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Lewis Acid-Promoted Oxidative Addition of Thioimidates to Pd(0)

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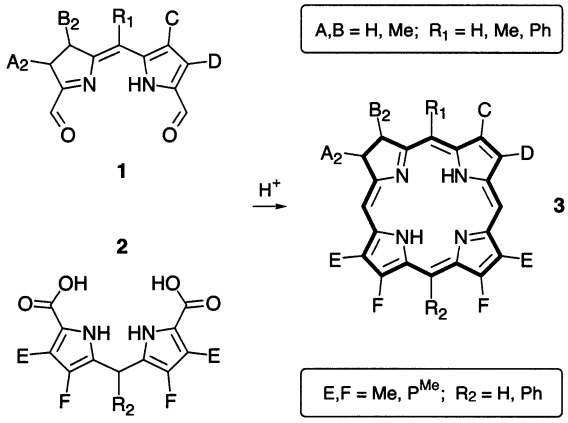
The isomeric *S*-methyldihydropyrrins **9**-*Z* and **9**-*E* exhibit markedly different behavior in Pd(0)-catalyzed cross-coupling reactions. Thioimidates **9**-*Z* are readily converted to imines **10**-*Z* employing Pd(0)/AlkZnI. Under identical conditions **9**-*E* are inert. Oxidative addition to Pd(0) requires activation by Zn or other Lewis acids, which is sterically unfavorable with **9**-*E*. Analogous results were obtained with the related thioimidates **11**-*E*,*Z* as well as with methylthiopyridines **19**α−γ. In the case of both **11** and **19** oxidative addition to Pd(0) was greatly facilitated in the presence of BF_3·Et_2O. The importance of Lewis acid activation to Pd(0) oxidative addition in such substrates appears to be a general phenomenon not previously recognized.

Introduction

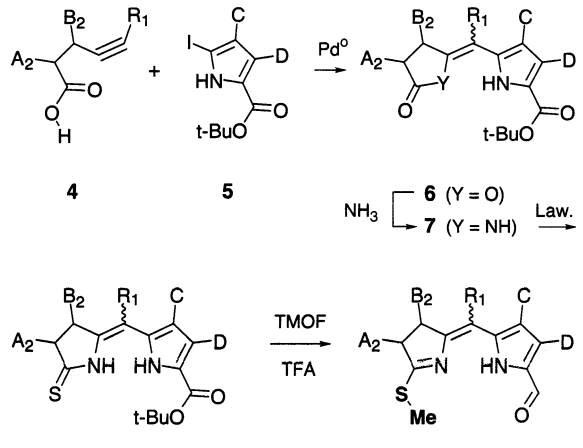
In a recent Letter we described a new synthesis of chlorins of general structure **3**[1] that were obtained in ∼45% yield by acid-catalyzed reaction of dihydropyrrins **1** with dipyrromethanes **2** (Scheme 1). Condensations of this type are experimentally facile, since they are effected under metal-free conditions and afford chlorins **3** directly in the proper oxidation state. Dipyrromethanes **2** were prepared following literature procedures,[2] while diformyl derivatives **1** were previously unknown.

SCHEME 1



The carbon skeleton of **1** was derived by Pd(0)-initiated coupling/cyclization of alkyne acids **4** with iodopyrroles **5**,[3] which gave excellent yields of enelactones **6** on multigram scales (Scheme 2). Enelactones **6** were then converted to the thioimidate derivatives **9** by a three-step sequence involving amination (**6** → **7**), treatment with Lawesson's reagent (**7** → **8**), and concomitant *S*-methylation/decarboxylative formylation employing trimethylorthoformate (TMOF) (**8** → **9**).[4] Under kinetic control lactones **6** were obtained predominantly as the *E*-isomers (>95%), in line with mechanistic considerations.[5] However, upon equilibration the *E*:*Z*-ratio for **6**−**9** was influenced by both hydrogen bonding and the nature of the meso-substituent R_1.

SCHEME 2



With an efficient synthesis of thioimidates **9** in hand, we planned to use the elegant chemistry of Liebeskind[6] and Fukuyama[7] to prepare cross-coupling products **10**, which upon oxidation would give the required diformyl derivatives **1** (Scheme 3). In practice this procedure worked well for *Z*-thioimidates **9**-*Z*, which gave high yields of cross-coupling products **10**-*Z* using the reagent

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(1) Jacobi, P. A.; Lanz, S.; Ghosh, I.; Leung, S. H.; Löwer, F.; Pippin, D. *Org. Lett.* **2001**, *3*, 831.

