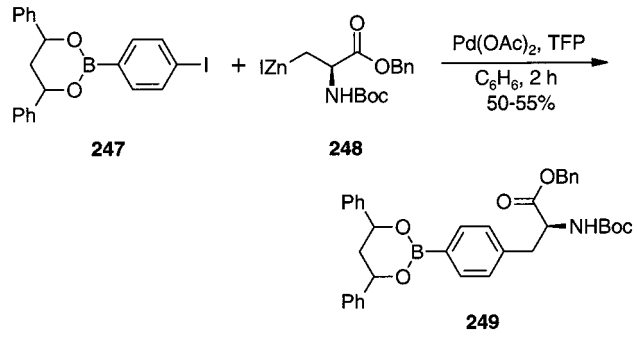
244 245 246

Ligand	Yield (%)
PPh_3	52
TFP	75
$AsPh_3$	0

8-halopurines as well as 8-haloadenosine nucleoside derivatives.

Morin and Malan[111] recently described a method for the preparation of boronic acid substituted amino acids using TFP-modified palladium catalysis (Scheme 47). Treatment of boronate ester **247** and enantiopure

Scheme 47

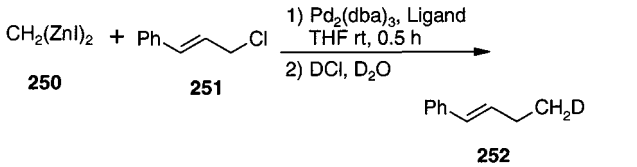


247 248 249

organozinc reagent **248** with a $Pd(OAc)_2$/TFP catalyst system in benzene afforded a 50−55% yield of the desired product **249** without evidence of competitive Suzuki-type coupling. Subsequent hydrogenolysis and removal of the Boc protecting group provided enantiopure 4-borono-L-phenylalanine in high yield.

The palladium-catalyzed functionalization of bis(iodozincio)methane (**250**) has been reported by Utimoto and co-workers[112] (Scheme 48). Coupling of **250**

Scheme 48



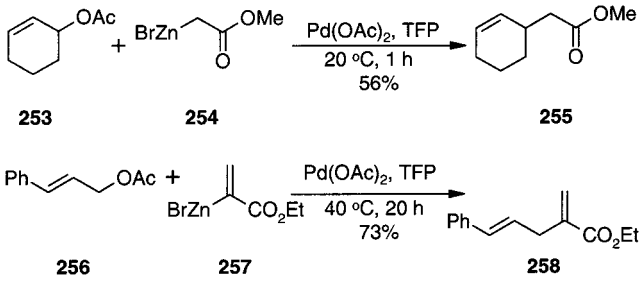
250 251 252

Ligand	Yield (%)
PPh_3	16
TFP	97

with cinnamyl chloride (**251**) in the presence of the TFP-derived catalyst system and subsequent quenching of the mixture with DCl/D_2O smoothly afforded product **252** in 97% yield. Under otherwise identical conditions, use of the PPh_3 palladium(0) catalyst gave only 16% of the desired product. Clearly, a ligand of low donor ability is highly beneficial to the present cross-coupling reaction. Utimoto used the described cross-coupling of bis(iodozincio)methane (**250**) with a large variety of electrophiles in a stepwise fashion to efficiently synthesize numerous difunctionalized methylene compounds.[112]

It has recently been demonstrated that the palladium(0)-catalyzed allylic alkylation of various allylic acetates with functionalized alkyl and alkenyl zinc reagents proceeds smoothly with the TFP catalyst system[113] (Scheme 49). Cross-coupling of cyclo-

Scheme 49



253 254 255

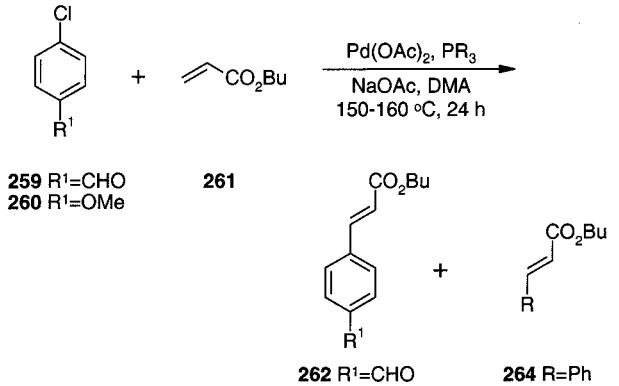
256 257 258

hex-2-enyl acetate (**253**) with Reformatsky reagent **254** at room temperature using a $Pd(OAc)_2$/TFP catalyst gave product **255** in 56% isolated yield. In all cases, employment of PPh_3- or P(*o*-Tol)$_3$-derived catalysts resulted in less than 25% yield of the desired ester **255**. Treatment of *E*-cinnamyl acetate (**256**) with alkenylzinc **257** at 40 °C for 20 h with the TFP catalyst gave product **258** in good yield via a regiospecific attack of the nucleophile on the less substituted terminus of the Pd π-allyl intermediate.

2. TFP-Mediated Arylation and Alkylation of Olefins by Organopalladium Compounds: The Heck Reaction and Related Processes

The palladium(0)-catalyzed Heck reaction[114] is a powerful method for the functionalization of a large variety of unsaturated substrates. Countless intermolecular, intramolecular, and asymmetric[115] versions of the Heck reaction have been reported in the literature,[116] and perhaps the only major limitation of the reaction is that the oxidative addition precursor may not contain β-hydrogen atoms. The Heck reaction between *n*-butyl acrylate (**261**) and aryl chlorides has recently been studied in considerable detail by Herrmann and co-workers[117] (Scheme 50). Treatment

Scheme 50



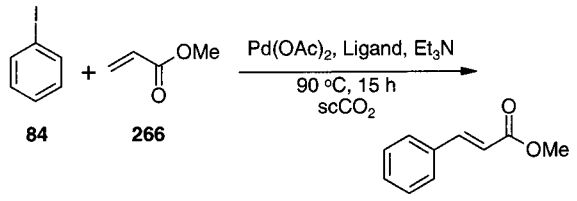
259 R¹=CHO
260 R¹=OMe
261
262 R¹=CHO
263 R¹=OMe
264 R=Ph
265 R=2-furyl

		Yield (%)			
R¹	PR_3	262	263	264	265
CHO	PPh_3	69		6.4	
CHO	TFP	64			4.1
OMe	PPh_3		41	6.4	
OMe	TFP		0		0

of activated aryl chloride **259** and acrylate **261** with $Pd(OAc)_2/PPh_3$ in DMA at 150 °C for 24 h afforded the desired Heck product **262** in 69% yield along with 6.4% *n*-butyl *E*-cinnamate (**264**). The latter product results from an unwanted phosphorus to palladium aryl migration process which occurs in the oxidative addition complex. Performing the reaction with TFP as the Pd ligand, under otherwise identical circumstances, gave the desired Heck product in 64% yield along with 4.1% of the furyl transfer byproduct **265**. Treatment of deactivated chloride **260** and acrylate **261** with the PPh_3-derived catalyst system at 160 °C for 24 h furnished 41% of the desired Heck product **263**, again containing 6.4% of compound **264**. However, employment of the TFP catalyst for this reaction completely failed to produce either product **263** or byproduct **265**. This result suggests that the TFP-modified Pd(0) species is not able to oxidatively add to *p*-chloroanisole (**260**).

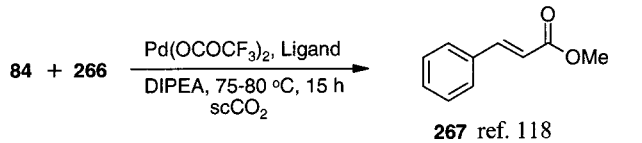
Recently, Tumas[56] and Rayner[118] independently studied the Heck coupling of iodobenzene (**84**) with simple olefins using a variety of phosphine catalysts in supercritical carbon dioxide. Tumas found that methyl acrylate (**266**) was efficiently arylated in $scCO_2$ at 90 °C after 12 h using a $Pd(OAc)_2$/TFP catalyst system (Scheme 51). In this study, tri-2-

Scheme 51



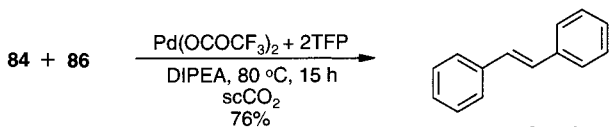
84 266 **267** ref. 56

Ligand	Conversion (%)	TOF (h^{-1})
P(*o*-Tol)$_3$	35	1
TFP	>95	2.7



267 ref. 118

Ligand	Conversion (%)
PPh_3	71
TFP	>95

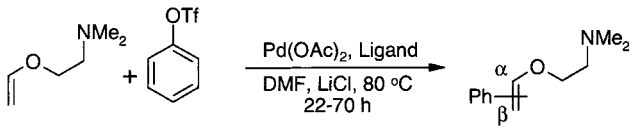


268 ref. 118

furylphosphine was found to be the best ligand in terms of both conversion and turnover frequency[119] (TOF (h^{-1})). Moreover, TFP was the only nonfluorinated phosphine to provide methyl *E*-cinnamate (**267**) in synthetically useful yield. Rayner and coworkers[118] found that the use of fluorinated palladium sources can be beneficial for $scCO_2$ Heck reactions. Employment of commercially available $Pd(OCOCF_3)_2$ as the precatalyst allowed for the use of lower reaction temperatures and catalyst loadings. Hence, treatment of methyl acrylate (**266**) and iodobenzene (**84**) at 80 °C for 15 h in $scCO_2$ with a $Pd(OCOCF_3)_2$/TFP catalyst system afforded coupled product **267** in excellent yield. Similarly, styrene (**86**) could be regioselectively arylated with iodobenzene (**84**) in $scCO_2$ to give *trans*-stilbene (**268**) in 76% isolated yield (Scheme 51). In either case, TFP was found the be the ligand of choice.

