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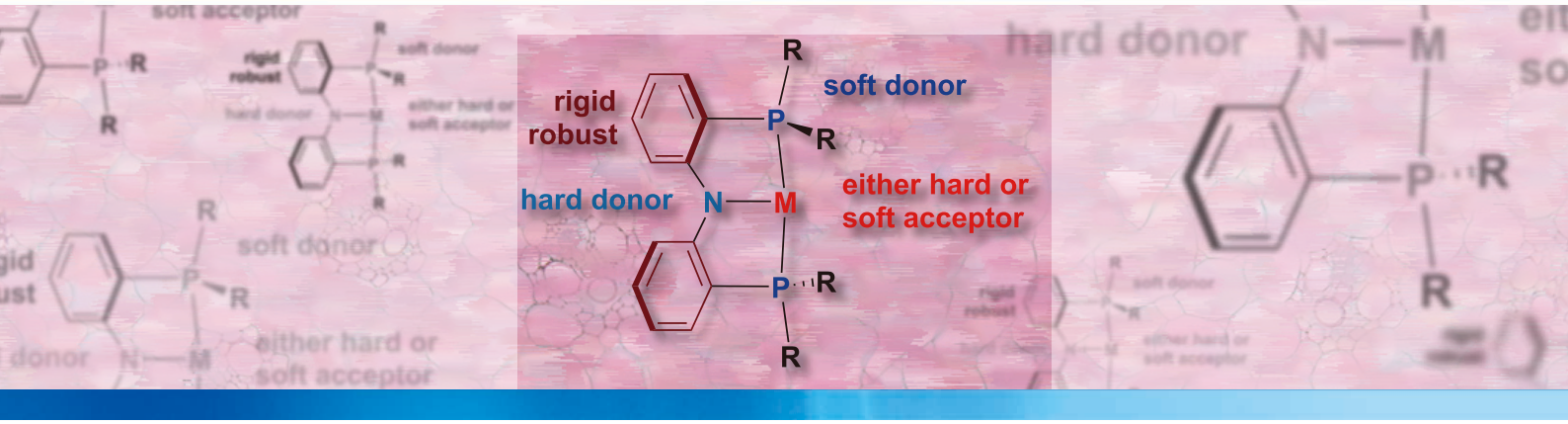

Contents

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Anilido PNP Pincer and Relevant Complexes

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Dedicated to Professor Richard R. Schrock on the occasion of his 74th birthday

Abstract: The origin of arylene bridged amido phosphine ligands and their subsequent metal complexes is described, so are the structural and reactivity features of these intrinsically mismatched donor-acceptor pairs. These metal complexes are versatile, not only capable of promoting inert chemical bond cleavage, e.g., arene C-H activation, but also active for catalytic C-C bond-forming reactions, e.g., Kumada, Heck, Suzuki, and Sonogashira couplings.

Keywords: amide, phosphine, PNP, C-H activation, cross-coupling

1. Preface

"*...what we accomplished...came through basic research without really knowing exactly how we were proceeding; we ultimately came to realize, step by step, that our basic research was leading to something really useful...and I think that's what the Nobel Prize is all about: to do work that turns out to be useful to society in some way and certainly other fields in science.*"[1] said Professor Richard R. Schrock, my PhD advisor at MIT, in the telephone interview right after the announcement of the 2005 Nobel Prize in Chemistry on 5 October 2005.

Basic research is valuable and can make significant impacts. Since the first reports[2-3] published by my group in 2003, anilido PNP pincer complexes and their relevant derivatives have attracted increasing attention and gained popularity worldwide. This review, instead of having full coverage of what has been achieved to date, aims to address in its initial stage how these compounds were conceptually devised and gradually evolved along with my personal perspectives and tracks of this particular research.

2. Concept

Anilido or amido ligands are intrinsically σ- and π-donors that prefer electron-deficient metals to those carrying π-electrons for thermodynamic reasons. Phosphine ligands, on the other hand, are typically good σ-donors, with the possibilities of also being excellent π-acceptors if bearing strong electron-withdrawing substituents. Electron-rich metals, as a result, are bound to phosphine ligands more readily and strongly than anilido or amido ligands. In terms of the Hard and Soft Acids and Bases (HSAB) theory, hard N donors prefer high oxidation state early transition metals whereas soft P donors prefer low oxidation state late transition metals. There have been a quite large number of amido (or anilido) complexes of early transition metals and phosphine complexes of late transition metals reported in the literature.

Chemical bonds between mismatched HSAB pairs are thermodynamically unstable and kinetically labile. To exemplify, nickel amides or anilides are usually reactive bases or nucleophiles that deprotonate acids rapidly or react with electrophiles readily.[4-6] The profound reactivity of these species is attributed to the inherent dπ-pπ repulsion in the Ni-N bond. Compared with the ample examples of known zirconium amides or anilides,[7-8]

phosphine complexes of zirconium are relatively rare. These mismatched donor-acceptor pairs are usually difficult to be stabilized thermodynamically or ligands in these pairs are sufficiently labile to kinetically dissociate readily, thereby easily resulting in coordinatively unsaturated species that transform subsequently or react rapidly.

Hybrid chelating ligands that contain both hard and soft donors are interesting as these chelates preserve the opportunities of creating simultaneously both matched and mismatched HSAB pairs upon coordination to a metallic element. While the matched pairs ensure thermodynamic stability of the derived metal complexes, the mismatched pairs endorse possible reactivity that is perhaps otherwise inaccessible. One remarkable example in this regard is the silyl bridged amido phosphine ligands (Figure 1) that have shown widespread reactivity with both hard and soft metals as pioneered by Fryzuk as of 1981.[9] Of particular note in this particular system is the success of the derived metal complexes in reactivity with respect to dinitrogen activation and subsequent functionalization.[10]

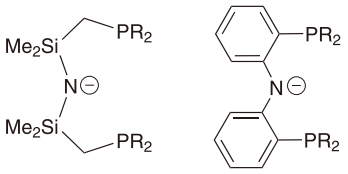


Figure 1. Representative amido phosphine ligands featuring distinct bridging backbones