(2) (a) Strachan, J.-P.; O'Shea, D. F.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem*. **2000**, *65*, 3160. (b) Taniguchi, M.; Ra, D.; Mo, G.; Balasubramanian, T.; Lindsey, J. S. *J. Org. Chem*. **2001**, *66*, 7342. Reference 2b also contains an excellent review of previous chlorin syntheses.

(3) Jacobi, P. A.; Liu, H. *J. Org. Chem*. **1999**, *64*, 1778.

(4) Arnott, D. M.; Harrison, P. J.; Henderson, G. B.; Sheng, Z.-C.; Leeper, F. J.; Battersby, A. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 265.

(5) Jacobi, P. A.; Liu, H. *J. Org. Chem* **2000**, *65*, 76776.

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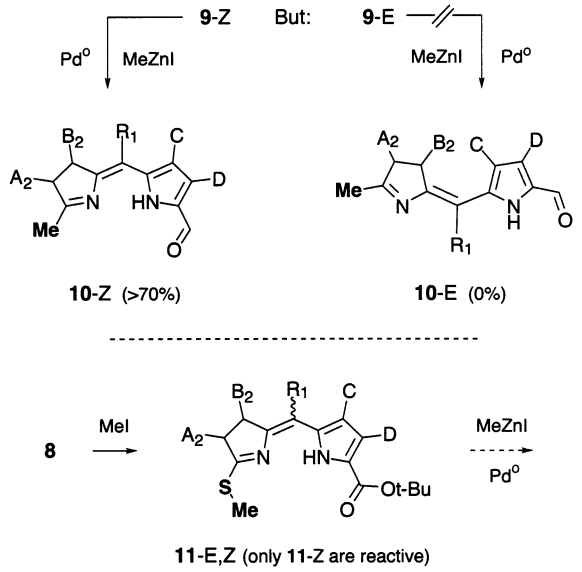
SCHEME 3

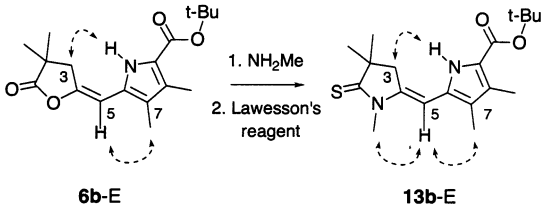


system MeZnI/Pd(0). Surprisingly, the *E*-thioimidates **9**-*E* were inert to the identical conditions and to various modifications in temperature, solvent, organozinc reagent, and Pd catalyst.[8] Furthermore, ester derivatives **11**-*E*,*Z*, prepared by alkylation of **8** with MeI, exhibited the same reactivity pattern (Scheme 3).[1] In every case the *Z*-isomers **11**-*Z* underwent clean cross-coupling with MeZnI/Pd(0), while the corresponding *E*-isomers were inert. In this paper we describe mechanistic studies of this reaction that have uncovered an unexpected role for Lewis acids.

Results and Discussion

Given the nature of these results we took particular care to validate the structures of the nonreactive isomers **9**-*E* and **11**-*E*. Of potential concern, *N*-methylation is a common side reaction in the synthesis of thioimidates related to **9** and **11**,[9] and this pathway would produce an unreactive thiolactam isomer. For the case of ester **11b**-*E* (Scheme 3, A, C, D = Me; R_1, B = H) this possibility was ruled out by unequivocal synthesis of the *N*-methyl derivative **13b**-*E*, by aminolysis of lactone **6b**-*E* with methylamine followed by treatment with Lawesson's reagent (Scheme 4). The structure of **13b**-*E* was clear from the NMR data. Especially diagnostic was the chemical shift of the *N*-methyl group (3.53 ppm vs 2.54 ppm for the *S*-methyl group in **11b**-*E*), and a strong NOE between the *N*-methyl group and the *meso*-H at C-5 (dashed arrow). Interestingly, both **6b**-*E* and **13b**-*E* adopt a nearly planar *E*-anti conformation. This was apparent from strong NOE's between H-5 and the C-7 methyl group, as well as between the pyrrole N−H and C-3 methylene hydrogens. Inspection of models indicates that the alternative *E*-syn conformations suffer from significant steric repulsion between the C-7 methyl group and the C-3 hydrogens. Finally, the structures of both **9a**-*E* and **9a**-*Z* (A, C, D, R_1 = Me; B = H) were established by extensive NMR studies and confirmed by X-ray analysis (vide infra).[10]

SCHEME 4



On the basis of literature precedent,[6] the conversion of thioimidates **9a** to cross-coupling products **10a** requires four steps: (1) oxidative addition, (2) activation of the Pd−S bond, (3) trans-metalation, and (4) reductive elimination (Figure 1). One of these steps is apparently