The Heck coupling of various organopalladium species with enol ethers[120] and other olefins which contain an α-heteroatom[121] has been studied in considerable detail. Unlike olefins which carry an electron-withdrawing functionality, unsaturated substrates carrying an α-heteroatom often exhibit poor regioselectivity in the Heck reaction.[122] Hallberg and co-workers[123] recently studied the Heck arylation of acyclic enol ether **269** with phenyl triflate (**270**) using a variety of catalyst systems (Scheme 52). In this

Scheme 52



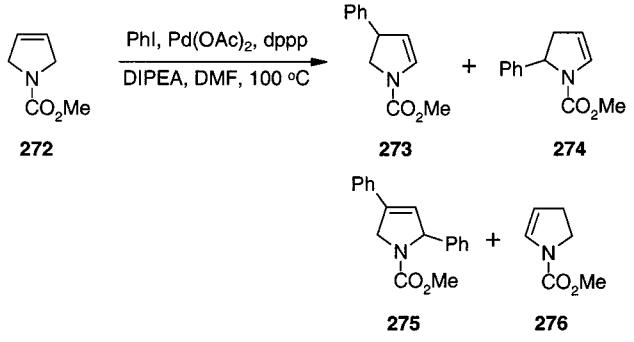
269 **270** **271**

Ligand	Yield (%)	*E*/*Z*	α : β
PPh_3	99	63/37	93 : 7
TFP	100	41/59	93 : 7
$AsPh_3$	8	23/77	94 : 6

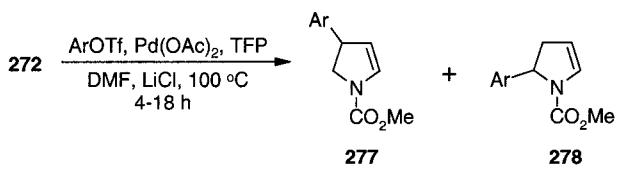
study, both the PPh_3- and TFP-derived catalyst systems were found to give coupled product **271** in high yield as a mixture of α- and *β*-regioisomers. While none of the phosphines tested were able to impart exclusive α-selectivity to the reaction, it is interesting to note the observed trend in the *β*-product double-bond geometry as the ligand becomes less coordinating. A reversal of selectivity can be seen in favor of the cis isomer upon changing the ligand from PPh_3 to $AsPh_3$ (Scheme 52).

Hallberg and co-workers[124] also studied the Heck arylation of various *N*-substituted 2,5-dihydropyrroles using the TFP catalyst system (Scheme 53). In this study, treatment of 1-(methoxycarbonyl)-2,5-

Scheme 53



272 **273** **274** **275** **276**

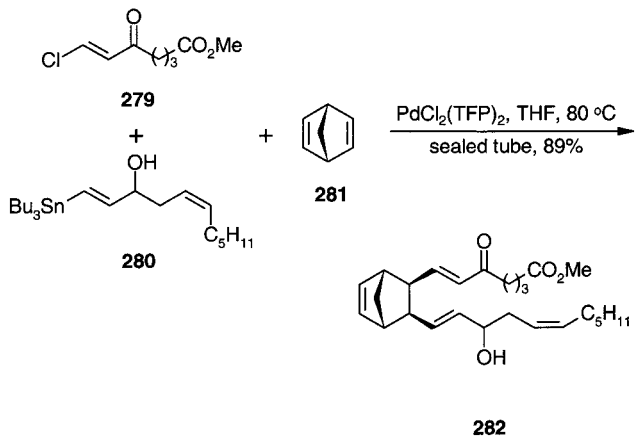


277 **278**

dihydropyrrole (**272**) and iodobenzene with a Pd(OAc)$_2$/dppp catalyst system in DMF at 100 °C afforded a mixture of products **273**−**276**. By using a large excess of the starting olefin, formation of the diarylated product **275** could efficiently be attenuated. In addition, changing the catalyst ligand to P(*o*-Tol)$_3$ and adding a silver salt suppressed the double-bond isomerization such that the desired product **273** could be obtained in >95% purity as evidenced by GCMS analysis. However, when triflates were employed as arylating agents, addition of lithium chloride and changing the catalyst ligand to TFP resulted in the formation of the desired product **277** and byproduct **278** in >96/4 ratio. This observation was found to be quite general for a variety of aryl triflates giving the desired 3-substituted-2,3-dihydropyrroles **277** in moderate yield and high isomeric purity.[124]

Kosugi and co-workers[125] reported using the TFP catalyst system in a ternary coupling reaction between chloride **279**, stannane **280**, and norbornadiene (**281**) to give adduct **282** in 89% yield as a single stereoisomer (Scheme 54). Subsequent retro Diels−

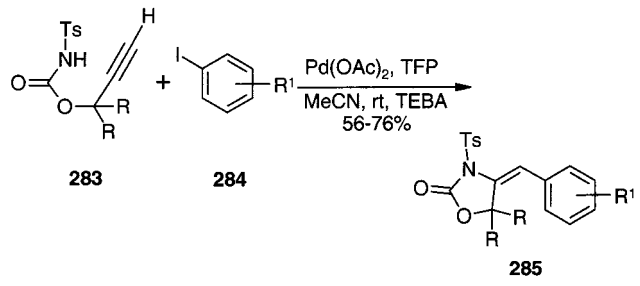
Scheme 54



Alder chemistry with product **282** provides an expedient, high-yielding route to fatty acid derivatives.

A powerful, stereodefined cyclization of tosyl carbamate **283** with various electrophiles **284** to furnish 4-arylidene-3-tosyloxazolidin-2-ones **285** has been described by Balme and co-workers[126] (Scheme 55).

Scheme 55[a]

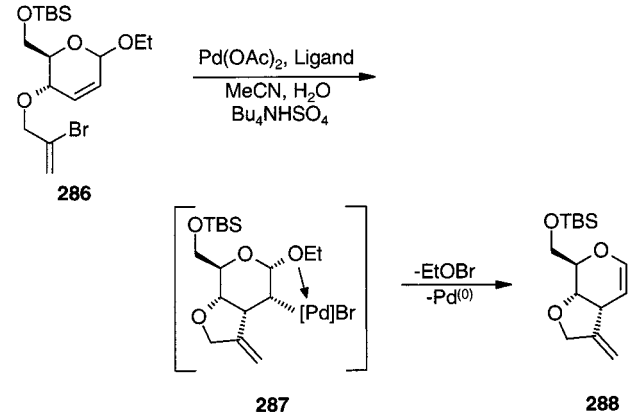


[a] TEBA = benzyltriethylammonium chloride.

Use of Pd(OAc)$_2$ as the palladium source in conjunction with the weakly coordinating TFP ligand in acetonitrile at room temperature was found to be optimal, providing the desired cyclized products in 56−76% yield. In all cases, ring closure occurred in a 5-*exo*-*dig* fashion giving the trans-arylated products **285** stereospecifically.

Sinou and co-workers[127] recently reported an unusual palladium-catalyzed annulation of vinyl bromide functionalized carbohydrates to provide bicyclic glycals (Scheme 56). Treatment of bromoalkene **286**

Scheme 56

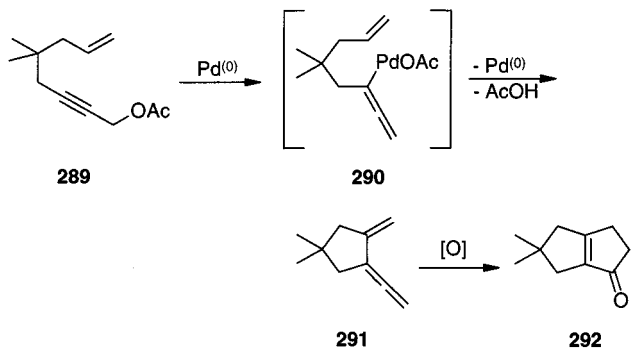


Ligand	Time (h)	Yield (%)
PPh_3	10	72
TFP	4	77
dppp	24	10

with a Pd(OAc)$_2$/PPh$_3$ catalyst system resulted in an intramolecular Heck cyclization to provide intermediate **287**, which underwent a β-dealkoxypalladation giving pyran **288** in 72% isolated yield. While few examples of such β-eliminations have been reported in the literature, these authors postulate that the anomeric oxygen facilitates the process by complexation to the metal center. Consistent with this hypothesis, use of a ligand with poor electron-releasing ability such as TFP resulted in an increased rate of reaction giving compound **288** in 77% yield. Conversely, employment of a highly basic, chelating phosphine such as bis(diphenylphosphino)propane (dppp) furnished **288** in 10% yield after a 24 h reaction period.

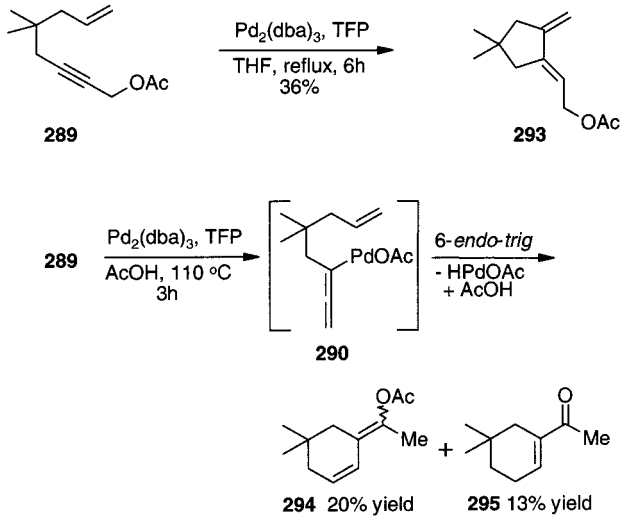
The palladium-catalyzed cyclization of dienes and enynes to produce five- and six-membered rings has been explored extensively by Trost and co-workers.[128] In an interesting study related to this chemistry, Goré[129] proposed that functionalized diquinanes such as **292** could be prepared by palladium-catalyzed annulation of propargylic ester **289** via a σ-allenylpalladium intermediate **290** (Scheme 57). Subse-

Scheme 57



quent oxidation of the allenic product **291** according to literature precedent[130] would then furnish the desired enone **292**. Unfortunately, treatment of acetate **289** with a variety of $Pd_2(dba)_3$/phosphine catalysts only led to slow decomposition of the starting material. However, utilization of the TFP ligand afforded diene **293** in 36% isolated yield (Scheme 58).