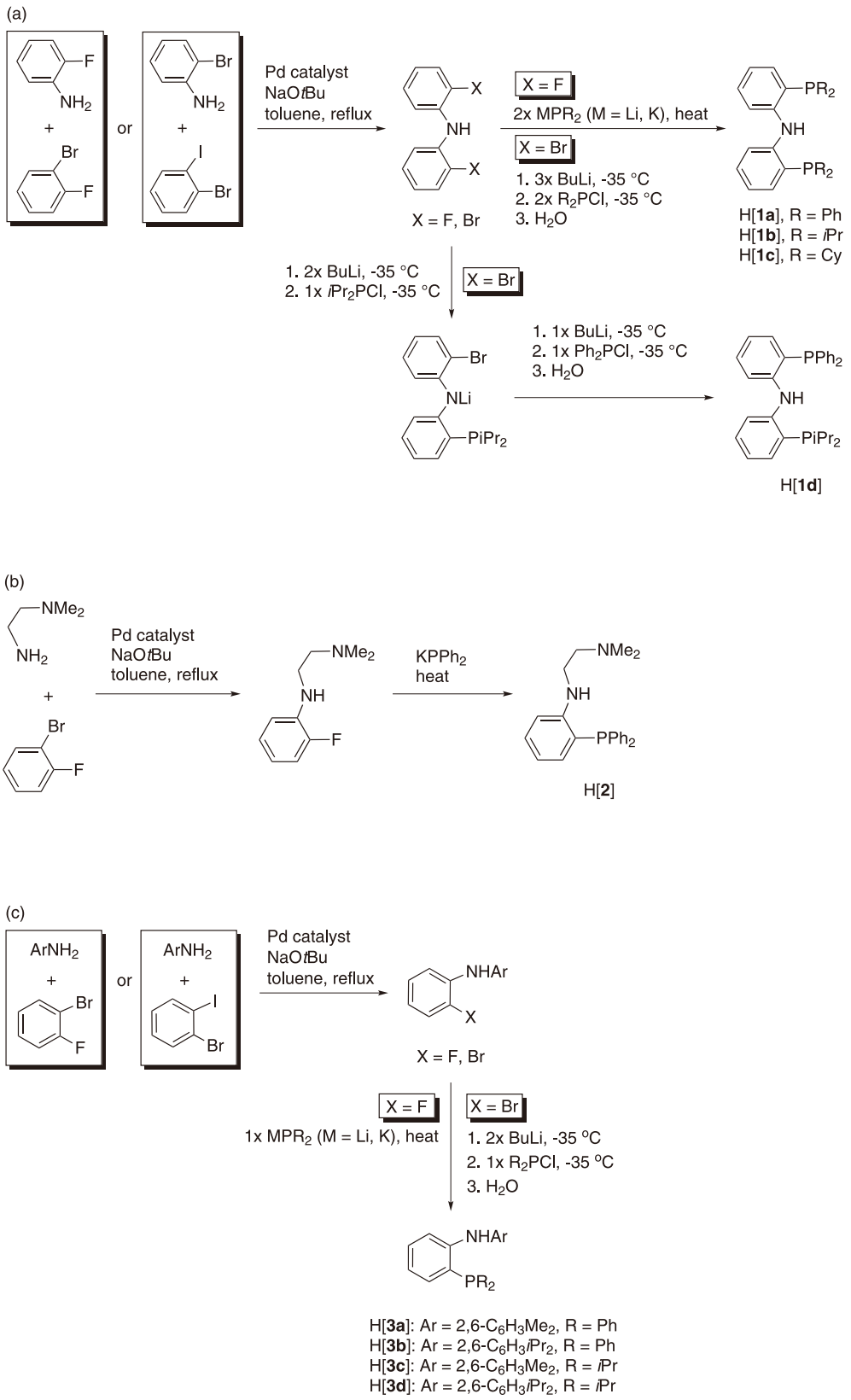
3. Evolution

Several drawbacks, however, are known in this silyl incorporated amido phosphine chemistry. With the embedded –$SiMe_2CH_2$– backbone that is inherently flexible, the soft phosphorus donors were found in some cases to dissociate readily from hard main group or transition metals.[11-12] Undesirable degradation, on the other hand, may also occur to involve the amido phosphine ligand itself in certain complexes by means of the cleavage of the N-Si bonds[13] or their adjacent C-H bonds,[14] making the subsequent reactivity exploration somewhat unfeasible.

The employment of *N*-silyl substituents in amidometallic chemistry is popular. Side reactions involving the aforementioned bond cleavage, though undesirable, are not uncommon. Replacement of the silyl substituents in amides with other moieties in order to preclude these disadvantages has been documented. One successful method employing *N*-arylated[15-16] instead of *N*-silylated[17] triamidoamine complexes has been reported for catalytic reduction of dinitrogen to ammonia.[18] Equally successful is another example concerning *ortho*-phenylene derived diamido/donor complexes for catalytic α-olefin polymerization,[19-20] where a living fashion was found if the *N*-substituents are *tert*-butyl[21] instead of trimethylsilyl groups.[22] Though other options were also available, we were inspired by the triumph of the established triamidoamine as well as diamido/donor chemistry and attracted to anilido phosphine derivatives (Figure 1) because anilines are ubiquitous and inherently the *ortho*-phenylene backbone is thermodynamically much more robust and conformationally more rigid than the –$SiMe_2CH_2$– bridges in connecting N and P donors. These features are extremely crucial as the strong N-C(sp^2) bonds are typically inert to enhance the possibilities of keeping the anilido phosphine ligands intact in the derived metal complexes during reactivity exploration and the rigid *ortho*-phenylene bridges sufficiently confine the N-C-C and C-C-P angles satisfactorily to diminish, to some extent, the propensities of donor arm dissociation.

