Cross-Coupling

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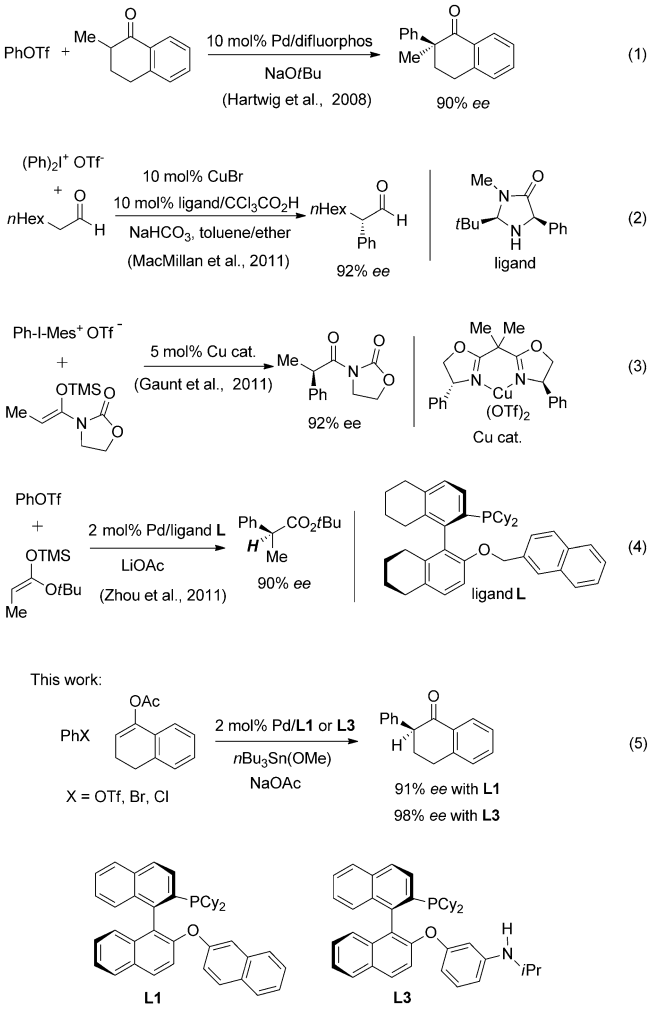
Arene CH–O Hydrogen Bonding: A Stereocontrolling Tool in Palladium-Catalyzed Arylation and Vinylation of Ketones**

*Zhiyan Huang, Li Hui Lim, Zuliang Chen, Yongxin Li, Feng Zhou, Haibin Su, and Jianrong (Steve) Zhou**

Transition-metal-catalyzed α-arylation of carbonyl compounds has become a very useful tool to prepare α-arylcarboxylic acids and derivatives.[1] Many asymmetric couplings have been developed for arylation of ketones,[2] aldehydes,[3] oxindoles[4] and α-methylacetoacetates,[5] etc. For example, in a nickel-catalyzed method reported by Hartwig, enolates were formed in situ from cyclic ketones and a strong base. They coupled efficiently with aryl triflates to form quaternary centers with high *ee* values [Eq. (1), Scheme 1].[2e] These asymmetric processes cannot be used to construct tertiary centers because arylated products contain acidic α-protons and the latter cannot survive the basic conditions. Thus, arylation of enolates to form tertiary centers must use preformed soft enolates with low basicity.[6] Only recently, MacMillan et al. and Gaunt et al. independently reported arylations of enamines derived from aldehydes as well as silyl enolates of imides to selectively form tertiary centers. [Eq. (2)–(3)].[7] Reactive diaryliodonium reagents must be used and ketone substrates were not reported. In 2011, we realized the first palladium-catalyzed, highly stereoselective arylation of ester enolates for construction of tertiary centers [Eq. (4)].[8] In an umpolung approach, Fu et al. reported asymmetric coupling between α-haloketone electrophiles and arylmetal reagents.[9] Herein, we report the first palladium-catalyzed coupling of ketones to produce tertiary centers with excellent *ee* values [Eq. (5)].