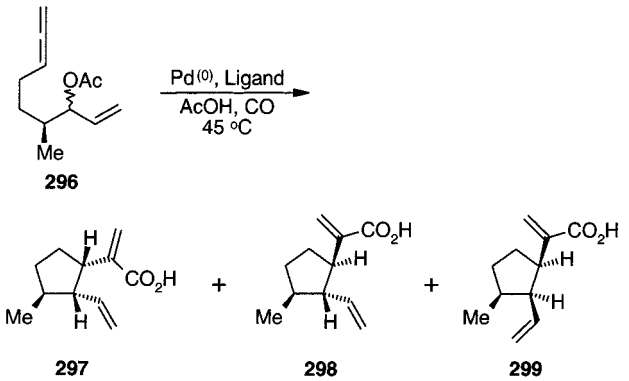
Scheme 58



Changing the solvent to acetic acid and heating the reaction to 110 °C resulted in the formation of diene **294** and enone **295** in 20% and 13% yield, respectively. The formation of these two products can be explained by a mechanism involving the expected σ-allenylpalladium intermediate **290** closing onto the double bond in an unusual 6-*endo-trig* fashion. Subsequent acid-catalyzed addition of AcOH or H_2O to the resulting cyclized product would then furnish acetate **294** and enone **295**, respectively. Use of the TFP catalyst system afforded the highest yield of enol acetate **294**, and further attempts to improve this process have unfortunately been unsuccessful.

The palladium(0)-catalyzed cyclization−carbonylation of allylic acetate **296** has recently been studied by Takahashi and co-workers[131] (Scheme 59). Treatment of **296** in acetic acid under an atmosphere of carbon monoxide with a $Pd_2(dba)_3/PPh_3$ catalyst

Scheme 59

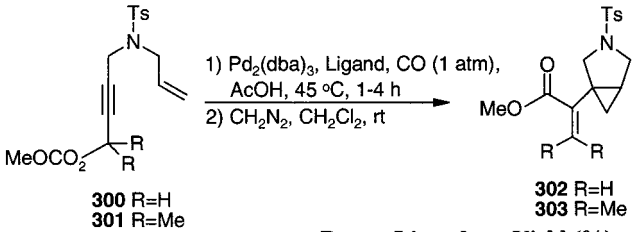


Ligand	Yield (%)	Ratio (%) 297	298	299
PPh_3	19	71	19	10
TFP	61	61	30	9

system furnished a mixture of three stereoisomeric products **297**−**299** in 19% isolated yield. Utilization of a TFP-derived catalyst was found to significantly improve the yield of the reaction but also resulted in reduced stereoselectivity. The major stereoisomer **297**, which contained the correct relative seterochemistry for a variety of natural products, and its epimer **298** were subsequently converted to (±)-isoiridomyrmecin via a three-step synthetic sequence in 47% yield.[131]

The palladium-catalyzed intramolecular cyclization of olefinic propargylic carbonates using the TFP catalyst system has been reported by Pimm and coworkers[132] (Scheme 60). Heating tosyl sulfonamide

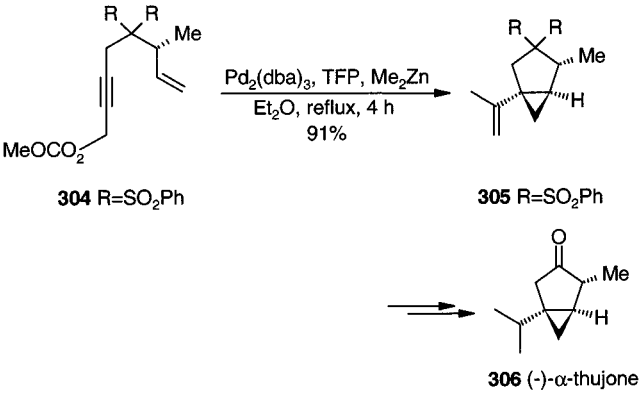
Scheme 60



R	Ligand	Yield (%)
H	PPh_3	10
H	TFP	93
Me	PPh_3	65
Me	TFP	93

300 or **301** under an atmosphere of CO with a $Pd_2(dba)_3/PPh_3$ catalyst in AcOH at 45 °C and subsequent esterification of the product with CH_2N_2 furnished cyclopropane derivatives **302** and **303** in 10% and 65% yields, respectively. However, use of the corresponding TFP catalyst afforded the desired products **302** and **303** in 93% isolated yield. Cyclization of carbonates **300** and **301** with trapping agents other than carbon monoxide, including organoboranes, dialkylzincs, and hydride sources, has been shown to be quite efficient using the TFP-derived catalyst.[132] Treatment of enantiopure *gem*-bis-sulfone **304** under the described conditions afforded cyclized product **305** in 91% yield (Scheme 61). Subsequent

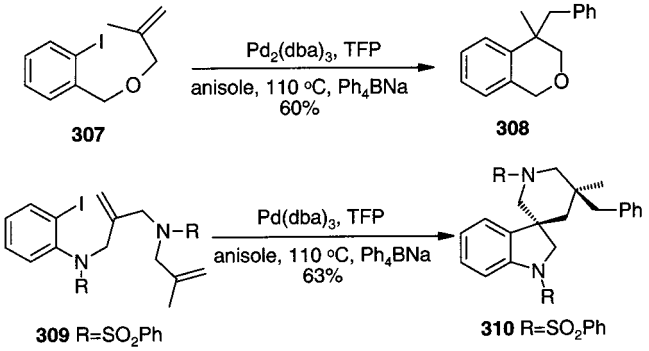
Scheme 61



reductive cleavage of a single sulfone group followed by MoOPh oxidation and catalytic hydrogenation afforded the monoterpene natural product (−)-α-thujone (**306**) in high yield.

Palladium(0)-catalyzed intramolecular cyclization followed by anion capture can be an extremely powerful synthetic sequence for the preparation of fused cyclic, spirocyclic, carbocyclic, and heterocyclic systems. Such processes have been studied in considerable detail by Grigg and co-workers[133] for a large variety of substrates and anion transfer agents. For example, treatment of aryl iodide **307** with a $Pd_2(dba)_3$/TFP catalyst in anisole at 110 °C along with a tetraphenylborate anion transfer agent afforded ether **308** in 60% isolated yield[133a] (Scheme 62). Similarly,

Scheme 62

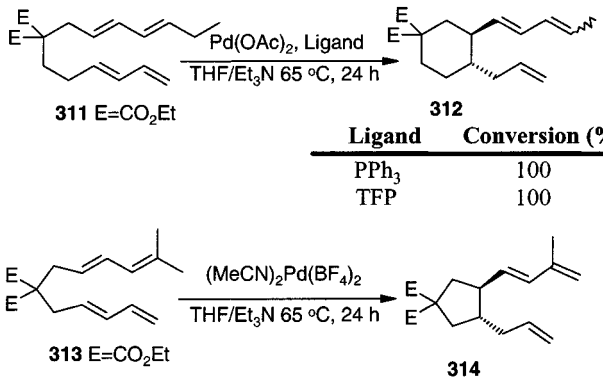


the palladium-catalyzed polyene cyclization of sulfonamide **309** and subsequent anion capture with $NaBPh_4$ gave spiro product **310** as a single diastereomer in 63% yield. Unfortunately, no comparisons have been presented for these two reactions using the standard PPh_3 catalyst system.

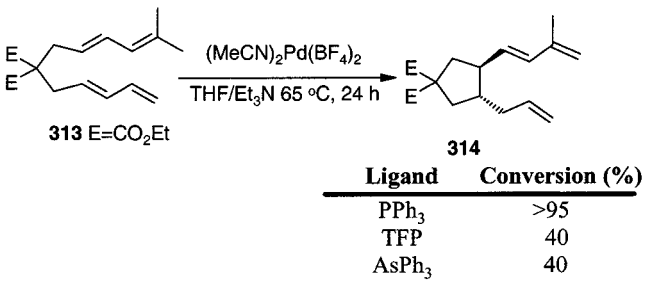
3. Palladium-Catalyzed Cycloisomerization of Dienes, Diynes, and Enynes

The palladium-catalyzed cycloisomerization of bisdienes to give carbocyclic five- and six-membered rings has recently been studied by Takacs and co-workers[134] using various ligands (Scheme 63). Treat-

Scheme 63



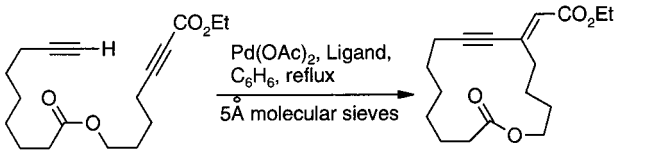
Ligand	Conversion (%)
PPh_3	100
TFP	100



Ligand	Conversion (%)
PPh_3	>95
TFP	40
$AsPh_3$	40

ment of unsymmetrical tetraene **311** with either a PPh_3- or TFP-derived catalyst system at 65 °C for 24 h was found to afford *trans*-cyclohexane derivative **312** in quantitative yield as a *E*,*E*:*E*,*Z* isomeric mixture. However, the cycloisomerization of bisdiene **313**, using a different catalyst precursor, gave compound **314** in near quantitative conversion with the PPh_3 ligand while the TFP and $AsPh_3$ catalyst systems resulted in only 40% of the desired cyclized product. Hence, catalysts which are comprised of poorly donating ligands seem to be less general for palladium-catalyzed cycloisomerization reactions. Trost and co-workers,[135] upon studying the cycloisomerization of α,ω-diynes using various phosphine ligands, also found the TFP ligand to be less effective (Scheme 64). Bisacetylene **315**, when treated with a $Pd(OAc)_2$/

Scheme 64

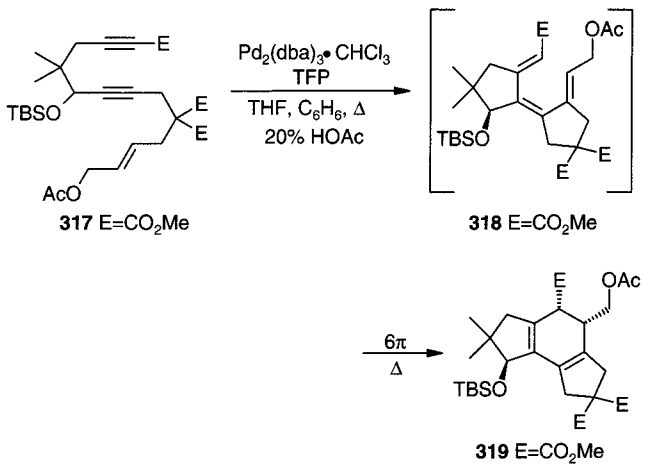


Ligand	Yield (%)
PPh_3	55
TFP	7.2

PPh_3 catalyst under high dilution conditions, could be cyclized to give macrocycle **316** in 55% yield a single double-bond isomer. Utilization of the TFP ligand, however, provided only 7.2% of the desired 15-membered ring **316**. Optimal conditions for this macrocyclization involved the use of the bulky, electron-rich ligands such as tris(*o*-methoxyphenyl)-phosphine.

