Cross-Coupling

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Weak Arene C–H···O Hydrogen Bonding in Palladium-Catalyzed Arylation and Vinylation of Lactones**

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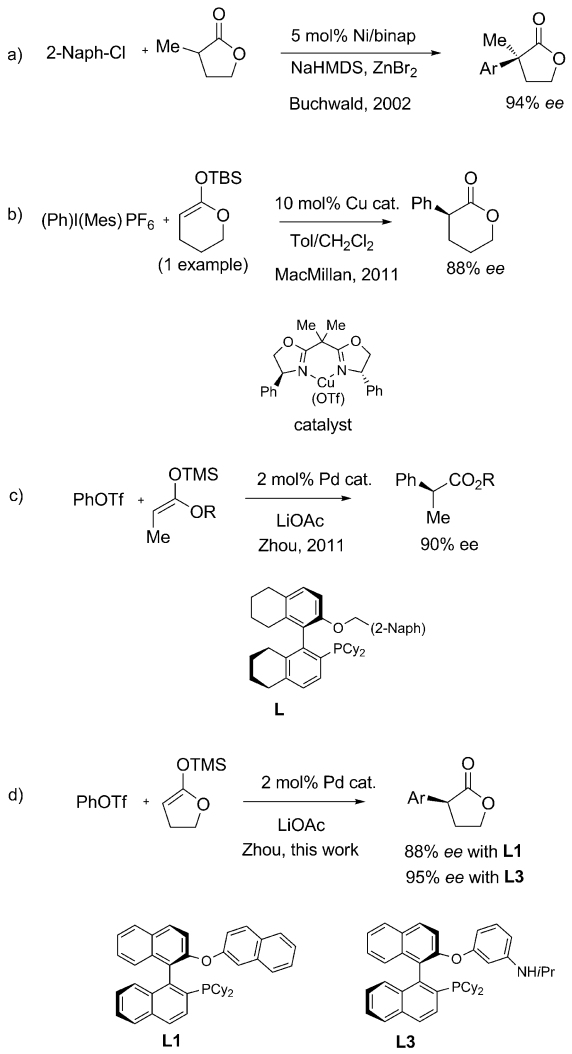
Metal-catalyzed α-arylation of enolates has become a useful tool to make biologically and pharmacologically interesting entities.[1] Several metal catalysts are now available for asymmetric couplings of enolates of ketones,[2] aldehydes,[3] and oxindoles,[4] etc. For example, Buchwald et al. reported asymmetric couplings of α-substituted-γ-butyrolactone in the presence of a strong base (Scheme 1a).[5] Most existing methods, however, were limited to formation of quaternary centers. Coupling to form more common tertiary centers proved to be more difficult, because of fast product racemization under basic conditions.

To address this deficiency, the groups of MacMillan and Gaunt independently reported copper-catalyzed arylation of silyl ketenimides and enamines formed in situ from aldehydes. One silyl enolate derived from valerolactone can react with several diaryliodonium salts to give about 90% *ee* (Scheme 1b).[6] Last year, we disclosed the palladium-catalyzed asymmetric arylation of acyclic esters (Scheme 1c).[7] When the α-alkyl chain of acyclic enolates carried an oxygen atom, poor coupling efficiency and selectivity resulted. Coupling of the silyl enolate of γ-butyrolactone led to less than 20% *ee* when Pd/**L** was used as catalyst.

Enzymatic and chemical resolution of α-aryllactones were not reported, and resolution of α-arylcarboxylic acids, derived from the lactones, was also not available.[8] Resolution of α-arylketones and α-arylsuccinic anhydrides has been reported to give enantioenriched α-aryllactones, but the *ee* values were unsatisfactory.[9] Asymmetric protonation of prochiral enolates such as silyl enolates of ketones was realized recently, but protonation of α-aryllactones was lacking.[10] In these approaches, aryl groups must be installed before the absolute configuration is set.