At first, we attempted to couple a silyl enolate of 1-tetralone using our ester coupling procedure (2 mol% Pd/ligand **L** and LiOAc in $PhCF_3$). However, no product was formed in the presence of LiOAc. With CsF, arylation occurred, but the product racemized. To our delight, we finally found that the tin enolate of 1-tetralone can couple very efficiently with 91% *ee* when **L1** was used. No erosion of the *ee* value was observed over time. The tin enolate was formed easily by stirring alkenyl acetate with nBu$_3$Sn(OMe) at room temperature, and it was used directly without purification.[10]



Scheme 1. Examples of asymmetric coupling of enolates. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

During catalyst discovery, the $Pd(OAc)_2$/difluorphos catalyst, which was previously used by Hartwig et al.,[2e] gave poor results with 38% *ee*. $[Ni(cod)_2]$/difluorphos (cod = cyclo-1,5-octadiene) was catalytically inactive.[2d] Pd/MOP showed low activity and gave moderate *ee* values (Scheme 2). We then modified MOP by installing the more donating PCy_2 group and *O*-2-naphthyl side chain. The resulting **L1** turned out to be both active and selective. Structural analogues carrying

[*] Dr. Z. Huang, L. H. Lim, Dr. Z. Chen, Dr. Y. Li, Prof. Dr. J. Zhou
Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University
21 Nanyang Link, Singapore 637371 (Singapore)
E-mail: jrzhou@ntu.edu.sg
F. Zhou, Prof. Dr. H. Su
Division of Materials Science, School of Materials Science and Engineering, Nanyang Technological University
50 Nanyang Avenue, Singapore 639798 (Singapore)

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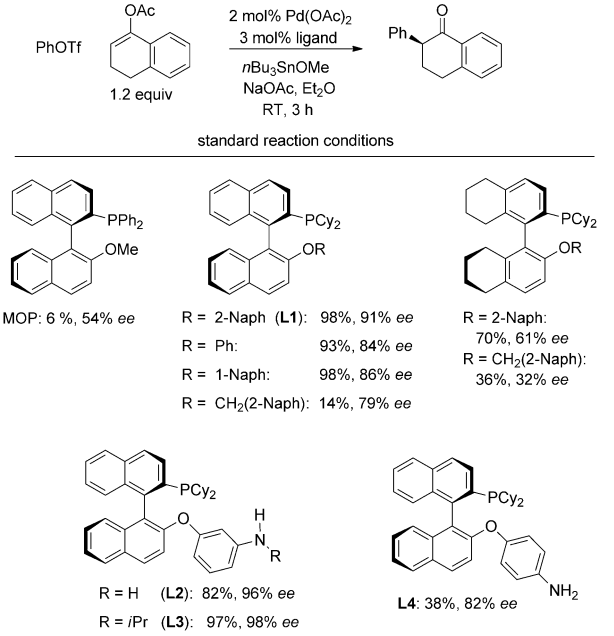
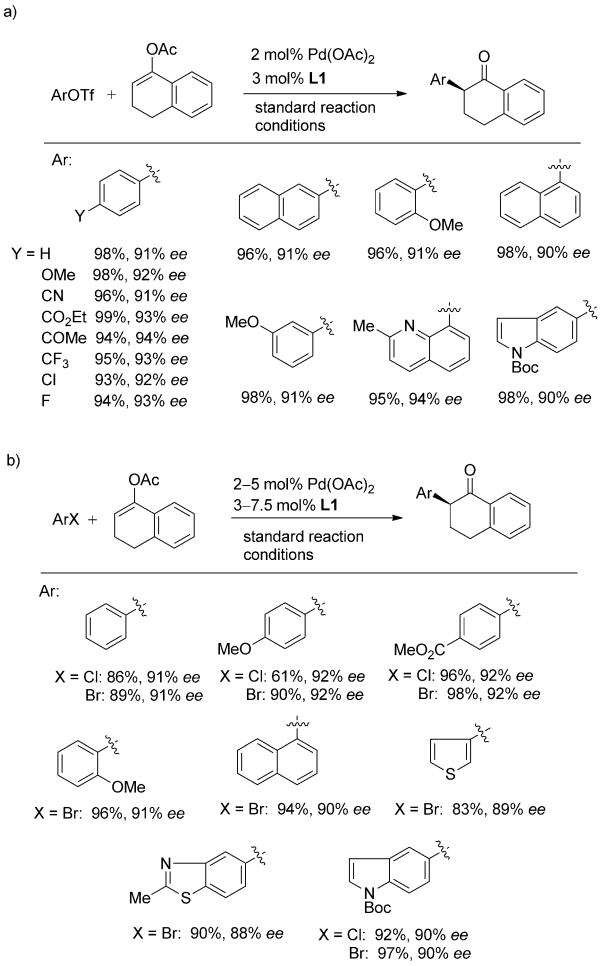