Trost[136] reported an elegant palladium-catalyzed cycloisomerization of endiyne **317** to give tricycle **319** in a single operation through **318** (Scheme 65). Using

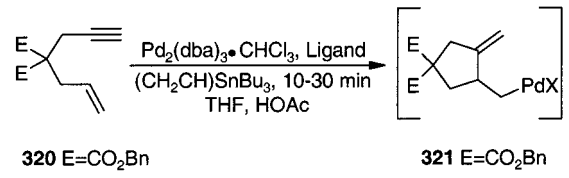
Scheme 65



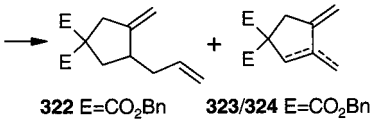
PPh_3 as the palladium ligand, reaction of acetate **317** gave a complex mixture of products, while use of the weakly coordinating TFP ligand afforded cycloisomer **319** in 61% yield as a single diastereomer. Interestingly, only the trans isomer of the starting olefin was found to undergo the subsequent 6π-electrocyclic ring closure giving the desired tricyclic diene **319**.

The cycloisomerization of enyne **320** and subsequent cross-coupling of σ-alkylpalladium intermediate **321** with various organostannanes has recently been studied by Kibayashi and co-workers[137] (Scheme

Scheme 66



320 E=CO_2Bn **321** E=CO_2Bn



322 E=CO_2Bn **323/324** E=CO_2Bn

Ligand	Yield (%) 322	323/324
PPh_3	28	30
TFP	trace	69
none	45	0

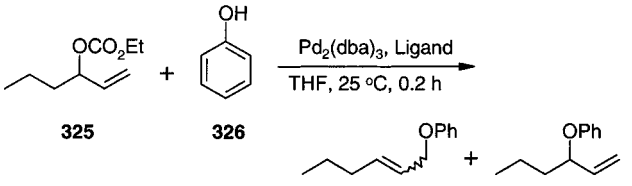
66). Heating 1,6-enyne **320** and vinyltributylstannane with a PPh_3-based catalyst system in THF/HOAc produced a 28% yield of the desired cross-coupled product **322** along with mixture of double-bond isomers, **323** and **324**, resulting from β-hydride elimination. Use of the TFP ligand resulted in a 69% yield of the unwanted elimination products with only a trace amount of the desired product being formed. Interestingly, a "ligandless" Pd catalyst provided the desired cross-coupled product **322** exclusively in 45% yield.

4. Palladium-Catalyzed Etherification and Lactonization Reactions Using TFP

The tri-2-furylphosphine ligand has recently been used in a number of palladium-catalyzed etherification and lactonization reactions. For example, Sinou and co-workers[138] studied the relationship between phosphine donor ability and regioselectivity of etherification using allyl carbonate **325** and phenol (**326**) (Scheme 67). The findings suggested that both steric and electronic effects govern which end of the π-allyl complex is attacked by the nucleophile. Specifically, ligands of low electron-releasing ability were found to increase the regioselectivity in favor of the unbranched product **327**. Conversely, highly basic phosphines generally gave sluggish catalysts which favored formation of the branched regioisomer **328**. In a subsequent study, the same workers investigated an intramolecular etherification of allylic carbonate **329** for the preparation of *cis*- and *trans*-linalyl oxides **330** and **331**, respectively (Scheme 67).[139] While both PPh_3- and TFP-derived catalysts smoothly furnished the desired cyclized products in good yield, the diastereomeric ratio was found to be independent of phosphine basicity. Furthermore, it was determined that the double-bond geometry of the starting diol had no effect on either the yield or diastereoselectivity of the reaction.

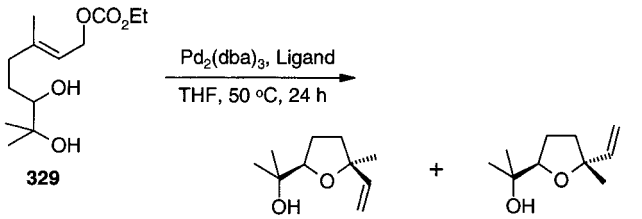
The palladium(0)-mediated lactonization of pentynoic acids has been investigated using the TFP-derived catalyst system. Treatment of acid **332** and acetylenic bromide **333** with potassium *tert*-butoxide

Scheme 67



325 **326** **327** **328**

Ligand	Conversion (%)	327: 328
PPh_3	100	49 : 51
TFP	100	63 : 37

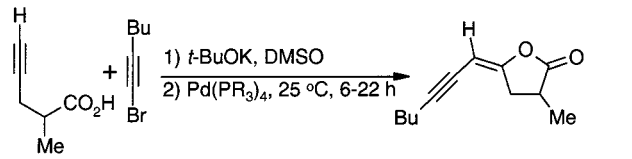


329 **330** **331**

Ligand	Yield (%)	330 : 331
PPh_3	70	81 : 19
TFP	65	82 : 18

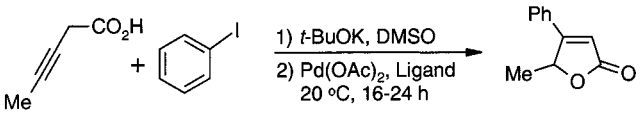
in DMSO and a palladium catalyst was found to give lactone **334** in moderate to excellent yield[140] (Scheme 68). The reaction proceeds by nucleophilic attack of

Scheme 68



332 **333** **334**

Ligand	Yield (%)
P(*o*-Tol)$_3$	42
TFP	90



335 **84** **336**

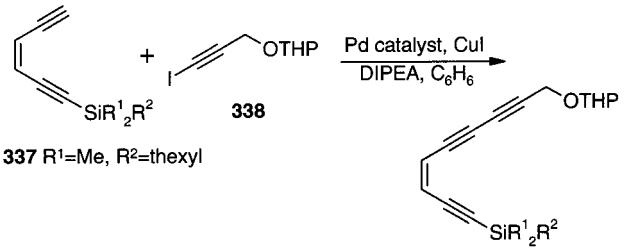
Ligand	Yield (%)
TFP	65
$AsPh_3$	46

the carboxylate anion onto the triple bond, which is presumably activated by the σ-ethynylpalladium complex, in an 5-*exo*-*dig* fashion. In this study, TFP was found to work remarkably well, giving the desired cyclized product **334** in 90% isolated yield. Similarly, treatment of 3-pentynoic acid (**335**) and iodobenzene (**84**) with *t*-BuOK in DMSO and a palladium catalyst afforded lactone **336** in moderate yield[141] (Scheme 68). In this case, cyclization proceeds in a 5-*endo*-*dig* manner giving initially the 3*H*-furan-2-one product. Subsequent base-catalyzed isomerization of the double bond furnishes enone **336**. For this process, TFP was found to be the ligand of choice and consistently outperformed Ph_3As in terms of both yield and rate of reaction.

5. Palladium-Catalyzed Cross-Coupling of Acetylenes

The palladium-catalyzed Sonogashira coupling[142] of terminal acetylenes with organohalides is a powerful method for the preparation of conjugated alkynes. Schreiber and co-workers[143] used TFP-derived catalysts to cross-couple a variety of alkynes for the preparation of enetetraynes (Scheme 69). Treatment

Scheme 69

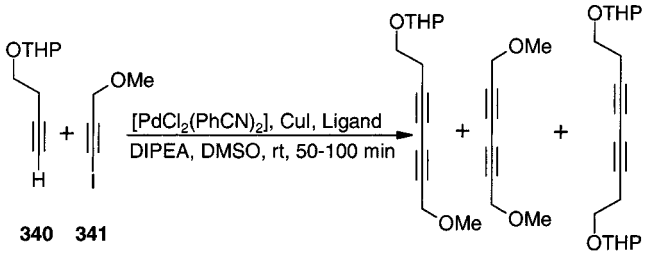


Catalyst	Yield (%)
$(MeCN)_2PdCl_2$	20
$Pd_2(dba)_3$/TFP	77

of thexyldimethylsilyl acetylene **337** and alkynyl iodide **338** with a $Pd_2(dba)_3$/TFP catalyst in benzene afforded the desired product **339** in 77% isolated yield. Schreiber and co-workers employed these optimized conditions for a variety of alkyne−alkyne coupling reactions obtaining the desired products in 59−77% yield.[143]

The cross-coupling of alkynes with haloalkynes has also been studied by Vasella and co-workers.[144] Treatment of THP-protected propargylic alcohol **340** and iodo alkyne **341** with a PPh_3-based catalyst system in DMSO at room temperature afforded the desired heterocoupled product **342** in 63% yield along with the corresponding homocoupled products **343** and **344** in 21% and 14% yields, respectively (Scheme 70). However, use the TFP ligand led to the highest

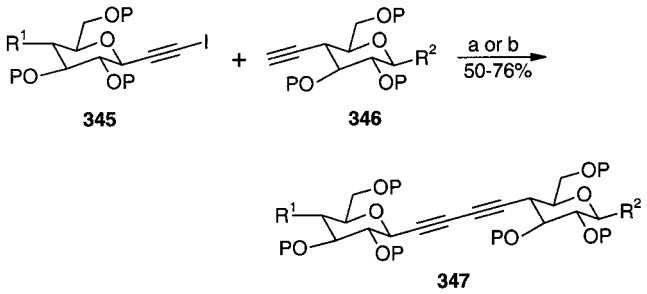
Scheme 70



Ligand	Yield (%)	Ratio (%) 342	343	344
PPh_3	98	63	21	14
TFP	88	65	19	4

rate of coupling and the best selectivity for the desired heterocoupled product **342**. Vasella and co-workers[145] successfully employed the TFP-modified catalyst system for the synthesis of a wide variety of bis-acetylene-linked carbohydrate compounds **347** starting with suitably protected haloalkynes **345** and terminal acetylenes **346** (Scheme 71).