Herein, we report new chiral phosphines which allow the α-arylation of lactones to produce tertiary centers in high stereoselectivity (Scheme 1d). This work describes the first general method for asymmetric arylation of lactones leading to the formation of tertiary centers. After lactone opening, the resulting hydroxy groups can be transformed to other functionalities and new C–C bonds. More importantly, a new mode of stereocontrol for metal catalysis was discovered. Specifically, **L1** and **L3** can form hydrogen bonds between the aryl C–H bonds of the ligand and the oxygen atom of palladium enolates.



Scheme 1. Overview of asymmetric couplings of enolates. HMDS = hexamethyldisilazide, Mes = mesityl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, TMS = trimethylsily.

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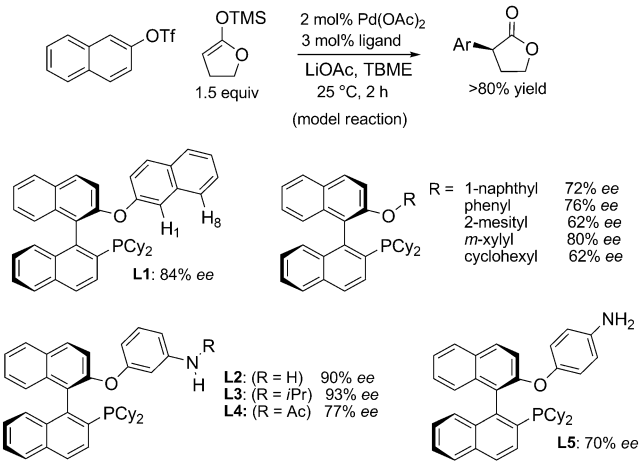
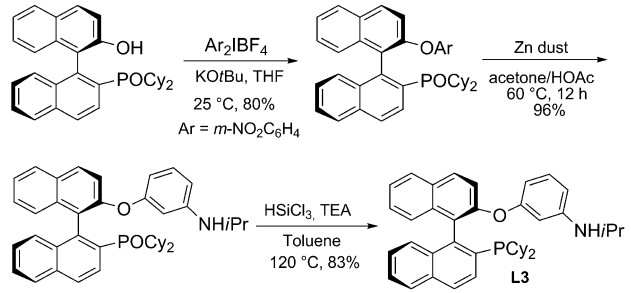


Scheme 2. Catalyst discovery in the model coupling. TBME = *tert*-butylmethyl ether.

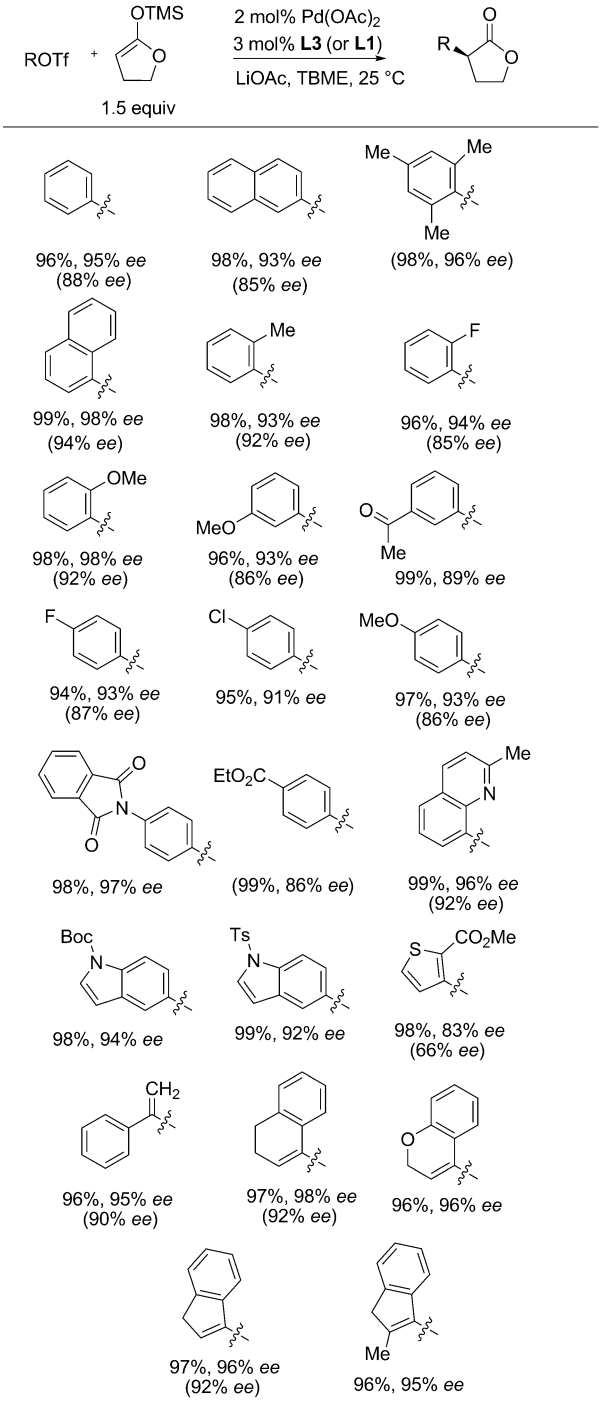
group, resulted in 84% *ee*. When the 2-naphthyl group of **L1** was replaced by other aromatic rings (phenyl, 1-naphthyl, *m*-xylyl, and 2-mesityl), the *ee* value fell. The use of a cyclohexyl ring also led to moderate *ee* values.