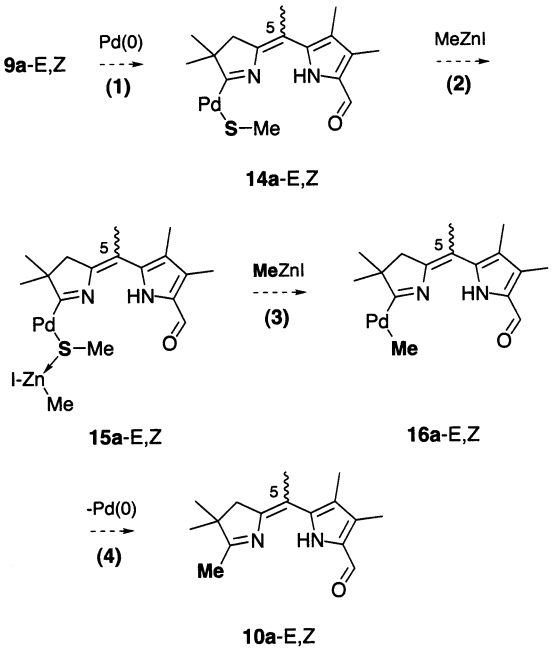


FIGURE 1. Steps involved in the conversion of thioimidtes **9a** to cross-coupling products **10a**: (1) oxidative addition; (2) complexation with Zn; (3) Zn-promoted trans-metalization; (4) reductive elimination.

unfavorable for the unreactive *E*-isomers. In their groundbreaking studies Liebeskind et al. emphasized the importance of Zn as a thiophile that facilitates transmetalation by complexation with a sulfur ligand (step 2).[6a,b,7] An extensive body of work supports this view.[11] However, in the case of **14a** it seemed unlikely that

(6) (a) Srogl, J.; Liu, W.; Marshall, D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 9449. (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3229. (c) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260. (d) Liebeskind et al. showed that trans-metalation of species related to **15a** requires an external source of RZnI (i.e. the alkyl group is not transferred from sulfur-complexed RZnI).[6a−c]

(7) Tokuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 3189.

(8) Including $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$, $PdCl_2$(dppf), $Pd_2(dba)_3$/tris-(2-furyl)phosphine. These experiments were carried out on compound **9a**-*E*.

(9) (a) Walter, W.; Krohn, J. *Chem. Ber.* **1969**, *102*, 922. (b) *The Chemistry of Amides*; Patai, S., Ed.; Wiley: New York, 1970; pp 442−445.

(10) We are grateful to Drs. Neil R. Brooks and Victor G. Young, of the X-ray Crystallographic Laboratory, Department of Chemistry, University of Minnesota, for carrying out these analyses.

(11) (a) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91. (b) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. Kusturin, C. L.; Liebeskind, L. S.; Neumann, W. L. *Org. Lett.* **2002**, *4*, 983.

S-complexation would significantly favor **14a**-*Z* over **14a**-*E*, since the *S*-Me group is far removed from the site of *E*,*Z* isomerization (Figure 1). Similarly, we doubted that steps 3 or 4 could account for such dramatic rate differences. We therefore focused our attention on step 1 and were surprised to find that *neither* **9a**-*Z* nor **9a**-*E* underwent oxidative addition with Pd(0) alone. These experiments were carried out with stoichiometric Pd-$(PPh_3)_4$, where even slow addition should be observable. To explain this result we carried out detailed structural studies on **9a**-*Z* and -*E*.

In both **9a**-*Z* and **9a**-*E* the S-methyl group is orientated anti to the geminal methyl groups at C-3, as shown by the absence of a discernible NOE (Figure 2). For **9a**-*Z*, however, there is a clear NOE between the *S*-methyl group and the hydrogen shared by both nitrogens (dashed arrow). The presence of a strong hydrogen bond in **9a**-*Z* was further indicated by the low field chemical shift for the N−H proton (12.21 ppm, vs 9.04 ppm for **9a**-*E*), which was independent of concentration. On the basis of these data **9a**-*Z* is planar (or nearly so), despite steric crowding between the C-5 and C-7 methyl groups. In contrast, thioimidate **9a**-*E* adopts a highly twisted conformation to avoid strong steric repulsion between the groups at C-3, C-5, and C-7. This is evident from the NOE experiments (dashed arrows), in which irradiation at N−H led to enhancement of *both* the C-5 methyl and C-3 methylene signals (12% and 9%, respectively). Finally, the structures for **9a**-*E* and **9a**-*Z* were corroborated by X-ray analysis,[10] which showed substantially the same interactions (Figure 2). In the crystalline state the deviation from planarity for **9a**-*Z* was 5.5° ($C_4-C_5-C_6-C_7$) while for **9a**-*E* this value was 52.2° ($C_4-C_5-C_6-C_7$). If anything, the *S*-Me group in **9a**-*Z* is slightly more crowded.