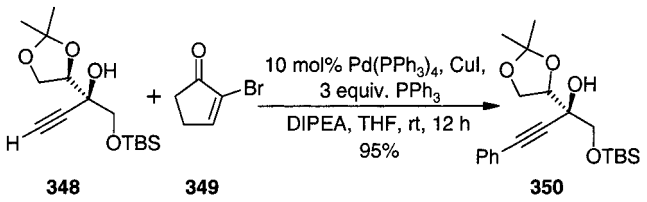
Scheme 71[a]



[a] Conditions: (a) $PdCl_2(PhCN)_2$, TFP, DIPEA, DMSO, 50 °C. (b) $Pd_2(dba)_3$, TFP, CuI, DMSO, rt.

The attempted Sonogashira coupling of alkyne **348** and α-bromo enone **349** has been reported by Buszek and Jeong[146] (Scheme 72). Using catalytic $Pd(PPh_3)_4$

Scheme 72



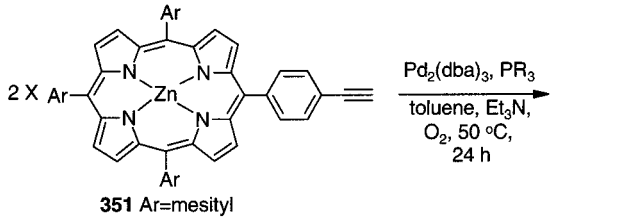
failed to furnish the desired cross-coupled product, so recourse was taken in a stoichiometric quantity of palladium. Under these conditions, the major product was determined to be phenyl derivative **350** resulting from an aryl migration from the phosphine ligand. Employing a catalytic quantity of $Pd(PPh_3)_4$ in conjunction with 3 equiv of added triphenylphosphine resulted in a 95% yield of **350**. Similarly, adding an excess of TFP to the mixture gave the corresponding furyl adduct in 95% yield contaminated with a small amount of the phenyl derivative **350**. In contrast, tribenzylphosphine, tributylphosphine, and tricyclohexylphosphine did not result in the transfer of benzyl, butyl, or cyclohexyl groups, respectively.[146]

The palladium-catalyzed oxidative dimerization of terminal acetylene **351** using different catalyst ligands has been studied by Lindsey and co-workers[147] (Scheme 73). Employing a $Pd_2(dba)_3/PPh_3$ catalyst system in toluene at 50 °C afforded porphyrin dimer **352** in 37% yield along with a significant amount of higher molecular weight material (HMWM). However, utilization of a TFP-derived catalyst was found to increase the yield and purity of the desired diyne **352**. Although $AsPh_3$ catalysts worked well in similar coupling reactions,[147] use of this catalyst with porphyrin acetylene **351** furnished dimer **352** in 56% isolated yield with a 0.80:1 HMWM:product ratio.

6. TFP-Modified Palladium(0)-Catalyzed Cross-Coupling of Organoboron Compounds: The Suzuki Reaction and Related Processes

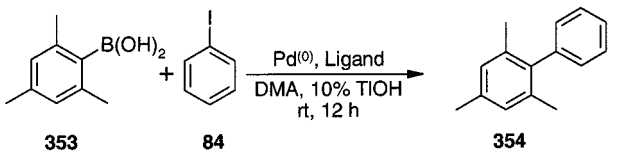
The effect of ligand donor ability on ambient temperature Suzuki coupling has recently been studied by Anderson and co-workers[148] (Scheme 74). Treatment of mesitylboronic acid (**353**) and iodobenzene (**84**) with tetrakis(triphenylphosphine)palladium(0) in DMA at room temperature using 10% aqueous

Scheme 73



PR_3	Yield (%)	HMWM : 352
PPh_3	37	0.94 : 1
TFP	67	0.30 : 1

Scheme 74

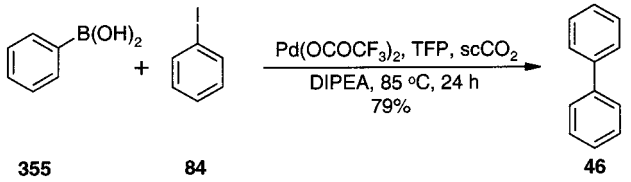


Ligand	Yield (%)
PPh_3	97
TFP	85
$AsPh_3$	51

TlOH as the base furnished biaryl **354** in near quantitative yield. Utilization of TFP and $AsPh_3$ as ligands, under otherwise identical conditions, resulted in diminished yields of the desired biaryl **354**. Moreover, these workers noted that the rate of Suzuki cross-coupling between mesityl boronic acid (**353**) and iodobenzene (**84**) did not increase upon using ligands of reduced donor ability.

The Suzuki cross-coupling of phenylboronic acid (**355**) and iodobenzene (**84**) in supercritical carbon dioxide has been reported by Rayner and co-workers[118] (Scheme 75). Using a fluorinated palladium

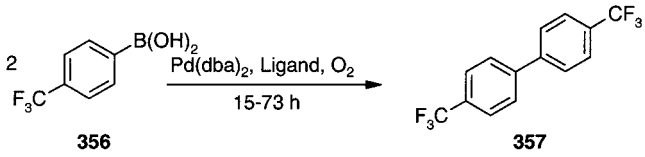
Scheme 75



source in conjunction with the TFP ligand gave biphenyl (**46**) in 79% isolated yield after a 24 h reaction period. Again, the favorable solubility of TFP in $scCO_2$ proved to be highly advantageous, making this the ligand of choice for the described conditions.

Palladium-catalyzed homocoupling of arylboronic acids to give symmetrical biaryls has recently been studied by Moreno-Mañas and co-workers[149] (Scheme 76). In this study, treatment of 4-(trifluoromethyl)-phenylboronic acid (**356**) with a $Pd_2(dba)_3/PPh_3$ catalyst system under an ambient atmosphere furnished

Scheme 76



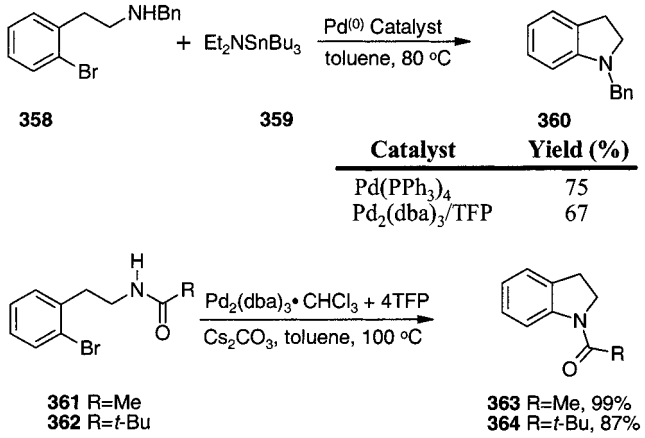
Ligand	Yield (%)	Time (h)
PPh_3	40	73
TFP	93	15

biaryl **357** in 40% yield after a 73 h reaction time. Alternatively, employment of a TFP-derived catalyst system was found to accelerate the reaction giving the desired homocoupled product **357** in 93% yield after a 15 h reaction period.

7. Palladium-Catalyzed Amination, Phosphonylation, and Sulfenylation of Aryl Halides

Early efforts by Buchwald and co-workers[150] to develop a palladium-catalyzed amination of aryl bromides resulted in conditions which require a stiochiometric equivalent of (*N*,*N*-diethylamino)tributyltin (**359**) (Scheme 77). Treatment of benzyl-

Scheme 77

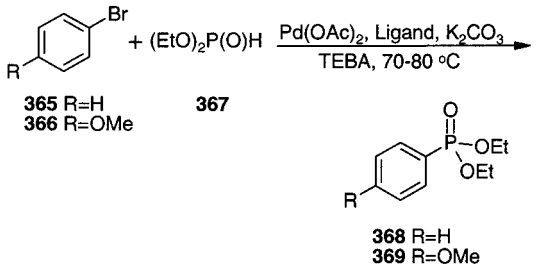


Catalyst	Yield (%)
$Pd(PPh_3)_4$	75
$Pd_2(dba)_3$/TFP	67

amine **358** with aminostannane **359** and a $Pd(PPh_3)_4$ catalyst at 80 °C furnished the desired dihydroindole **360** in 75% isolated yield. Utilization of a $Pd_2(dba)_3 \cdot CHCl_3$/TFP catalyst system was slightly less efficient, providing the desired heterocycle in 67% yield. Under main-group-free conditions,[150a] optimal results for the intramolecular amidation of bromide **361** or **362** were achieved with $Pd_2(dba)_3$/TFP as the catalyst and Cs_2CO_3 as the base. Hence, the desired cyclized products **363** and **364** were obtained in 99% and 87% isolated yields, respectively. Employment of PPh_3-based catalysts either required longer reaction times or provided lower yields.