4. Synthesis of anilido phosphine ligand precursors

As summarized in Scheme 1, the arylene bridged amido phosphine ligands are versatile, characteristic of having different hapticities, options of the third donor atom, varied bridges in connecting different donors, and distinct identities of substituents at these donors. In addition, alterations in anionic charges and incorporations of extra substituents into the arylene rings are also feasible.[23]



Scheme 1. Representative examples of protio precursors of monoanionic anilido phosphine ligands

We reported in 2003 the syntheses of bis(2-diphenylphosphinophenyl)amine (H[**1a**])[2] and *N*-(2-diphenylphosphinophenyl)-2,6-diisopropylaniline (H[**3b**])[3] that were the first examples ever of precursors of any *N*-arylated anilido phosphine ligands. Relevant derivatives were soon developed to include monoanionic PNP **1** (Scheme 1a),[24-25] PNN **2** (Scheme 1b),[26] NP **3** (Scheme 1c),[27-28] and dianionic NPN,[29] etc. Coincidentally, Kaska *et al*. also independently published a bit later the preparation of H[**1a**] though the synthesis of its bis(2-bromophenyl)amine precursor by way of the Chapman rearrangement of an imidate as the key strategy requires much more experimental steps with quite harsher conditions thus characteristic of being comparatively more laborious, time consuming, and resulting in an extremely low overall yield.[30] Our approach outlined in Scheme 1 involves palladium catalyzed C-N bond-forming reactions followed by either nucleophilic or electrophilic phosphanylation, affording the protio ligand precursors H[**1**], H[**2**], and H[**3**] more efficiently in much higher yields.

Substituents at the two P donors in PNP **1** can be intentionally varied as exemplified by **1d**.[25] Such desymmetrization is beneficial as the two phosphorus donors could be electronically and sterically distinguished so as to finely tune the electronic and steric structures of the derived metal complexes and deliberately induce vacant or active sites at the metal center for subsequent reaction chemistry. In view of this, PNN **2** was devised as an example of different approaches.[26] Conformationally, the electronic and steric properties of **2** lie somewhere in between tridentate **1** and bidentate **3**. Tethered with a more flexible ethylene bridge, the amino donor in **2** is in principle hemilabile upon coordination to a metal. All in all, the anilido phosphine ligands PNP **1**, PNN **2**, NP **3** and their corresponding relevant analogues have integrated as a library entity, allowing us to examine exploratory chemistry with judicious pairing these ligands with appropriate metals.

Following the same concepts, phenolate phosphines with distinct hapticities, anionic charges, and having extra substituents at the arylene bridges are also hybrid chelates, providing equally interesting coordination chemistry with both hard and soft metals. Examples of these ligands and chemistry derived thereafter can be found somewhere else.[31-36]

5. Representative anilido phosphine complexes

These anilido phosphine ligands, as planned, bind to both hard and soft transition and main group metals. Figure 2 illustrates some representative examples.