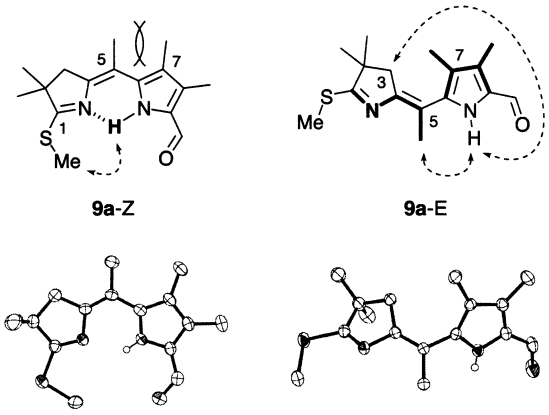


FIGURE 2. NMR and crystal structures of **9a**-*Z* and **9a**-*E*.

Since the thioimidate C−S bond is sterically accessible to Pd(0) in both **9a**-*Z* and **9a**-*E*, we considered other reasons why oxidative addition might fail. Relatively few studies have examined substituent effects on the rate of oxidative addition to Pd(0),[12] which is influenced by a number of factors. In general, however, electron-withdrawing groups on the substrate have an accelerating effect. In a recent paper Liebeskind and Srogl noted that oxidative addition of electron-rich aryl thioethers to Pd(0) is sluggish compared to that of more electron-deficient heteroaryl thioethers.[11b] Also, these authors found that $Zn(OAc)_2$ is an "essential additive" in certain cross-coupling systems containing both nitrogen and boronic acid groups.[11b,c] This effect was ascribed to the ability of Zn to "tie up basic nitrogen atoms that potentially interfere with the reaction system".[11b] In the present case, however, we believe N→Zn complexation plays a more fundamental role, that of facilitating oxidative addition.

As illustrated for thioimidates **9a** (Figure 3), the reactive *Z*-isomers can accommodate N→Zn complexation in either of two ways: (1) formation of "traditional" σ-chelate structures of type Zn-**9a**-$Z(\eta^1)$[13] or (2) formation of "slipped sandwich" σ-η^5-complexes of type Zn-**9a**-$Z(\eta^5)$. The latter configuration is well precedented in zincocene chemistry,[14] and would eliminate the strong peri-interaction between the C-5 and C-7 methyl groups. In both Zn-**9a**-$Z(\eta^1)$ and Zn-**9a**-$Z(\eta^5)$ oxidative addition of Pd(0) is favored by increased polarization of the C−S bond. In contrast, activation of this type is impossible with **9a**-*E*, which cannot form a chelated structure analogous to Zn-**9a**-*Z*. Moreover, the X-ray data show that the imidate nitrogen in **9a**-*E* is sterically shielded by the flanking *S*- and *C*-5-methyl groups (Figure 2).[15] These interactions inhibit the formation of Zn complexes of type Zn-**9a**-*E*, and thus oxidative addition does not occur.

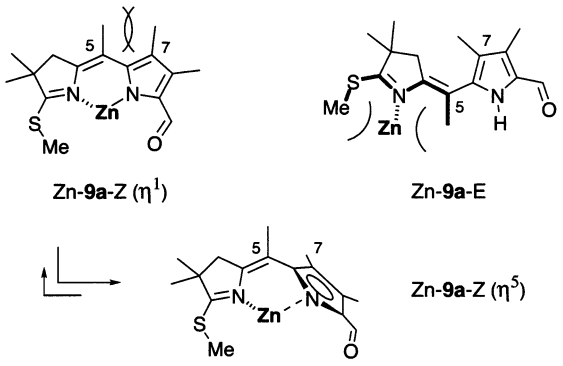


FIGURE 3. Zn complexation with **9a**-*E* and **9a**-*Z*. Zn-**9a**-*E* is sterically congested. Zn-**9a**-*Z* can be either η^1 or η^5.

The experimental data support this hypothesis. In every case Pd(0)-catalyzed cross-coupling of substrates **9**-*Z* and **11**-*Z* required a minimum of 3 equiv of RZnI. This stoichiometry is consistent with a mechanism involving Zn-coordination at *both* nitrogen and sulfur, with the third equivalent of RZnI participating in transmetalation (cf. also Figure 1).[6d] In the presence of RZnI oxidative addition of **9**-*Z* and **11**-*Z* to Pd(0) is facile. In contrast, isomers **9a**-*E* and **11a**-*E* were unreactive even with stoichiometric Pd(0) and a large excess of RZnI. NMR studies in CD_2Cl_2 reinforced these observations (Supporting Information). With **9a**-*E*, addition of excess EtZnI liberated ethane but induced only modest shifts in peak positions.[16] All absorptions remained sharp. However, under identical conditions **9a**-*Z* exhibited ex-

(12) Kochi, J. K. *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978.