Palladium-catalyzed phase-transfer phosphonylation of aryl iodides and bromides **365** and **366** with **367** using the TFP ligand has recently been reported by Beletskaya and co-workers[151] (Scheme 78). In this study, both the PPh_3- and TFP-derived catalyst systems provided the desired arylphosphonates **368** and **369** in high yield, although significantly reduced reaction times were observed using latter catalyst. These workers showed that dimethyl, diethyl, and diisopropyl phosphonates may be cross-coupled with

Scheme 78[a]



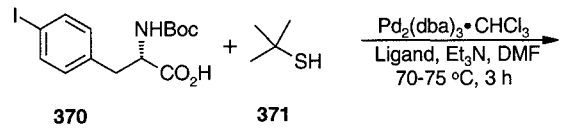
R	Ligand	Time (h)	Yield (%)
H	PPh_3	40	100
H	TFP	19	100
OMe	PPh_3	46	98
OMe	TFP	20	98

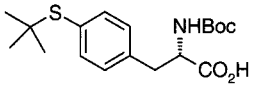
[a] TEBA = benzyltriethylammonium chloride.

a variety of aryl halides, bearing electron-donating or -withdrawing functionalities, in high yield using the TFP catalyst system.

In an effort to prepare unnatural amino acid derivatives, Tomich and co-workers[152] sought to cross-couple *N*-protected *p*-iodophenylalanine **370** with *tert*-butylthiol (**371**) under palladium catalysis (Scheme 79). Although the dppf ligand furnished the

Scheme 79





372

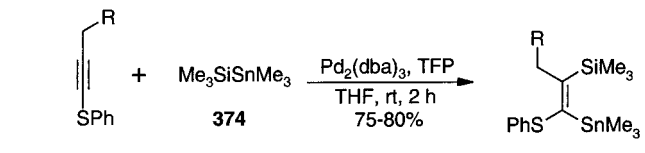
Ligand	Yield (%)
PPh_3	26
TFP	trace
dppf	99

desired thiophenylalanine derivative **372** in near quantitative yield, utilization of PPh_3 or TFP for the coupling resulted in poor yields. In the latter case, only a trace amount of the desired cross-coupled product was detected by HPLC analysis. Hence, ligands of low donor ability appear to have an adverse effect on the present cross-coupling reaction.

8. Palladium-Catalyzed Silylstannylation Using TFP

Kocienski and co-workers[153] reported the use of TFP in the palladium-catalyzed silylstannylation of 1-phenylthio-1-alkynes (Scheme 80). Treatment of a variety of thioalkynes **373** and $Me_3SiSnMe_3$ (**374**) in THF at room temperature for 2 h with a $Pd_2(dba)_3$/

Scheme 80



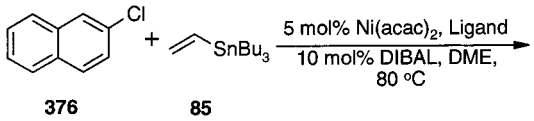
373 R=OH, OMe, OTHP, $(CH_2)_2OH$, *n*-Pr, CO_2Ar

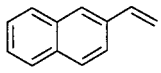
TFP catalyst system furnished the desired olefins **375** in good yields. Using a $Pd(PPh_3)_4$ catalyst required heating and extended reaction times to provide the same set of silylstannanes **375** in only 11−58% yield. In either case, the regioselectivity of the reaction highly favored formation of the desired α-stannylated isomer **375**.

D. Nickel-Catalyzed Reactions Using Tri-2-furylphosphine

Shirakawa and co-workers[154] recently reported the nickel-catalyzed cross-coupling of aryl halides and sulfonates with organostannanes. Although this process is analogous to the palladium-catalyzed Stille reaction, the TFP catalyst system has proven to be less effective than the corresponding PPh_3 catalyst for the cross-coupling of 2-chloronaphthalene (**376**) and tributylvinyltin (**85**) to give **377** (Scheme 81).

Scheme 81





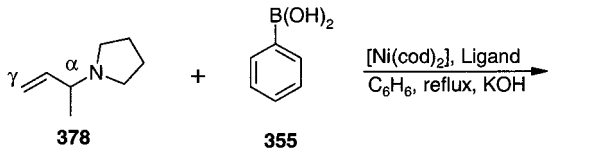
377

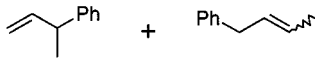
Ligand	Yield (%)
PPh_3	86
TFP	64

Unfortunately, in these studies use of the TFP catalyst has been limited to aryl chloride precursors, and it is therefore unclear whether Farina's observations regarding TFP in the Stille process[10] apply to the present cross-coupling reaction.

Trost and co-workers[155] studied the nickel-catalyzed coupling of allylamines with boronic acids using a variety of phosphine ligands. Treatment of allylamine **378** and phenyl boronic acid (**355**) with a $[Ni(cod)_2]/PPh_3$ catalyst system in refluxing benzene furnished a mixture of coupled products **379** and **380** in 72% yield (Scheme 82). Under otherwise identical

Scheme 82





379 380

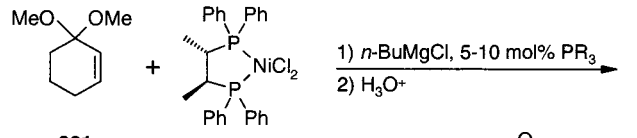
Ligand	Yield (%)	α : γ
PPh_3	72	1.6 : 1
TFP	54	1.6 : 1

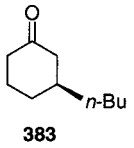
conditions, the corresponding TFP catalyst provided compounds **379** and **380** in the same relative ratio but in reduced yield. Although the isomeric ratio of products remained constant using the PPh_3- and

TFP-derived catalysts, Trost and co-workers showed that strongly donating and sterically demanding ligands such as triisopropylphosphine tend to favor bond formation at the less substituted γ-position of allylamine **378**.

Nickel-catalyzed asymmetric addition of Grignard reagents to unsaturated cyclic acetals has recently been studied by Hoveyda and co-workers[156] (Scheme 83). Interestingly, treatment of dimethyl acetal **381**

Scheme 83





383

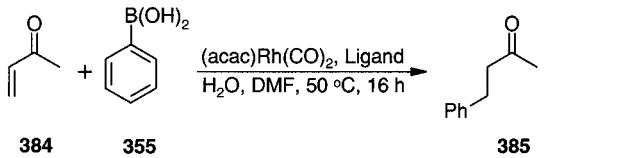
PR_3	Conversion (%)	ee (%)
PPh_3	61	82
TFP	60	40

and *n*-BuMgCl with 5 mol % of nickel complex **382** in THF at room temperature afforded ketone **383** in 10% ee (80% yield) after an acidic workup. However, using a 10 mol % PPh_3 additive, under otherwise identical conditions, provided the desired cross-coupled product **383** in 82% ee with 61% conversion. The reasons for the observed enhancement in stereoselectivity upon the addition of excess achiral phosphine have not yet been established, although it has been shown that PPh_3 affords optimal results. Treatment of acetal **381** and *n*-BuMgCl with 5 mol % catalyst **382** and 5 mol % TFP gave product **383** in 40% ee (60% conversion). Although highly basic phosphines generally increased the yield of the desired product, these ligands also proved to be detrimental to enantioselectivity.

E. Rhodium-Catalyzed Conjugate Addition Using the TFP Ligand

The rhodium(I)-catalyzed conjugate addition of phenyl boronic acid (**355**) with methyl vinyl ketone (**384**) using various phosphine ligands has been reported by Miyaura and co-workers[157] (Scheme 84).

Scheme 84



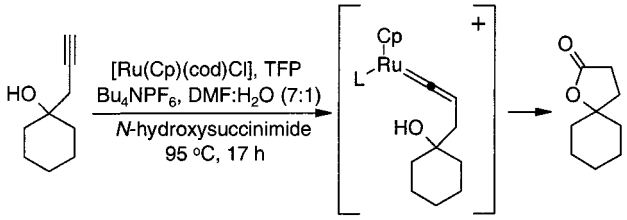
Ligand	Yield (%)
PPh_3	83
TFP	94

Heating a mixture of MVK (**384**) and boronic acid **355** in aqueous DMF solution with a [Rh(acac)$(CO)_2$]/PPh_3 catalyst system furnished the desired product **385** in 83% yield. Under otherwise identical conditions, utilization of the TFP ligand afforded ketone **385** in 94% yield. Although the TFP ligand performs well in this process, optimal conditions for the desired conjugate addition have been shown to include the use of seven-membered chelate ligands such as bis-(diphenylphosphino)butane (dppb).[157]

F. Ruthenium-Catalyzed Cycloisomerization–Oxidation of Homopropargyl Alcohols

Trost and Rhee[158] recently developed a novel ruthenium-catalyzed cycloisomerization−oxidation of homopropargyl alcohols for the synthesis of γ-butyrolactones (Scheme 85). Treatment of alkyne **386** with

Scheme 85



7 mol % cyclopentadienyl(1,4-cyclooctadiene)ruthenium chloride, 10 mol % TFP, and 45 mol % tetra-*n*-butylammonium bromide in the presence of 3 equiv of *N*-hydroxysuccinimide in aqueous DMF at 90 °C for 17 h afforded spiro-lactone **388** in 76% isolated yield. In this study, TFP was found to be the ligand of choice due to its small size and low electronic availability. Presumably, the poor σ-donor ability of the TFP ligand facilitates the nucleophilic addition step by increasing the electrophilicity of ruthenium while minimizing steric hindrance. This efficient access to functionalized γ-butyrolactones has been applied to a wide diversity of homopropargyl alcohols and has been used in a concise enantioselective synthesis of the acetogenin (−)-muricatacin.[158]

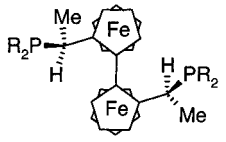
III. 2-Furyl Phosphines in Asymmetric Metal-Mediated Organic Synthesis

Although there are numerous examples of 2-furyl phosphine containing structures reported in the literature, very few of these materials have been employed as ligands in metal-catalyzed organic reactions. The sections which follow comprehensively detail the use of novel 2-furyl phosphine ligands in synthetic processes.[159,160] Where possible, the results obtained with these ligands are compared to those attained with structurally similar phosphine analogues.