Scheme 2. Catalyst discovery in the model arylation reaction. MOP = 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl. Yields are those measured by GC, and the *ee* values were determined by HPLC analysis with a chiral stationary phase.



Scheme 3. Arylation of 1-tetralone enolate using ligand **L1**. See Scheme 2 for standard reaction conditions. Yields are those reported for isolated products, and the *ee* values were determined by HPLC analysis with a chiral stationary phase.

other O-groups, such as phenyl, 1-naphthyl, and arylmethyl, all gave lower *ee* values. Notably, partial saturation of the binaphthyl backbone led to worse results. O-aryl groups in ligands were introduced by arylation of naphthol using diaryliodonium salts.[11]

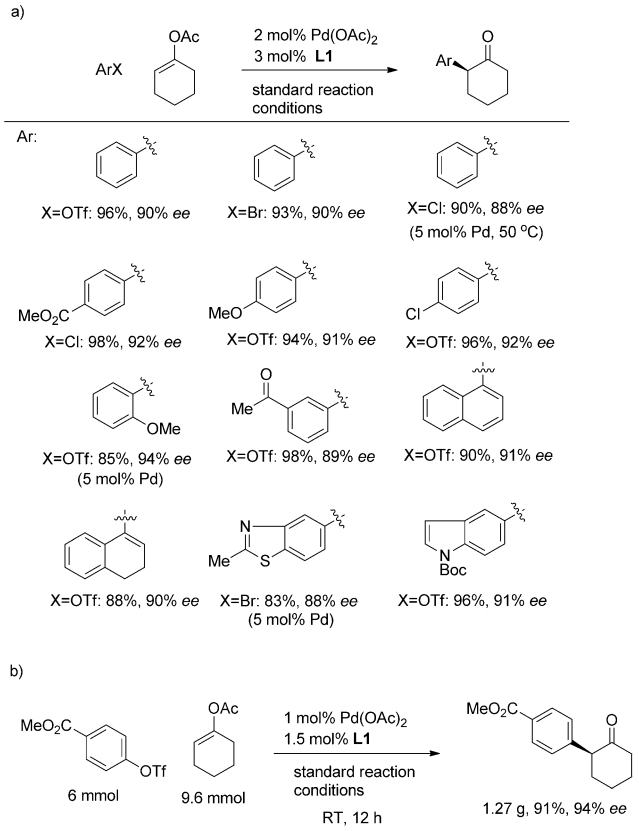
The Pd/**L1** catalyst can be applied to couplings of various aryl and heteroaryl triflates (Scheme 3a). For aryl triflates carrying aryl–Cl and aryl–F bonds, the coupling was selective at the Ar–OTf bond. The same method can be applied to aryl bromides and chlorides (Scheme 3b). The absolute configuration of the major stereoisomer was established to be *2S*, by X-ray diffractional analysis of one benzothiazole product. Coupling of PhI resulted in low conversion, probably because of fast decomposition of oxidative adducts of palladium.[2e]

The enolate of cyclohexanone coupled well with many aryl and heteraryl triflates, bromides, and chlorides (Scheme 4a). One exception was electron-rich aryl chlorides, which coupled slowly. The coupling procedure can be conducted on a gram scale using 1 mol% palladium (Scheme 4b). The crude reaction mixture was directly passed through a pad of silica gel and the filtrate, after concentration, was washed with *n*-pentane to give the solid product in 91% yield and 94% *ee*. ICP analysis indicated the purified sample contained 28 ppm of the residual tin. Thus, most of organotin was removed by washing with *n*-pentane. The sample was then stirred with basic alumina in CH_2Cl_2 at room temperature for 3 h to reduce the tin content to 3 ppm.