(13) March, F. C.; Couch, D. A.; Emerson, K.; Fergusson, J. E.; Robinson, W. T. *J. Chem. Soc. (A)* **1971**, 440.

(14) Burkey, D. J.; Hanusa, T. P. *J. Organomet. Chem.* **1996**, *512*, 165.

(15) Steric crowding cannot be alleviated by rotation about the *S*-methyl bond, due to the adjacent geminal methyl groups.

(16) Charette, A. B.; Marcoux, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4539.

tensive peak broadening and few distinct resonances remained (Supporting Information).[17] This behavior can be attributed to slow interconversion of species of type Zn-**9a**-*Z*(η^1) and Zn-**9a**-*Z*(η^5) (Figure 3).[14]

To further probe the effect of steric hindrance on Lewis acid complexation, we studied the reactivity of thioimidate derivatives **11a**-*E* (R_1 = Me) and **11b**-*E* (R_1 = H) (Figure 4). Not surprisingly, **11a**-*E* was unreactive toward Pd(0)-catalyzed cross-coupling with EtZnI. *meso*-H derivative **11b**-*E* was also unreactive, although in this case steric hindrance is presumably less. Indeed, upon employing the smaller (and harder) Lewis acid BF_3·Et_2O we obtained good yields of the coupling product **18b**-*E*, but again no reaction with **11a**-*E*.[18] NMR experiments were consistent with the intermediate formation of complex **17b**-*E* (Supporting Information).

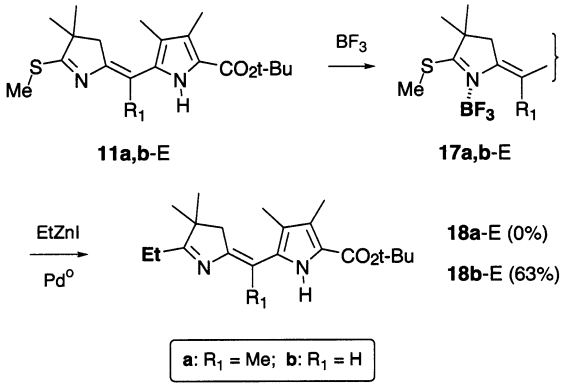
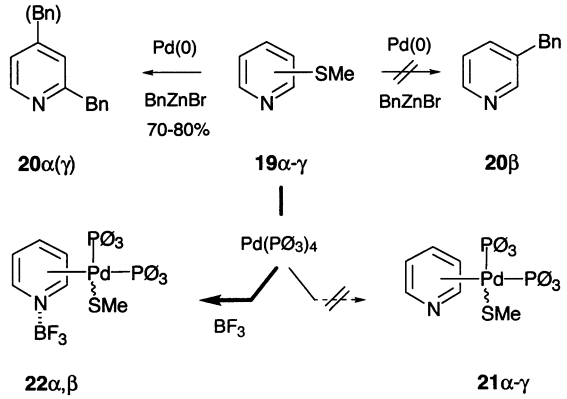


FIGURE 4. BF_3 complexation facilitates the cross-coupling of EtZnI with **11b**-*E* (R_1 = H) but not with **11a**-*E* (R_1 = Me).

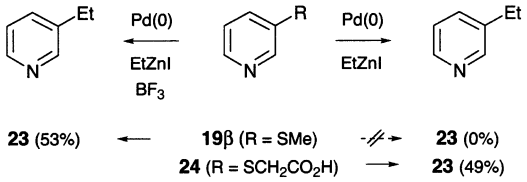
Our results with thioimidates **9** and **11** led us to reexamine several literature reports describing similar Pd(0)-catalyzed cross-coupling reactions. An intriguing observation in this area was made by Casalnuovo et al.,[19] who noted that β-methylthiopyridine (**19**β) was unreactive toward BnZnBr/Pd(0) (Scheme 5). In contrast, the corresponding α- and γ-isomers **19**α,γ gave 70−80% yields of cross-coupling products **20**α and **20**γ, respectively. This reactivity pattern was attributed to the greater electron deficiency of pyridine at the α- and γ-positions, which presumably facilitates oxidative addition. Interestingly, upon repeating this work we discovered that none of the isomeric methylthiopyridines **19**$\alpha-\gamma$ undergoes oxidative addition in the absence of Lewis acids, even with stoichiometric Pd(0) (i.e. **19**→**21**). Evidently with **19**α,γ the C−S bond is not sufficiently polarized without added BnZnBr. For the less reactive **19**β, even Zn complexation is not sufficient. However, we found that reactivity was markedly increased by addition of BF_3·Et_2O, which complexes strongly at nitrogen. Under these conditions **19**α,β readily incorporate Pd(0) to afford the corresponding insertion products **22**α,β. Isomer **22**α was isolated as a moderately stable solid that was characterized by NMR (Supporting Information).