A. Reactions Using 2,2′-Bis[1-(di-2-furylphosphino)ethyl]-1,1′-biferrocene

A series of trans-chelating chiral phosphine ligands **389a**−**e**, abbreviated as TRAPs, containing a biferrocene core structure have been introduced by Ito and co-workers[161] (Chart 3). These ligands have been shown to be effective in a variety of rhodium(I)-catalyzed asymmetric reactions including hydrogena-

Chart 3. Selected Trans-Chelating Chiral Diphosphine Ligands (TRAPs)

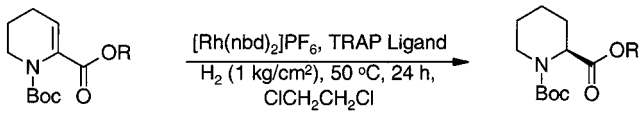


(*S,S*)-(*R,R*)-TRAP

389a, R=Ph
389b, R=2-furyl
389c, R=(*p*-$CF_3C_6H_4$)
389d, R=Et
389e, R=*n*-Bu

tion of prochiral olefins, Michael addition to α-cyanocarboxylates, and hydrosilylation of ketones. The 2-furyl-substituted TRAP **389b** (FurTRAP)[162] has recently been employed in the asymmetric hydrogenation of various α,β-unsaturated esters. For example, heating a solution of ester **390** under a hydrogen atmosphere in the presence of a Rh(I)−PhTRAP catalyst furnished the desired product **391** in 90% ee having the *S*-configuration[163] (Scheme 86).

Scheme 86

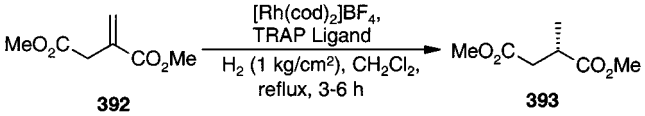


390 R=i-Bu **391**

TRAP Ligand	Conv. (%)	ee (%)	Config.
(*S,S*)-(*R,R*)-PhTRAP (**389a**)	100	90	*S*
(*S,S*)-(*R,R*)-FurTRAP (**389b**)	100	35	*S*

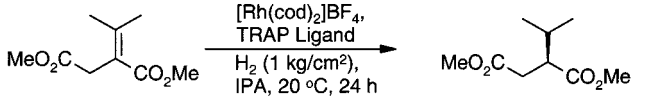
Although the corresponding FurTRAP catalyst also provided product **391** in high yield, a significant reduction in enantioselectivity was observed. Ito and co-workers obtained similar results in the rhodium(I)-catalyzed asymmetric hydrogenation of dimethyl itaconate (**392**)[164] (Scheme 87). Using a $[Rh(cod)_2]BF_4$/

Scheme 87



392 **393**

TRAP Ligand	Conv. (%)	ee (%)	Config.
(*R,R*)-(*S,S*)-EtTRAP (**389d**)	100	96	*S*
(*R,R*)-(*S,S*)-PhTRAP (**389a**)	100	26	*R*
(*R,R*)-(*S,S*)-FurTRAP (**389b**)	100	7	*R*



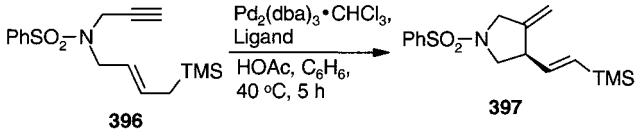
394 **395**

TRAP Ligand	Conv. (%)	ee (%)	Config.
(*R,R*)-(*S,S*)-BuTRAP (**389d**)	98	71	*S*
(*R,R*)-(*S,S*)-PhTRAP (**389a**)	trace	--	--
(*R,R*)-(*S,S*)-FurTRAP (**389b**)	13	6	*R*

PhTRAP catalyst under an atmosphere of H_2 provided (*R*)-dimethyl 2-methylsuccinate (**393**) in 26% ee, while the FurTRAP-based catalyst only resulted in a 7% enantiomeric excess. Ligands of higher electronic availablity, such as ethyl analogue **389d**, proved to be highly efficient catalysts giving the desired diester **393** in 96% ee. Interestingly, hydrogenation of dimethyl 2-isopropylidenesuccinate **394** with various TRAP ligands resulted in similar findings with the formation of **395**; however, the sense of enantioselection was opposite to that obtained with olefin **392**. In either case, incorporation of the electron-withdrawing 2-furyl moiety into the TRAP ligand clearly results in diminished stereoselectivity.

Ito and co-workers[165] also applied the FurTRAP ligand **389b** in the palladium-catalyzed enantioselective cycloisomerization of 1,6-enynes (Scheme 88).

Scheme 88



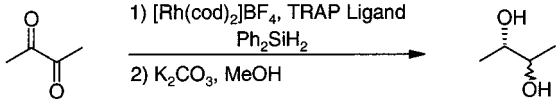
396 **397**

TRAP Ligand	Yield (%)	ee (%)
(*S,S*)-(*R,R*)-**389c**	72	48
(*S,S*)-(*R,R*)-PhTRAP (**389a**)	77	36
(*S,S*)-(*R,R*)-FurTRAP (**389b**)	76	4

Treatment of sulfonamide **396** with a $Pd_2(dba)_3$/PhTRAP catalyst system furnished cyclopentane derivative **397** in 77% yield and 36% ee. The corresponding FurTRAP catalyst afforded nearly racemic product in comparable yield. However, utilization of the *p*-$CF_3C_6H_4$-derived TRAP ligand **389c** provided the desired cyclized product **397** in 76% yield and 48% ee. Further improvement of the enantioselectivity using ligand **389c** was achieved (76% ee) by performing the reaction at 0 °C, albeit at the expense of product yield (24%).[165]

The Rh-catalyzed asymmetric hydrosilylation of ketones has recently been investigated using TRAP ligands (Scheme 89).[166] In this study, 2,3-butanedione

Scheme 89



398 **399**

TRAP Ligand	*dl*:*meso*	ee (%)
(*R,R*)-(*S,*S)-FurTRAP (**389b**)	86:14	91
(*R,R*)-(*S,S*)-PhTRAP (**389a**)	49:51	29

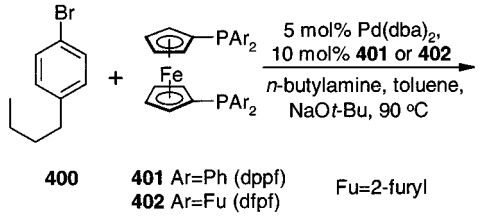
(**398**) was reduced using a (*R,R*)-(*S,S*)-FurTRAP-derived catalyst to provide the corresponding diol **399** in 86:14 DL:*meso* diastereoselectivity with 91% ee. Employing the standard (*R,R*)-(*S,S*)-PhTRAP catalyst system significantly reduced both the diastereo- and enantioselectivity of the process. Although this substrate provided higher stereoselectivity with the FurTRAP ligand, the result is not of general scope. In particular, Ito and co-workers demonstrated that the hydrosilylation of acetophenone is best achieved using TRAP ligands bearing *P*-linear alkyl substituents.[166]

B. Reactions Using 1,1′-Bis(di-2-furylphosphino)-ferrocene

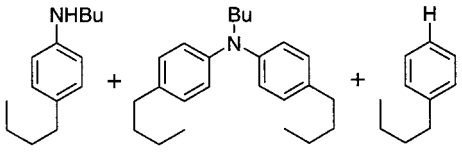
Steric and electronic effects in the palladium-catalyzed amination of aryl bromides have recently

been studied in considerable detail by Hartwig and co-workers.[167] Using dppf ligand (**401**), aryl bromide **400** was treated with *n*-butylamine to provide the desired secondary amine **403** in 52% yield along with 21.6% diarylamine **404** and 4.4% *n*-butylbenzene (**405**) (Scheme 90). Changing the catalyst ligand to

Scheme 90



400 **401** Ar=Ph (dppf) **402** Ar=Fu (dfpf) Fu=2-furyl



403 **404** **405**

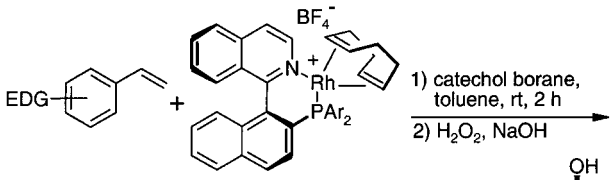
Ligand	Yield (%) 403	404	405
401, dppf	52	21.6	4.4
402, dfpf	40	2.9	16

bis(di-2-furylphosphino)ferrocene (**402**) resulted in an increased selectivity for the desired monoarylated amine **403** vs the diarylamine **404** albeit with a diminished overall yield. In addition, the amount of protodehalogenated material **405** increased to 16% upon employing the furyl phosphine ligand. While the proportion of this byproduct was found to increase, Hartwig showed in a related study that electron-poor phosphines such as **402** generally give less byproduct resulting from phosphorus to palladium aryl migration.[167]

C. Reactions Using 1′-[2-(Di-2-furyl-phosphino)-1-naphthyl]isoquinoline as Ligand

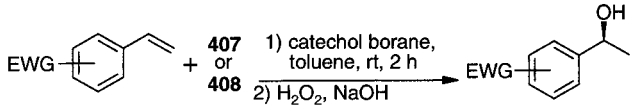
The rhodium-catalyzed asymmetric hydroboration/oxidation of various substituted styrenes has recently been investigated by Brown and co-workers using furyl phosphine catalyst **408**[168] (Scheme 91). A series of five styrenes **406** bearing electron-donating groups (EDG) smoothly provided the desired secondary alcohols **409** in high yields (75−82%) and enantioselectivities (86−94%) with phenyl catalyst **407**. Employment of the furyl catalyst **408** on the same series of starting materials **406** generally led to slightly lower product yields and enantioselectivities. However, the furyl phosphine catalyst **408** provided superior results, in terms of both yield and stereoselectivity in forming **411**, to catalyst **407** in the hydroboration/oxidation of electron-poor styrenes **410**. On the basis of these results, Brown and co-workers postulated that the smaller molar volume of the $P(Fu)_2$ group relative to PPh_2 may be responsible for the diminished ee's in the electron-rich series. Moreover, these workers suggested, based on models of olefin complexation to the metal center,