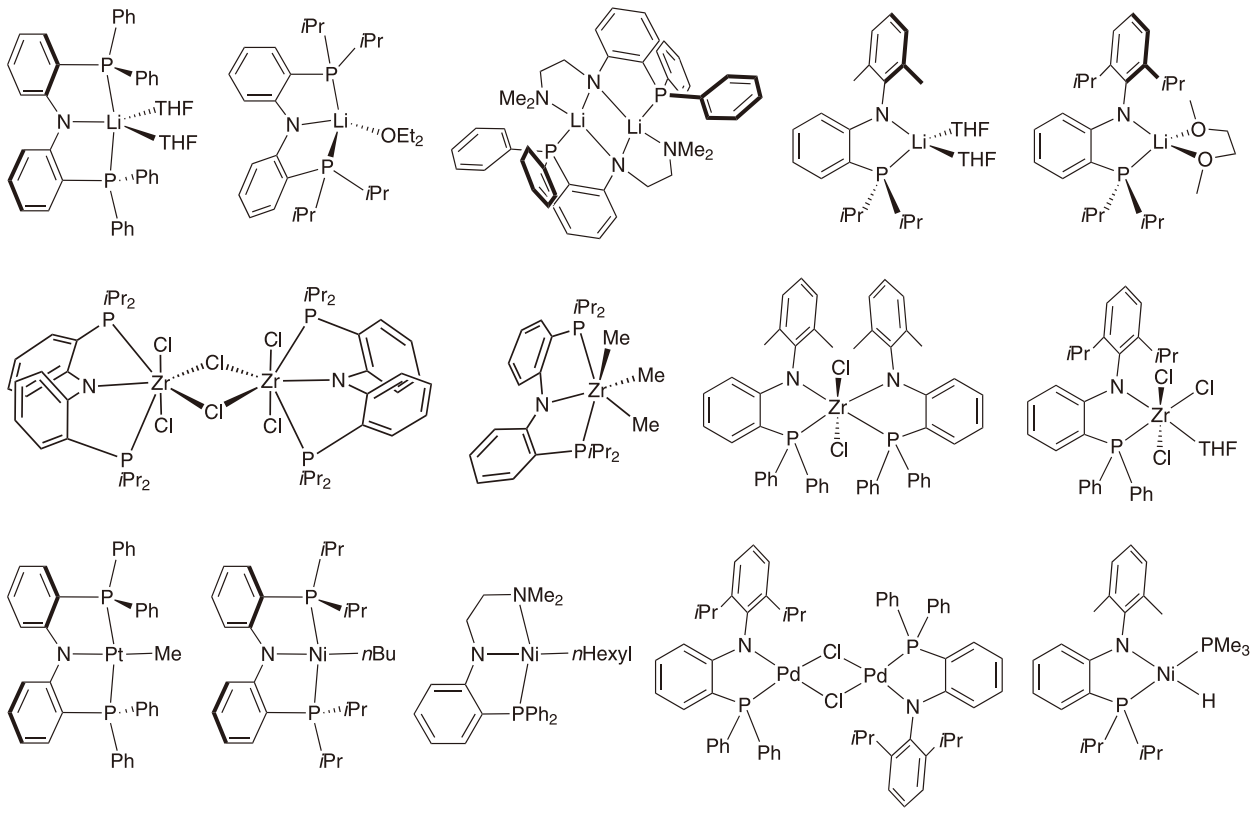


Figure 2. Representative examples of anilido phosphine complexes

Lithium amides are often versatile and convenient starting materials employed in metathetical reactions with metal (pseudo)halides. Lithium complexes of **1**, **2**, and **3** were successfully prepared from the reactions of *n*BuLi with H[**1**], H[**2**], and H[**3**], respectively, in either hydrocarbon (pentane, toluene) or ethereal (Et_2O, THF, DME) solutions.[2-3,24,28,37-38] Upon formation from ethereal solutions, these lithium complexes may be isolated as either ethereal free or ethereal adducts, the number of coordinated Et_2O, THF, or DME in which ranges from 0 to 2 depending on the identity of anilido phosphine ligands and ethereal solvents employed. These species, except {[**2**]Li}$_2$ that is an amide bridged dimer,[37] are all mononuclear as indicated by X-ray diffraction studies. As a result, the lithium atom in these complexes is 4- or 5-coordinate. X-ray studies also confirm the coordination of the soft P donors in these species to the hard Li atoms, even though these bonds are constructed with mismatched HSAB pairs. These Li-P bonds also retain in solutions as indicated by solution ^{7}Li and ^{31}P NMR studies.

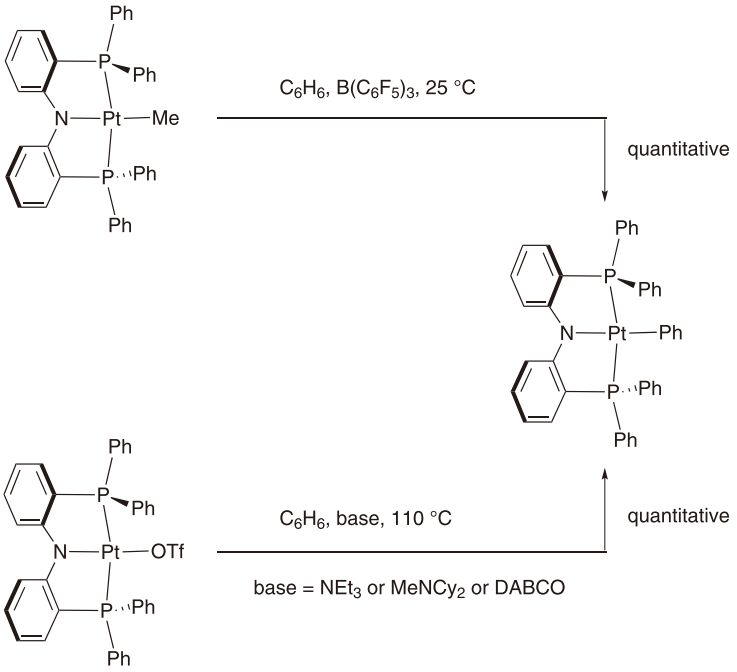
Zirconium chemistry of anilido phosphine complexes was explored. While {[**1b**]$ZrCl_2$(μ-Cl)}$_2$ is a chloride bridged dimer, [**1b**]$ZrMe_3$ and [**1b**]$Zr(CH_2SiMe_3)_3$ are mononuclear as elucidated by X-ray studies.[39] Consistent with the steric bulkiness of the trimethylsilylmethyl ligands, one of the P donors in [**1b**]$Zr(CH_2SiMe_3)_3$ is forced to dissociate from Zr, making this species 5-coordinate. In contrast, the trimethyl [**1b**]$ZrMe_3$ is 6-coordinate while the chloride {[**1b**]$ZrCl_2$(μ-Cl)}$_2$ is 7-coordinate. Collectively, the mismatched Zr-P bonds are retained in these species. Derived from the bidentate anilido phosphine ligands, complexes [**3a**]$_2ZrCl_2$ and [**3b**]$ZrCl_3$(THF), on the other hand, are 6-coordinate, also featuring the mismatched Zr-P bonds as confirmed by X-ray diffraction studies.[40]

A number of divalent group 10 metal complexes of **1**, **2**, and **3** have been prepared and subject to reactivity studies on bond-breaking and bond-forming reactions. X-ray studies reveal that these complexes are all 4-coordinate, having an approximately square planar geometry with the mismatched M-N (M = Ni, Pd, Pt) bond constructed, thus conformationally characteristic of being amido PNP pincer complexes. An exogenous ligand is required for complexes of bidentate **3**, usually involving a PMe_3 or a dative Cl bridge in a dimeric chloride complex.[38,41] Remarkably, these complexes are extremely thermally stable even at elevated temperatures, e.g., 5.90 mM [**1a**]PdCl in *N*-methylpyrrolidone (NMP) at 200 °C for > 100 h,[42] or air or water stable, e.g., 5.1 mM {[**3b**]Pd(μ-Cl)}$_2$ in 1,4-dioxane at 120 °C for > 2 days in the presence of 2000 equiv of water under aerobic conditions[43] or 12.7 mM [**1a**]PtMe in benzene at 150 °C for 3 days under aerobic conditions.[44] These results are phenomenal as amido complexes of late transition metals are typically reactive and not to survive from atmospheric air or moisture even at ambient temperature. Even more interesting is the unusual thermal stability of [**1**]$NiCH_2CH_2R$ and [**2**]$NiCH_2CH_2R$ that bear β-hydrogen atoms but refuse to undergo the ubiquitous β-hydrogen elimination even at elevated temperatures,[2,24,37] e.g., 12 mM [1c]Ni(*n*Bu) in benzene at 80 °C for > 3 days. After having performed a number of controlled experiments involving olefin insertion into the Ni-H bonds of isolated [**1**]NiH, we conclude that [**1**]NiH is higher in energy than their corresponding β-hydrogen containing nickel alkyl complexes.[25] As a result, β-hydrogen elimination from these β-hydrogen containing nickel alkyl complexes is thermodynamically uphill, a phenomenon that is in sharp contrast to what is typically known in organometallic chemistry.