SCHEME 5



In the case of **19**β the choice of activating Lewis acid has important consequences (Scheme 6). Employing excess EtZnI as Lewis acid we observed no oxidative addition to Pd(0) and hence no cross-coupling to afford β-ethylpyridine (**23**). This result is in agreement with the report of Casalnuovo et al., and may help to explain the unusual regio- and chemoselectivity observed by these authors.[19] In contrast, with the reagent combination EtZnI/Pd(0)/BF_3·Et_2O we obtained a >50% yield of **23** (not optimized). Finally, it is worth noting that strong complexation with sulfur is also effective at promoting Pd(0) oxidative addition. Thus, utilizing Liebeskind's Zn-chelating ligand,[6c] we found that thiopyridine derivative **24** required no additional activation, and was readily converted to **23** with EtZnI and Pd(0).[20,21] It is well-established that the thioacetate ligand accelerates transmetalation by weakening the Pd−S bond after oxidative addition (Zinc-chelation).[6,11] However, in the case of **24** we believe the more important effect is in polarizing the C−S bond *prior* to Pd insertion. This activating effect of the Liebeskind ligand has not been fully appreciated.

SCHEME 6



Undoubtedly other examples exist where the importance of substrate activation prior to oxidative addition to low-valence metals has not been recognized. In future papers we will describe the interrelation of such activation with the choice of zinc reagent and catalyst.

Experimental Section[22]

***E*-3,4-Dimethyl-5-(1,4,4-trimethyl-5-oxo-pyrrolidin-2-ylidenemethyl)-1*H*-pyrrole-2-carboxylic Acid *tert*-Butyl Ester (12b-*E*).** A solution of 320 mg (1.0 mmol, 1.0 equiv) of

(17) NMR studies of this phenomenon will be published separately.

(18) Imine **18b**-*E* is invariably contaminated with small amounts of the thermodynamically more stable isomer **18b**-*Z*. Isomerization is rapid in the presence of Bronsted acids.

(19) Angiolelli, M. E.; Casalnuovo, A. L.; Selby, T. P. *Synlett* **2000**, *5*, 905.

(20) Liebeskind et al. have previously reported the cross-coupling reaction of **24** with Zn(*o*-Tol)$_2$ employing the Ni catalyst $NiCl_2(PPh_2Me)_2$ (cf. ref 6a). In the present work we found that $NiCl_2(PPh_2Me)_2$ also effects the conversion of **19**β to **23** in 91% yield. These results reflect the far greater reactivity of Ni(0) vs Pd(0) in oxidative additions.

(21) For a related example of chelate-assisted oxidative addition with a Rh catalyst, see: Shaver, A.; Uhm, H. L.; Singleton, E.; Liles, D. C. *Inorg. Chem.* **1989**, *28*, 847.

(22) Experimental procedures and characterization data for **1**−**11** have appeared previously.[1]

lactone **6b-*E*** in 6 mL of freshly distilled THF was cooled to 0 °C under argon, and treated dropwise with 10 mL (20 mmol, 20.0 equiv) of $MeNH_2$ (2 M in THF). After addition was complete, the reaction mixture was maintained at 0 °C for 1 h, and then allowed to warm to room temperature and concentrated to dryness under reduced pressure. The residue was taken up in 10 mL of dry THF and treated with 0.75 g of Montmorillonite clay to effect dehydration. After being stirred for 1 h at room temperature, the reaction mixture was concentrated under reduced pressure and purified by flash chromatography (silica gel, EtOAc:hexanes = 2:3) to afford 281 mg (84%) of lactam **12b**-*E* as a white solid, mp 158−59 °C dec; R_f (2:3 EtOAc/hexanes) 0.48; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (s, 6H), 1.57 (s, 9H), 1.98 (s, 3H), 2.23 (s, 3H), 2.80 (d, J = 2.0, 2H), 3.06 (s, 3H), 5.59 (t, J = 2.0, 1H), 8.49 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.3, 10.8, 25.9, 27.2, 28.7, 39.8, 40.1, 80.7, 91.9, 119.0, 119.5, 126.3, 129.3, 139.7, 161.9, 180.3. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.65; H, 8.49; N, 8.43; O, 14.44. Found: C, 68.47; H, 8.55; N, 8.34.