Scheme 91



406 EDG=Me, OMe, OEt **407** Ar=Ph **408** Ar=Fu **409**, 5 examples

Catalyst	Yield (%)	ee (%)
407	75-82	86-94
408	72-81	78-93



410 EWG=F, Cl, CF_3 **411**, 9 examples

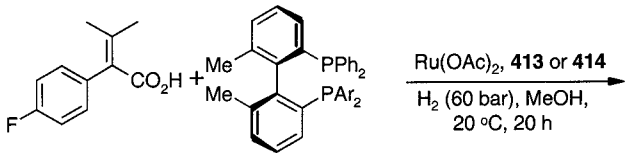
Catalyst	Yield (%)	ee (%)
407	59-82	37-80
408	74-82	69-89

that a bulkier ligand with the electronic properties of the furyl moitey should provide the best results.[168]

D. Reactions Using Biphenyl-Derived Furyl Phosphines

The ruthenium-catalyzed asymmetric hydrogenation of acrylic acid derivative **412** has recently been reported by Scalone and co-workers[169] using a variety of bidentate phosphine ligands (Scheme 92). The

Scheme 92



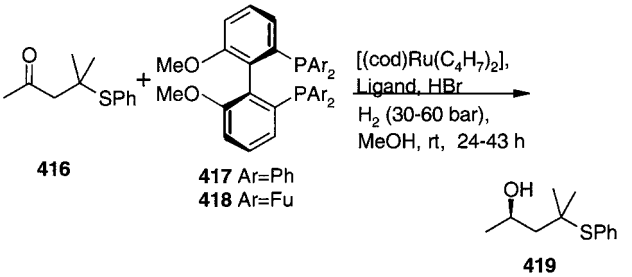
412 **413** Ar=Ph **414** Ar=Fu **415**

Catalyst	Conversion (%)	ee (%)
413	100	88
414	100	90

desired product **415**, a key building block for the calcium antagonist mibefradil, was obtained in 88% ee with the *S*-configuration using the (*R*)-BIPHEMP ligand (**413**). Alternatively, utilization of furyl ligand **414**[170] furnished acid **415** in 90% ee. Optimal results for this hydrogenation reaction included using chiral bis(diphenylphosphino)ferrocene-derived catalysts whereby compound **415** could be obtained in >99% conversion and 98% optical purity.[169]

Genêt and co-workers[171] reported using furyl phosphine ligand **418**[170] in the ruthenium-catalyzed asymmetric hydrogenation of phenylthio ketone **416** (Scheme 93). Treatment of a methanolic solution of compound **416** under H_2 (30 bar) at room tempera-

Scheme 93

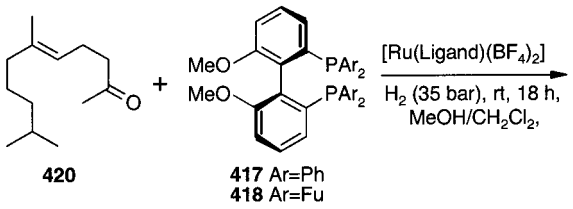


416 **417** Ar=Ph, **418** Ar=Fu → **419**

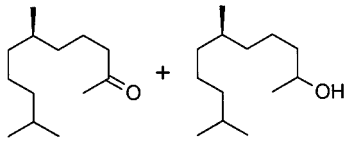
Ligand	Yield (%)	ee (%)
417	100	90
418	100	88

ture for 24 h with a (*R*)-MeOBIPHEP (**417**)-derived catalyst furnished the desired product **419** in 90% ee having the *R*-configuration. Using the analogous 2-furyl ligand **418** under conditions of higher pressure and longer reaction time provided the desired alcohol **419** in comparable enantioselectivity (88% ee). Superior results have been obtained using furyl catalyst **418** for the ruthenium-catalyzed asymmetric hydrogenation of dihydrogeranylacetone (**420**)[172] (Scheme 94). Treatment of ketone **420** with a MeO-

Scheme 94



420 **417** Ar=Ph, **418** Ar=Fu



421 **422**

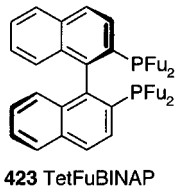
Ligand	421:422	ee of 421 (%)
417	97:3	77
418	98:2	91

BIPHEP (**417**)-derived catalyst at room temperature under H_2 (35 bar) furnished a 97:3 mixture of compounds **421** (77% ee) and **422**, respectively. Employment of the corresponding furyl phosphine catalyst resulted in a significant enantioselectivity enhancement with the desired product **421** being isolated in 91% optical purity. Similar results have been obtained for a variety of other terpenoid starting materials.[172]

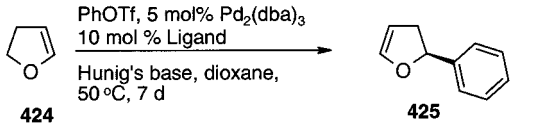
E. Reactions Using Binaphthyl-Derived Furyl Phosphines

Keay and co-workers[173] synthesized 2,2′-bis(di-2-furylphosphino)-1,1′-binaphthalene (**423**, TetFuBINAP) (Scheme 95) and developed a new resolution procedure for resolving electron-poor phosphines.[174] The intermolecular Heck reaction with 2,3-dihydrofuran (**424**), phenyltriflate and (*R*)-TetFuBINAP **423** provided a higher % ee of **425** but with a lower overall

Scheme 95

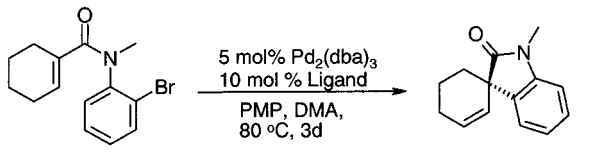


423 TetFuBINAP



424 **425**

Ligand	Yield (%)	ee (%)
(*R*)-TetFuBINAP (**423**)	17	89
(*R*)-BINAP	53	66



426 **427**

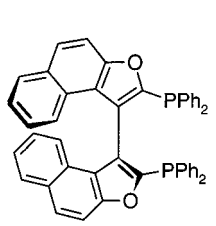
Ligand	Yield (%)	ee (%)
(*R*)-TetFuBINAP (**423**)	57	64
(*R*)-BINAP	61	18

yield when compared to (*R*)-BINAP. Interestingly, the % ee of **427**, formed from the intramolecular Heck reaction with bromide **426**,[175] increased from 18% to 64% when (*R*)-TetFuBINAP was used as the catalyst instead of (*R*)-BINAP without the need for silver salts.

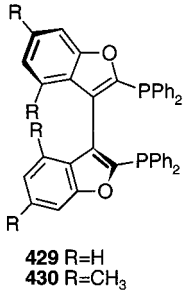
F. Reactions Using a Binaphthofuran-Derived Phosphine

Keay and co-workers[176] synthesized and resolved[174] (±)-2,2′-bis(diphenylphosphino)-3,3′-binaphtho[2,1-*b*]-furan (BINAPFu, **428**, Scheme 96). This is the first example of a configurationally stable (<150 °C) bifuran atropisomeric ligand being successfully used

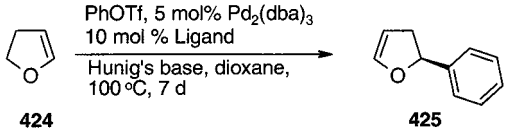
Scheme 96



428 BINAPFu



429 R=H
430 R=CH_3



424 **425**

Ligand	Yield (%)	ee (%)
(*R*)-BINAPFu (**428**)	90	77
(*R*)-BINAP	73	41

in an asymmetric transformation. Sannicolò and co-workers[177] reported the synthesis of 2,2′-bis(diphenylphosphino)-3,3′-bibenzofuran (**429**) and 4,4′,6,6′-tetramethyl-2,2′-bis(diphenylphosphino)-3,3′-bibenzofuran (**430**). Bibenzofuran **429** was found to be configurationally unstable, and **430** has not been used in asymmetric transformations to date. BINAPFu outperformed BINAP in an asymmetric Heck reaction between 2,3-dihydrofuran (**424**) and phenyltriflate when the reaction was performed at 100 °C in dioxane (Scheme 96). Dihydrofuran **425** was obtained in 90% yield with a 77% ee compared to BINAP, which only provided **425** with a 41% ee (73% yield).

IV. Conclusions.

Although tri-2-furylphosphine (TFP) is similar in size to triphenylphosphine, the electronic properties of TFP relative to PPh_3 are very different. The former phosphine is substantially less Lewis basic and is therefore a poorer σ-donor ligand in transition-metal-mediated organic reactions. Pioneering work by Farina showed the use of TFP-derived palladium catalysts to be highly advantageous in the Stille cross-coupling reaction with significant rate accelerations being observed over traditional PPh_3-based catalysts. Numerous workers have since sought to evaluate the performance of TFP in a wide variety of metal-catalyzed reactions for the preparation of small molecules, complex natural products, and polymers. In many cases, Stille coupling with the TFP ligand allows for milder reaction conditions and hence the attenuation of unwanted side reactions.

In many cases, clear advantages to using TFP have been identified, while in other cases this ligand performs poorly when compared to bulky or electron-rich phosphines. Unfortunately, accurate prediction of whether a poor σ-donor ligand will lead to beneficial effects for a given process remains elusive, and indeed the choice of reaction solvent, temperature, and the use of additives can be more decisive than the choice of phosphine ligand.

On the basis of the investigations of the TFP ligand summarized herein, several research groups have sought to develop novel phosphines which incorporate the 2-furyl moiety. While these efforts are still in their infancy, some promising results have been obtained and further research should prove to be very interesting.

V. Acknowledgments

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