6. Arene C-H activation

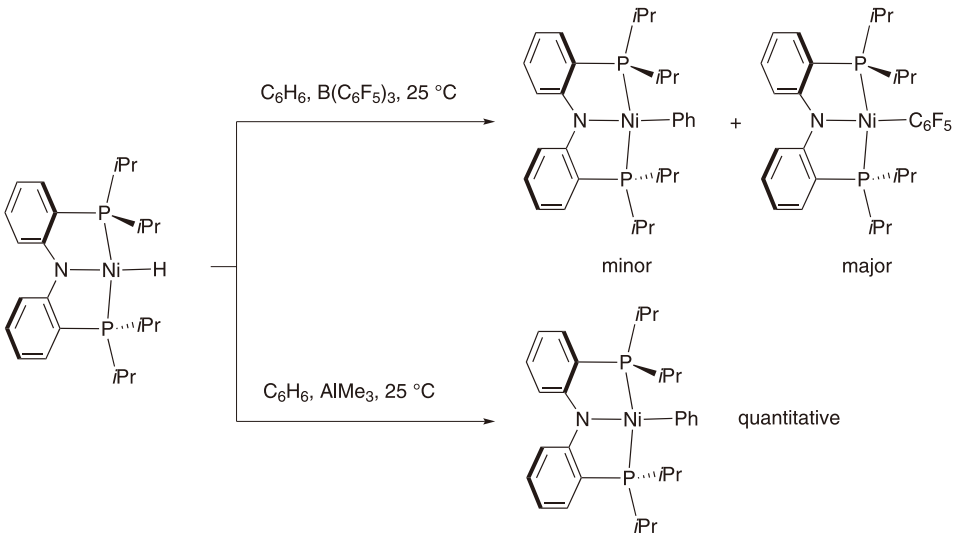
Benzene, toluene, and xylenes are inert molecules and often used as solvents for organic syntheses. These arenes, however, are reactive enough to undergo C(sp^2)-H bond cleavage under extremely mild conditions upon reactions with divalent nickel and platinum complexes of **1**.

As aforementioned, [**1a**]PtMe remains intact upon heating in benzene at 150 °C for 3 days under aerobic conditions. In the presence of one equiv of $B(C_6F_5)_3$, however, the same solution at 25 °C was found to afford in 31 hours [**1a**]PtPh quantitatively (Scheme 2), a consequence resulting from benzene C-H activation.[44] Alternatively, [**1a**]PtOTf also reacts with benzene at 110 °C or higher temperatures in the presence of aliphatic amines such as NEt_3, $MeNCy_2$, or 1,4-diazabicyclo[2.2.2]octane (DABCO) to generate quantitatively [**1a**]PtPh.



Scheme 2. Benzene C-H activation by [**1a**]PtX (X = Me, OTf)

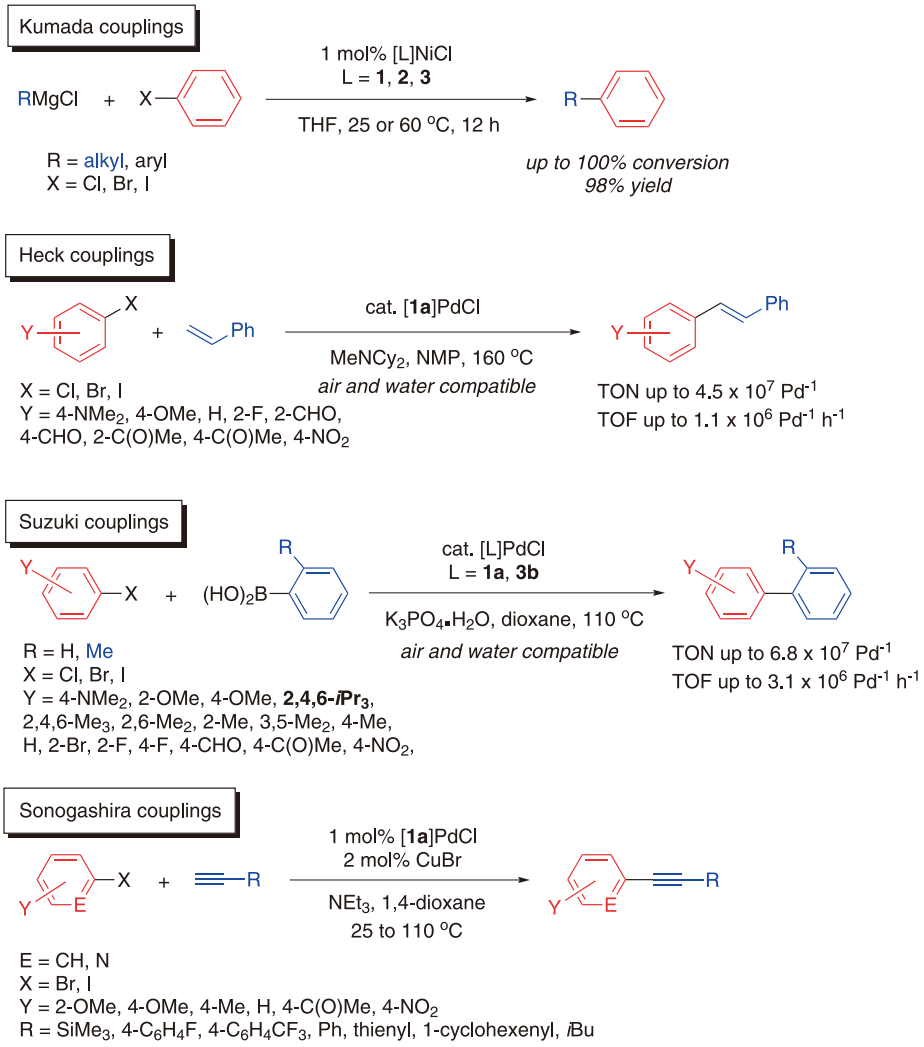
Nickel complexes of **1** are also reactive in this bond activation chemistry (Scheme 3).[45] In the presence of one equiv of $B(C_6F_5)_3$, the hydride complex [**1b**]NiH reacts with benzene at 25 °C to give [**1b**]NiPh successfully, though not as clean as what is found for the aforementioned platinum chemistry. The desired [**1b**]NiPh is produced as a minor product (*ca.* 20% as judged by ^{31}P NMR spectroscopy), accompanied inevitably by the major [**1b**]Ni(C_6F_5) throughout the reaction. The concomitant formation of [**1b**]Ni(C_6F_5) and [**1b**]NiPh is suggestive of the competitive occurrence of C_6F_5 transfer from boron to nickel and intermolecular benzene C-H activation. Similar results are also found for [**1c**]NiH. Interestingly, replacing Lewis acidic $B(C_6F_5)_3$ with $AlMe_3$ allows for both [**1b**]NiH and [**1c**]NiH to react cleanly with benzene at 25 °C, affording quantitatively [**1b**]NiPh and [**1c**]NiPh, respectively. Reactions employing toluene and xylenes also proceed similarly, producing quantitatively [**1b**]NiAr and [**1c**]NiAr (Ar = tolyl, xylyl) with the least sterically hindered C(sp^2)-H bond being mainly or exclusively activated.[45]