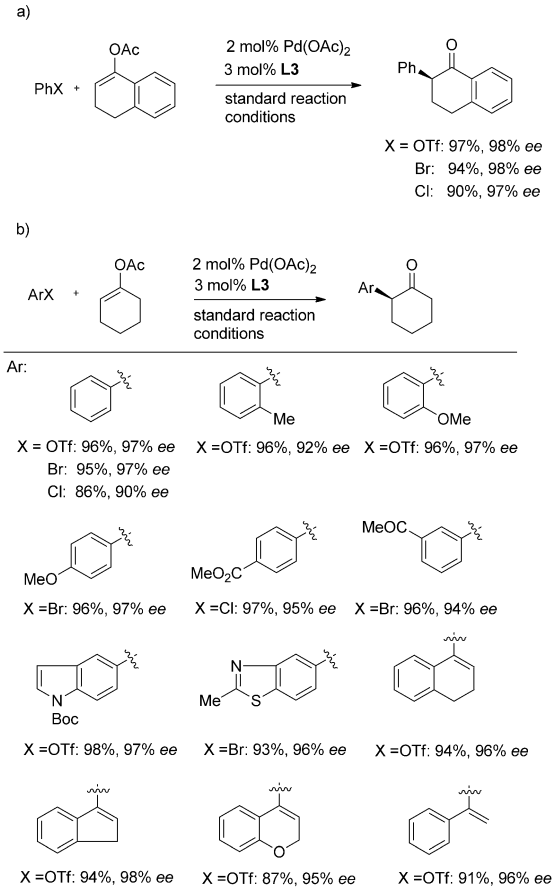
Recently, we conducted DFT calculations to determine the origin of stereoselectivity from the Pd/**L1** catalyst. We were surprised to find that **L1** formed a CH–O hydrogen bond between the side-chain naphthyl group and one palladium-bound enolate in both the ground and transition states of C–C reductive elimination (see below). This inspired us to investigate new ligands, **L2** and **L3**, which are capable of NH–O hydrogen bonds. Indeed, **L2** and **L3** gave better results (Scheme 2). When **L3** was used in the coupling of either cyclohexanone or 1-tetralone enolates, the *ee* values were generally better than that obtained with **L1** (Scheme 5). Various aryl bromides and triflates worked very well at room temperature, and some aryl chlorides, except the electron-rich ones, also coupled smoothly.

We explored the use of various ketones, such as substituted 1-tetralones and cyclohexanones (Scheme 6). Seven- and eight-membered cyclic ketones also underwent the coupling reaction. Notably, the *ee* value of the cyclopentanone product fell over time from 83% *ee* at the first 0.5 h. In fact, 2-aryl cyclopentanones are known to undergo facile racemization, even on silica gel.[12] 4-Oxa-1-tetralone can couple to give isoflavanones, which inhibit the growth of microbes and tumors.[13] The acyclic (*E*)-propiophenone enolate gave only 33% *ee* in the presence of Pd/**L1**.

The arylation products can be easily converted into other chiral building blocks. For example, reduction of 2-phenyl-



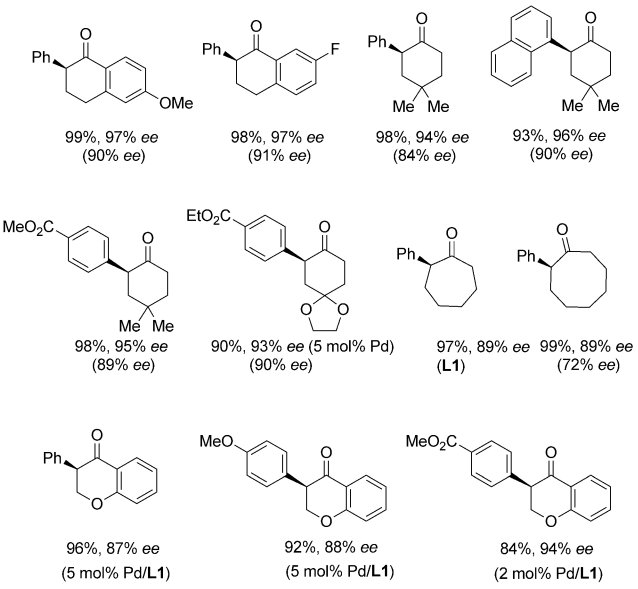
Scheme 4. Arylation and vinylation of cyclohexanone using ligand **L1**. See Scheme 2 for standard reaction conditions. Yields are those reported for isolated products, and the *ee* values were determined by HPLC analysis with a chiral stationary phase.