***E*-3,4-Dimethyl-5-(1,4,4-trimethyl-5-thioxo-pyrrolidin-2-ylidenemethyl)-1*H*-pyrrole-2-carboxylic Acid *tert*-Butyl Ester (13b-*E*).** A solution of 100 mg (0.3 mmol) of lactam **12b**-*E* and 74 mg (0.18 mmol, 0.61 equiv) of Lawesson's reagent in 20 mL of toluene was stirred for 30 min at 100 °C under argon. The reaction mixture was then cooled to room temperature and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc:hexanes = 1:2 to 1:5) to afford 101 mg (96%) of thiolactam **13b**-*E* as an off-white solid, mp 185−86 °C dec; R_f (2:3 EtOAc/hexanes) 0.88; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 6H), 1.59 (s, 9H), 2.01 (s, 3H), 2.23 (s, 3H), 2.90 (d, J = 2.0, 2H), 3.53 (s, 3H), 5.92 (t, J = 2.0, 1H), 8.51 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 9.4, 10.8, 28.7, 29.4, 32.9, 41.0, 50.3, 81.0, 95.5, 120.3, 120.6, 126.3, 128.4, 142.1, 161.8, 212.0. Anal. Calcd for $C_{19}H_{28}N_2O_2S$: C, 65.48; H, 8.10; N, 8.04. Found: C, 65.57; H, 8.02; N, 8.11.

BF_3 complex 17b-*E* (NMR studies): A vacuum-dried NMR tube was charged with 10 mg (0.03 mmol, 1.0 equiv) of thioimidate **11b**-*E*, and the tube was sealed with a septum and purged several times with argon. CD_2Cl_2 (0.5 mL) was then added via syringe followed by 4 μL (0.03 mmol, 1.0 equiv) of $BF_3{\cdot}Et_2O$ to generate the BF_3 complex **17b**-*E*. The NMR spectrum of **17b**-*E* exhibited the expected downfield shifts for the vinylic, *S*-Me, and NH protons (cf. Supporting Information): ^{1}H NMR (500 MHz, CD_2Cl_2) δ 1.50 (s, 6H), 1.58 (s, 9H), 2.05 (s, 3H), 2.22 (s, 3H), 2.89 (s, 3H), 3.11 (d, J = 2.0, 2H), 7.05 (t, J = 2.0, 1H), 11.87 (br s, 1H);

***E*-5-(5-Ethyl-4,4-dimethyl-pyrrolidin-2-ylidenemethyl)-3,4-dimethyl-1*H*-pyrrole-2-carboxylic Acid *tert*-Butyl Ester (18b-*E*).** A solution of 25 mg (0.07 mmol, 1.0 equiv) of thioimidate **11b**-*E* in 0.9 mL of freshly distilled toluene was treated with 28 μL (0.21 mmol, 3.0 equiv) of $BF_3{\cdot}Et_2O$ under a stream of argon, followed by 0.27 mL (0.21 mmol, 3.0 equiv) of EtZnI (0.8 M in THF) and 5.0 mg (0.007 mmol, 0.1 equiv) of $PdCl_2(PPh_3)_2$. The reaction flask was then evacuated and purged three times with argon and the orange solution was stirred at room temperature for 3 h. At the end of this period the reaction mixture was diluted with 20 mL of Et_2O and washed with saturated NH_4Cl and brine. At this point TLC analysis of the organic layer showed no starting material and indicated **18b**-*E* as the major product with trace amounts of the corresponding *Z*-isomer. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified using flash chromatography (silica gel, Et_2O:hexanes = 1:3 containing 1% Et_3N) to afford 14 mg (63%) of **18b**-*E* contaminated with trace amounts of the corresponding *Z*-isomer.

18b-*E*: R_f (1:3 Et_2O/hexanes) 0.21; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (s, 6H), 1.27 (t, J = 7.5, 3H), 1.59 (s, 9H), 2.02 (s, 3H), 2.23 (s, 3H), 2.43 (q, J = 7.5, 2H), 2.74 (d, J = 2.0, 2H), 6.64 (t, J = 2.0, 1H), 8.55 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$); nearly complete *E*/*Z* isomerization occurred during data acquisition (see **18b**-*Z* below).

18b-*Z*: R_f (1:3 Et_2O/hexanes) 0.65; IR (Thin film) 3311, 2966, 1677, 1650 cm^{-1}; H NMR (500 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.35 (t, J = 7.5, 3H), 1.57 (s, 9H), 2.00 (s, 3H), 2.28 (s, 3H), 2.44 (q, J = 7.5, 2H), 2.60 (d, J = 1.5, 2H), 6.64 (br t, J = 1.5, 1H), 10.93 (br s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 8.9, 10.7, 11.1, 22.3, 26.0, 28.9, 45.1, 48.6, 79.9, 103.7, 130.6 (2C), 132.2, 151.53, 192.1; HRMS (FAB) calcd for $C_{20}H_{30}N_2O_2$ 330.2307, found 330.2312.