Scheme 3. Benzene C-H activation by [**1b**]NiH

7. Cross-coupling catalysis

Scheme 4 summarizes a number of cross-coupling reactions catalyzed by nickel or palladium complexes of these anilido phosphine chelates. In particular, divalent nickel complexes of **1**, **2**, and **3** are all active catalyst precursors for Kumada couplings of Grignard reagents with phenyl halides.[24,37,41] Both alkyl and aryl Grignard reagents are suitable nucleophiles in this catalysis. Depending on the identity of the anilido phosphine ligands, iodo, bromo, and even chloro electrophiles are compatible. In general, the activities of these catalysts increase following the order [**1**]NiCl < [**2**]NiCl < [**3**]NiCl. Of particular note are reactions employing chloro electrophiles and alkyl nucleophiles that contain β-hydrogen atoms. Catalysis having up to 100% conversion with 98% yield is achieved.



Scheme 4. Cross-coupling reactions catalyzed by Ni or Pd complexes of **1**, **2**, and **3**

The pincer complex [**1a**]PdCl is a versatile catalyst precursor, capable of mediating catalytic Heck olefination,[42] Suzuki arylation,[46] and Sonogashira alkynylation[47] of (hetero)aryl halides. Compounds {[**3b**]Pd(μ-Cl)}$_2$ and [**3b**]PdCl(PCy$_3$), on the other hand, are also active in catalytic Suzuki-type reactions.[43] The characteristic stability of these complexes in the presence of water under aerobic conditions at elevated temperatures makes these catalysts very user-friendly due to their easy manipulation and storage. A number of functional groups are compatible with these name reactions, including those characteristic of being sterically hindered, electronically activated, electronically neutral, and electronically deactivated. Extremely high turnover

numbers and turnover frequencies have been found for Heck- and Suzuki-type catalysis.[42-43] Employment of a trace amount (e.g., ppm) of these anilido phosphine complexes is thus sufficient for these catalytic reactions to operate satisfactorily. Of particular interest in the Suzuki couplings is also the effective construction of sterically encumbered tri-*ortho*-substituted biaryls such as 2,2',4,6-tetramethylbiphenyl and 2,4,6-triisopropyl-2'-methylbiphenyl. Though [**1a**]PdCl and [**3b**]PdCl exhibit comparable activities in the production of 2,2',4,6-tetramethylbiphenyl (87% and 82% yield, respectively), the former outperforms the latter for the generation of 2,4,6-triisopropyl-2'-methylbiphenyl (72% and 34% yield, respectively) under similar conditions. Contrasting with [**1a**]PdCl, complex [**1b**]PdCl that is characteristically more electron-releasing and sterically demanding exhibits substantially unsatisfactory activities in both Suzuki- and Sonogashira-type catalysis under identical conditions, highlighting significantly the profound P-substituent effects of these anilido phosphine complexes on these coupling reactions.

8. Conclusions

The origin and evolution of arylene bridged amido phosphine ligands and their subsequent metal complexes are described. Having hybrid characteristics, these ligands bind to both hard and soft metals as exemplified in this review by lithium, zirconium, and group 10 metals, respectively. With the rigid and robust arylene bridges in these ligands, the derived metal complexes are remarkably thermally stable. Of note are those also stable in the presence of water under aerobic conditions. These results are unusual taking into account the inherent stability and reactivity of mismatched HSAB pairs. Though markedly stable, these complexes are reactive enough to promote inert chemical bond cleavage and to mediate catalytic C-C bond-forming reactions. The exploration of this basic research is truly fun and rewarding.

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Lan-Chang Liang is a Distinguished Professor of Chemistry at National Sun Yat-sen University and a joint Professor of Medicinal and Applied Chemistry at Kaohsiung Medical University, Taiwan. He undertook his PhD studies in 1995-1999 at Massachusetts Institute of Technology with Professor Richard R. Schrock on early transition metal chemistry of complexes containing amido chelates. After a postdoctoral stay with Professor T. Daniel P. Stack at Stanford University studying functional molecular models of copper oxygenases, he began his independent career in 2000 at NSYSU where his research program focuses on the development and application of new mismatched coordination compounds, particularly those competent in inert chemical bond activation and subsequent catalytic functionalization. His work has been recognized by Thieme Chemistry Journals Award (2006), one of top international inorganic chemists under 40 years of age (Inorganica Chimica Acta 2007), and Chemical Society of Japan with Distinguished Lectureship Award (2008).