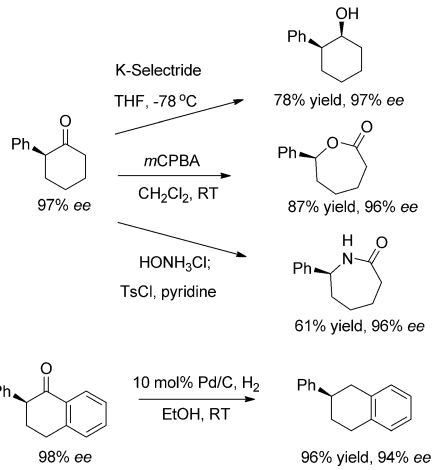
Scheme 5. Arylation and vinylation of ketones using ligand **L3**. See Scheme 2 for standard reaction conditions. Yields are those reported for isolated products, and the *ee* values were determined by HPLC analysis with a chiral stationary phase. Boc = *tert*-butoxycarbonyl.

cyclohexanone using K-Selectride gave the *cis* alcohol (d.r. 80:1) without erosion of the *ee* value (Scheme 7).[14] Li/naphthalene reduction of the same ketone can selectively give *trans*-2-arylcycohexanol,[15] which is commonly used as chiral auxiliary in asymmetric transformations.[16] The 2-arylketones can also be converted into aryllactones by Baeyer–Villiger oxidation and into aryllactams by Beckmann rearrangement. Notably, it is important to prepare the *E*-oxime selectively, since the *Z*-isomer can rearrange to give a different lactam.[17] One more example is deoxygenation of 2-aryltetralones by catalytic hydrogenolysis. Some 2-aryltetralins are potential drugs for treatment of arrhythmias (irregular heartbeat), by acting as inhibitors of the Na^+/Ca^{2+} exchange mechanism.[18] No asymmetric synthesis of these compounds has been reported previously.

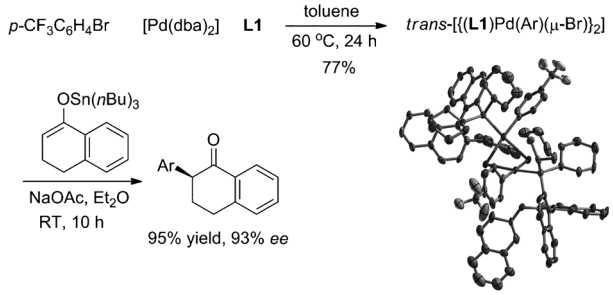
We have prepared an oxidative adduct from an aryl bromide, $[Pd(dba)_2]$, and **L1** (Scheme 8). The dimeric palladium complex is bridged by two bromides.[19] **L1** binds to each palladium center in a monodentate fashion and the putative interaction between palladium and the bottom naphthyl ring of **L1** was lost. When the complex was treated with a tin enolate, coupling occurred in good yield in 93% *ee*. If the stoichiometric coupling was conducted with the tin enolate (1 equiv per Pd) in the presence of 3 equivalents of *p*-$CF_3C_6H_4Br$ per Pd, the newly formed $[(\mathbf{L1})Pd^0]$ underwent fast oxidative addition at room temperature to regenerate the



Scheme 6. Arylation of various ketones using ArOTf and 2 mol% Pd/**L3** unless indicated otherwise. Results in parentheses were obtained with 2 mol% Pd/**L1**.



Scheme 7. Synthetic application of 2-arylketones. *m*CPBA = *meta*-chloroperbenzoic acid, Ts = 4-toluenesulfonyl.