Pd Insertion Compound 22α. A solution of 27 mg (0.22 mmol, 1.0 equiv) of **19**α in 1 mL of distilled CH_2Cl_2 was treated with 28 μL (0.22 mmol, 3.0 equiv) of $BF_3{\cdot}Et_2O$ under a stream of argon. The reaction mixture was stirred for 5 min at room temperature during which period a white precipitate formed. The precipitate was collected by vacuum filtration, washed with CH_2Cl_2, and dried under vacuum to afford the BF_3 complex **19**α·BF_3 as an off-white solid: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 2.79 (s, 3H), 7.52−7.57 (dt, 1H), 7.65 (d, 1H), 8.11−8.16 (dt, 1H), 8.62 (dd, 1H). Without purification, **19**α·BF_3 was treated with 254 mg (0.22 mmol, 1.0 equiv) of $Pd(PPh_3)_4$ and 4.4 mL of distilled THF and the mixture was allowed to stir at ambient temperature overnight. After this period the precipitate formed was filtered, washed several times with distilled EtOAc, and dried under vacuum to afford 7 mg of the Pd insertion compound **22**α as a yellow-orange solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (s, 3H), 6.69 (t, 1H), 6.77 (d, 1H), 7.2−7.6 (br m, Pd-[PPh_3]$_2$), 7.65−7.69 (dd, 1H), 7.89 (d, 1H).

3-Ethylpyridine (23). Method A: A 10-mL round-bottom flask was flame-dried under vacuum and cooled under a stream of argon. The flask was then charged with 100 mg (0.8 mmol, 1.0 equiv) of **19**β[23] and 6.5 mL of freshly distilled THF. The resulting solution was treated with 102 μL (0.8 mmol, 1.0 equiv) of $BF_3{\cdot}Et_2O$ and stirred for 5 min at room temperature. After this period the reaction was treated with 28 mg (0.04 mmol, 0.05 equiv) of $PdCl_2(PPh_3)_2$ followed by 1.4 mL (1.12 mmol, 1.4 equiv) of EtZnI (0.8 M in THF). The reaction flask was then evacuated and purged three times with argon before heating at 50−55 °C for 20 h. After this period, the reaction mixture was allowed to cool to room temperature and diluted with 40 mL of Et_2O. The organic layer was washed with saturated NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, Et_2O:hexanes = 1:1) to afford 47 mg (53%) of **23** as a colorless liquid, R_f (2:3 EtOAc/hexanes) 0.30; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, J = 7.5, 3H), 2.62 (q, J = 7.5, 2H), 7.16−7.19 (m, 1H), 7.47−7.49 (m, 1H), 8.41 (dd, J = 2.0, 5.0, 1H), 8.44 (d, J = 2.0 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 15.4, 26.2, 123.4, 135.3, 139.3, 147.3, 149.7.

Method B: A 10-mL round-bottom flask was flame-dried under vacuum and cooled under a stream of argon. The flask was then charged with 100 mg (0.6 mmol, 1.0 equiv) of **24**[6a] and 4.2 mL of freshly distilled THF. The resulting solution was treated with 0.75 mL (0.6 mmol, 1.0 equiv) of EtZnI (0.8 M in THF) and stirred for 5 min at room temperature. After this period the reaction was treated with 21.0 mg (0.03 mmol, 0.05 equiv) of $PdCl_2(PPh_3)_2$ followed by 1.05 mL (0.84 mmol, 1.4 equiv) of EtZnI (0.8 M in THF). The reaction flask was then evacuated and purged three times with argon before heating at 50−55 °C for 20 h. After this period, the reaction mixture was allowed to cool to room temperature and diluted with 40 mL of Et_2O. The organic layer was washed with saturated NH_4Cl and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel,

(23) Jacob, P., III; Shulgin, A. T. *Synth. Commun.* **1981**, *11*, 957.

Et_2O:hexanes = 1:1) to afford 43 mg (49%) of **23** as a colorless liquid.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for **6b**-*E*, **9a**-*E*, **9a**-*Z*, **11b**-*E*, **12b**-*E*, **13b**-*E*, **17b**-*E*, **18b**-*E*, **18b**-*Z*, **19**α, **19**α**·BF$_3$**, **22**α, and **23** (including pertinent NOE and complexation studies); X-ray crystal data for **9a**-*Z* and **9a**-*E* (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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