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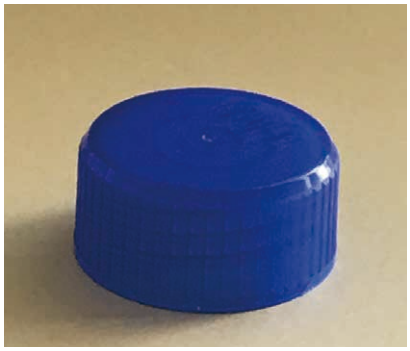
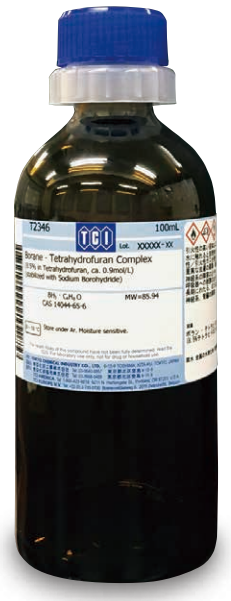
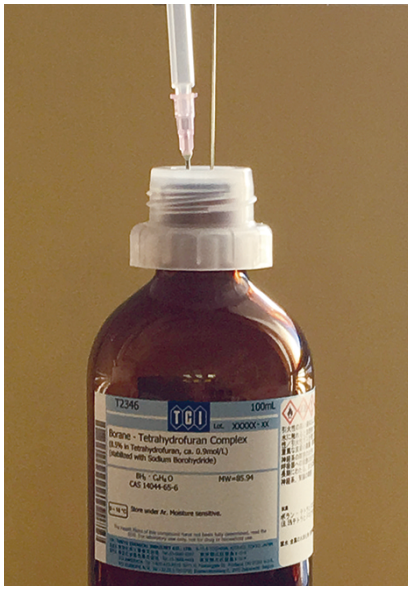
Septum Cap



Cover Cap



On the Whole



Normal Usage

TCI has recently introduced a new capped bottle design called DualSeal, which offers a superb air-free environment for oxygen and moisture sensitive reagents saves labile. DualSeal makes it possible to preserve and handle the content via air-free technique without lost in reagent quality or atmospheric exposure to pyrophoric and reactive reagents. Both the glass bottle and the Teflon-lined plastic cap are separable and allow for easy disposal. TCI will soon be expanding our product lineup of reagents packed in our DualSeal-equipped bottles.

Small Ring Building Blocks for Medicinal Chemistry

2-Oxa-6-azaspiro[3.3]heptane (1) Product Number: **O0466** **1g**

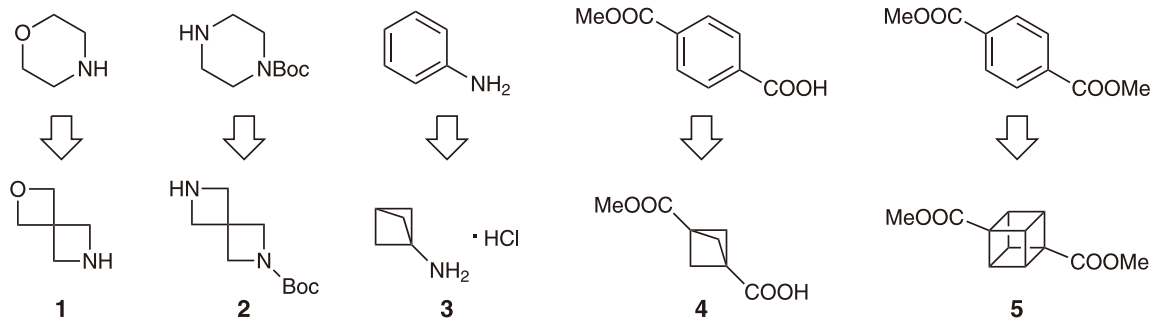
***tert*-Butyl 2,6-Diazaspiro[3.3]heptane-2-carboxylate (2)** Product Number: **B5032** **200mg**

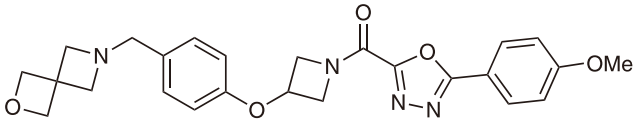
Bicyclo[1.1.1]pentan-1-amine Hydrochloride (3) Product Number: **B5479** **200mg 1g**

3-(Methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic Acid (4) Product Number: **M3149** **200mg 1g**

Dimethyl Cubane-1,4-dicarboxylate (5) Product Number: **D5542** **100mg 1g**

Cross-coupling reactions have become ubiquitous in synthesis and are essential in enabling the expansion of building block libraries, which has notably had a positive impact on the synthesis of pharmaceuticals with a high sp^2 carbon ratio. Unfortunately, reviews of clinical trial data has shown drug candidates with high planarity were more likely to fail.[1] It was speculated that the planarity of compounds caused unpredictable and undesirable bioavailability and toxicity owing to their insolubility. This pitfall has demonstrated the importance of sp^3 character in drug candidates and its needed emphasis. Spiro type building blocks comprised of an oxetane and azetidine (**1**,**2**)[2,3] are bioisosteres of morpholine and piperazine respectively. The related bicyclo[1.1.1]pentane or cubane (**3**,**4**,**5**)[4,5] are bioisosteres of benzene rings. The introduction of these unique functionalities from selected building blocks are expected to assist in the introduce more sp^3 carbon character to drug candidates while still retaining paralleled biological properties to their bioisosteres, lending to improved solubility and increase 3-dimensionality.





MCHr1 antagonist [6]

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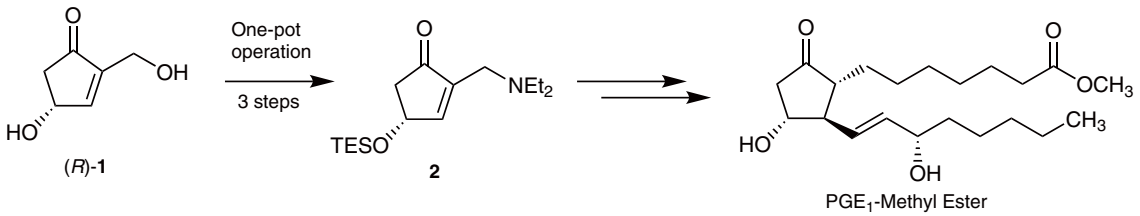
Polyfunctional Carbon 5-Membered Ring Building Blocks

4-Hydroxy-2-(hydroxymethyl)-2-cyclopenten-1-one (1) Product Number: **H1723**
100mg