Scheme 8. Stoichiometric reaction of a [(**L1**)Pd(Ar)(Br)] complex and a tin enolate. The ORTEP of *trans*-[{(ligand **L1**)Pd(Ar)(μ-Br)}$_2$] is shown. Thermal ellipsoids shown at 50% probability with hydrogen atoms omitted for clarity. dba = dibenzylideneacetone.

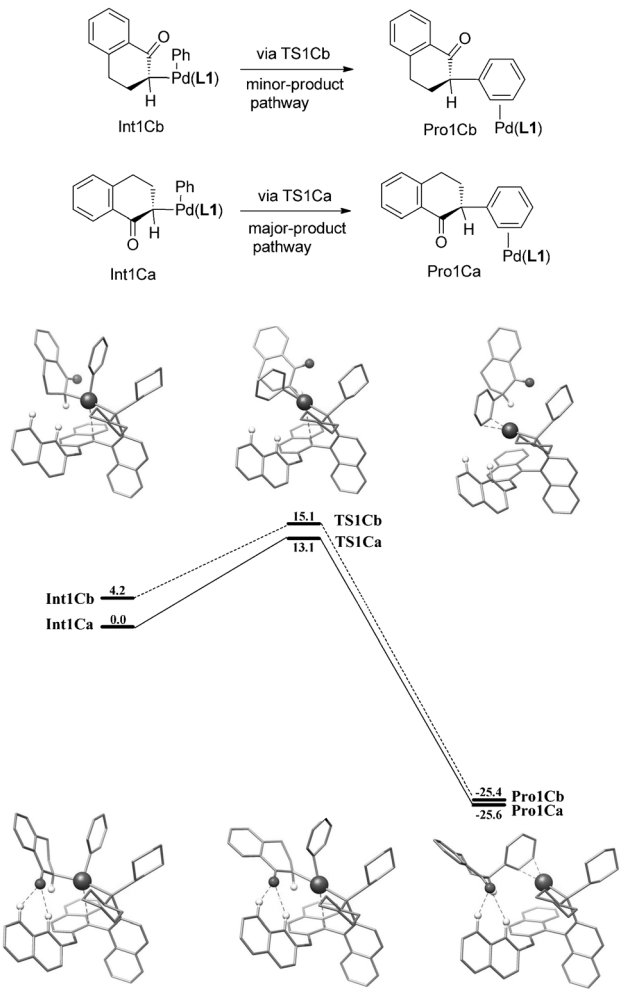


Figure 1. Calculated C–C reductive elimination from C-enolate complexes supported by ligand **L1**.

same dimeric complex in greater than 95% yield (based on ^{31}P NMR spectroscopy).

We conducted DFT calculations (B3LYP) of the reductive elimination of the model reaction shown in Figure 1 to learn why the naphthyl side chain of **L1** was special in promoting stereoselectivity. First, we established the bonding mode of the bottom ring of **L1** in the complexes [(**L1**)Pd(aryl)(enolate)]. The bonding of palladium with the ipso carbon atom of the bottom ring was found to be more stable than Pd–O bonding with the aryl ether by about 5–6 kcal mol^{-1}. Furthermore, isomerization of the ether-bound form to the arene-bound form was almost barrier free. Thus, we focused on studying enolate complexes with the palladium–arene interaction.

Next, we explored possible C–C bond formation from O-enolate complexes.[20] No smooth pathway can directly lead to coupling products. Instead, an abrupt "jumping" of atoms was observed at one point as the C-C distance was reduced. In addition, isomerization of the O-enolate complexes to C-enolates has relatively high barriers (15–18 kcal mol^{-1}). We discovered that C-enolate complexes can undergo facile C–C reductive elimination (Figure 1). The barriers were 13 and 15 kcal mol^{-1} leading to major and minor products, respectively. In the pathway leading to the major product, the ground state (Int1Ca) and transition state (TS1Ca) were stabilized by 4.2 and 2.0 kcal mol^{-1}, respectively, relative to those of the minor-product pathway. The source of the stabilization was the double CH–O hydrogen bonds between two O-naphthyl CH bonds and the enolate oxygen atom. In the minor-product pathway, the carbonyl group pointed away from the naphthyl side chain and no hydrogen bond was possible.

The weak hydrogen bonding of the arene CH—O type is typically worth 0.5–4 kcal mol^{-1} of stabilization.[21] This weak interaction has been found in crystals and biomacromolecules such as proteins. However, it has not been observed in asymmetric metal catalysis. In our optimized structures of enolate complexes, the bond angles and lengths of the hydrogen bonds all fall into the expected ranges.[22]

We also calculated the reductive elimination step of C-enolate complexes of Pd/**L2** (Figure 2). Again both the ground state (Int2Ca) and transition state (TS2Ca) were stabilized by 4.5 and 3.2 kcal mol^{-1}, respectively, for the major-product pathway, and the stabilization was derived from one NH–O and one CH–O hydrogen bond.

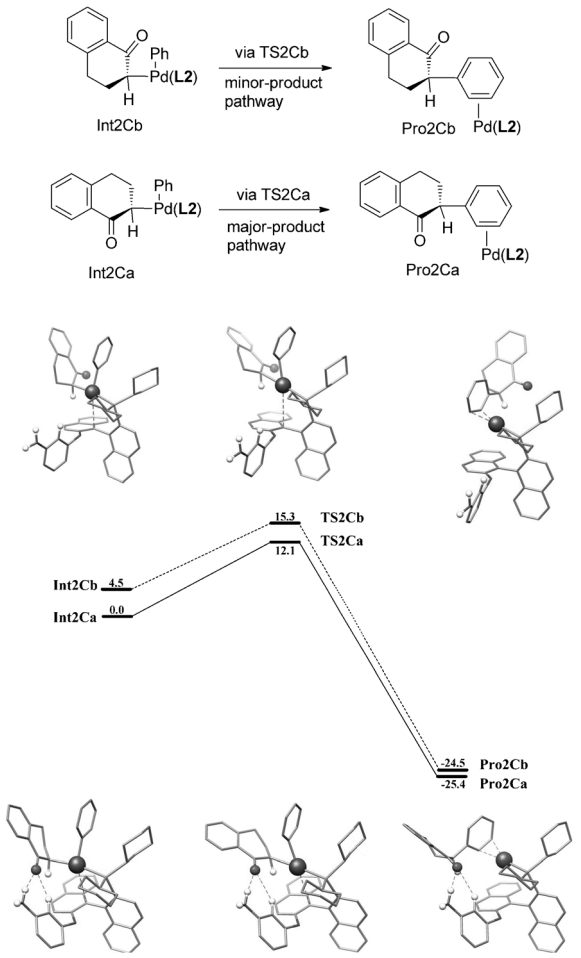


Figure 2. Calculated C–C reductive elimination from C-enolate complexes supported by ligand **L2**.

Experimentally, we gained some support for the hydrogen bonding. For example, inclusion of 3 equivalents of hexamethylphosphoramide (HMPA), a hydrogen-bond disruptor, in the model reaction of tetralone led to an appreciable decrease in the *ee* values (91→77 % *ee* with **L1** and 98 %→66 % *ee* with **L3**). The catalytic activity was not significantly altered by HMPA.

We also calculated the energies of the transmetalation step. Previously, it was assumed that transmetalation of metal enolates to [(**L1**)Pd(Ar)(OAc)] will first give O-bound enolates.[20] However, we found palladium-acetate-assisted transmetalation has high barriers on the way to either O- or C-enolate complexes. Instead, we found the cationic complex $[(\text{tin enolate})\text{Pd}(\text{Ar})(\mathbf{L1})]^+$, wherein tin enolate was bound to the palladium center through its β-carbon atom, thus acting very much like an electron-rich olefin. Upon attack of external acetate anion on tin, barrier-free transmetalation occurred to form C-bound enolate complexes directly. No O-enolate complex was formed, and overall, the C–C reductive elimination is irreversible and is stereodetermining.

In summary, we have developed a palladium-catalyzed method for asymmetric α-arylation and vinylation of ketones and it can establish tertiary centers with high *ee* values. The 2-arylketones can be used to access pharmacologically active entities.[23] More significantly, the Pd/**L1** catalyst employs attractive arene CH–O hydrogen bonding to induce chirality. This is the first example of its kind in asymmetric metal catalysis.

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