(*R*)-4-Hydroxy-2-(hydroxymethyl)-2-cyclopenten-1-one ((*R*)-1) Product Number: **H1721**
50mg

(*S*)-4-Hydroxy-2-(hydroxymethyl)-2-cyclopenten-1-one ((*S*)-1) Product Number: **H1722**
50mg

The polyfunctional cyclopentenones (**1**, (*R*)-**1**, (*S*)-**1**) have the potential to be key building blocks in the synthesis of natural products (notably prostaglandins), pharmaceuticals, flavors, *etc*.[1] For example, Kasai *et al*. used (*R*)-**1** as a starting material in one pot to facilitate the synthesis of the key intermediate **2** in the total synthesis of prostaglandin E1 (PGE_1), a useful therapeutic drug for the treatment of chronic arterial occlusion.[2] This route allowed for a much shorter synthesis compared to previous PGE synthesis methods.[3] It is anticipated that products will be applied to total synthesis and the production of valuable compounds which bearing a chiral cyclopentanone core.



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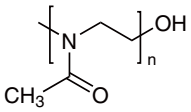
Water-soluble Polymers with Biocompatiblility: Poly(2-oxazoline)s

ULTROXA® Poly(2-methyl-2-oxazoline) (n=approx. 100) (1) Product Number: **P2506** **200mg**

ULTROXA® Poly(2-propyl-2-oxazoline) (n=approx. 100) (2) Product Number: **P2508** **200mg**

Poly(2-oxazoline)s are biocompatible and non-immunogenic pseudo-polypeptide-structured polymers. ULTROXA® poly(2-methyl-2-oxazoline) (**1**), a highly-defined polymer with narrow molar mass distribution, is more hydrophilic than poly(ethylene glycol) (PEG).[2a] ULTROXA® poly(2-propyl-2-oxazoline) (**2**) with a narrow molar mass distribution transitions to a hydrophobic state in water when heated.[3a] **1** and **2** have been applied to surface coating,[1] drug delivery systems,[2] and thermoresponsive material.[3]



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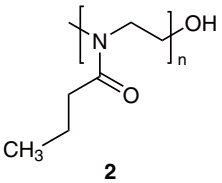

2

ULTROXA® is a registered trademark of Ghent University.

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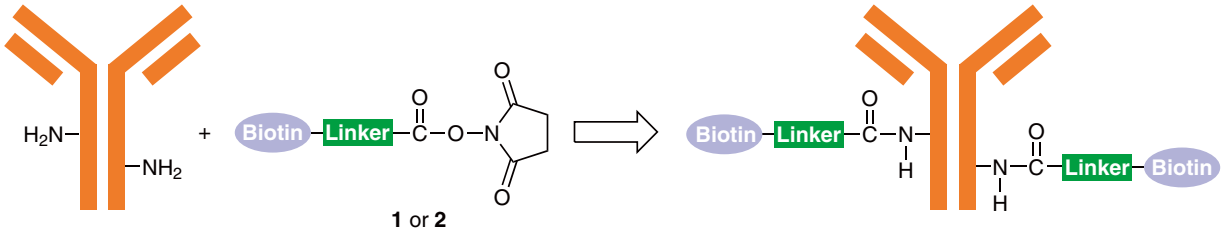
Pre-Weighed Biotinylation Reagents

Biotin-LC-LC-NHS (2mg×5) (1) Product Number: **B6096**
2mg×5

Biotin-PEG$_2$-NHS (2mg×5) (2) Product Number: **B6097**
2mg×5

Detection and purification of proteins are the core methods in life science experiments. The biotin-avidin interaction is often used to detect or purify proteins because of its high binding affinity. **1** and **2** are biotinylation reagents containing both a linker and an *N*-hydroxysuccinimidyl ester (NHS) moiety and are pre-weighed in suitable amounts for protein biotinylation. They can biotinylate proteins by reacting with amino groups (-NH$_2$) of proteins and by forming amide bonds at pH between 7 and 9. Below is the direction for use.



Preparation:
It is recommended to prepare a 10 mM biotinylation solution. In order to efficiently biotinylate a sample, biotinylation solution should be used at a 15-fold molar excess over the amount of amine-containing protein. Here shows the calculation of the 10 mM biotinylation solution amount.
Calculate Example: A μL of 10 mM biotinlation solution for biotinylation 2 mg IgG (150,000 M.W.)
2 [mg IgG] x 10^{-3} [g/mg] x 1/150,000 [mol/g] x 15 [fold]
= A [μL of 10 mM biotinylation solution] x 10^{-6} [L/μL] x 10 [mmol/L] x 10^{-3} [mol/mmol]

A = 20 [μL of 10 mM biotinylation solution]

Direction for Use
1. Bring **1**, **2** to room temperature and dissolve 2 mg of **1** in 350 μL of DMSO or DMF, or 2 mg of **2** in 400 μL of PBS to prepare a 10 mM biotinylation solution.
2. Dissolve the sample (1-10 mg/mL) in an appropriate buffer with pH between 7 and 9 such as PBS. Do not use buffers including amines (such as Tris).
3. Add A μL (calculated above) of 10 mM biotinylation solution to the sample solution and incubate the mixed solution for 30 min at room temperature.
4. Remove unreacted and hydrolyzed reagent by a desalting column or dialysis.

Reference

D. Savage *et al*., in *Avidin-Biotin Chemistry: A Handbook*, 2nd ed., Pierce Chemical, **1992**, pp. 42-43.

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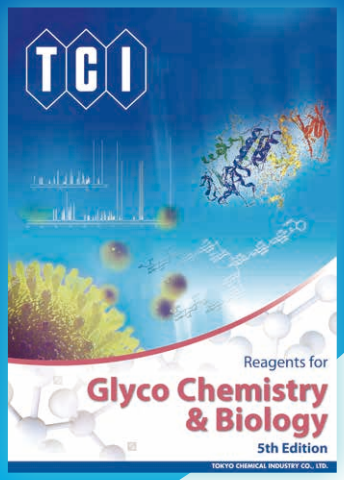

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