Later, we used DFT calculations to understand the origin of the stereoselectivity of **L1**. To our surprise, both hydrogen atoms H1 and H8 can form hydrogen bonds with palladium-bound C-enolates (see below). Based on this new finding, we designed the ligand **L2** having an aromatic NH_2 group, which can form NH···O hydrogen bonds. Indeed, it gave 90% *ee* in the coupling reaction (Scheme 2). A similar ligand **L3**, bearing an NH(*i*Pr) group, gave 93% *ee*. **L4**, having an NHAc group, gave a lower *ee* value because of in situ N-silylation (as detected by ESI). A related ligand **L5**, having the NH_2 group in the *para* position, gave only 70% *ee*. The O-aryl ligands can be easily made by modification of Buchwald's synthesis.[11] The O-aryl groups were introduced from diaryliodonium salts (Scheme 3).



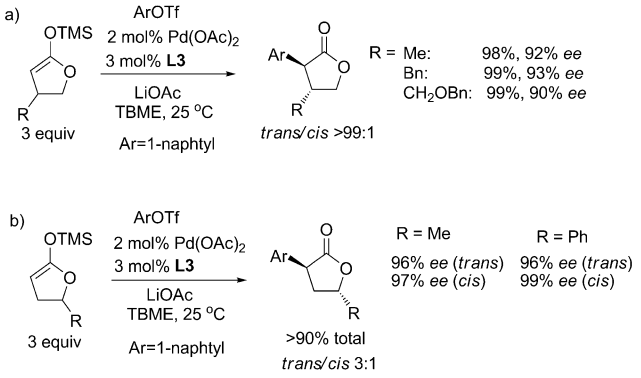
Scheme 3. Synthesis of chiral phosphine **L3**. TEA = triethylamine, THF = tetrahydrofuran.

The Pd/**L3** catalyst can be applied to the coupling of various aromatic triflates with γ-butyrolactone (Scheme 4). **L3** gave higher *ee* values than **L1** in most cases. Furthermore, the catalysts tolerated groups such as ester, ketone, and phthalimide, as well as aromatic C–F and C–Cl bonds. Some typical heterocycles were also tolerated, and included quinoline, indole, and thiophene. Notably, vinyl triflates provided the products with excellent *ee* values.



Scheme 4. Coupling of γ-butyrolactone. The values in parentheses refer to the *ee* value obtained with **L1**. Boc = *tert*-butoxycarbonyl, Ts = 4-toluenesulfonyl.

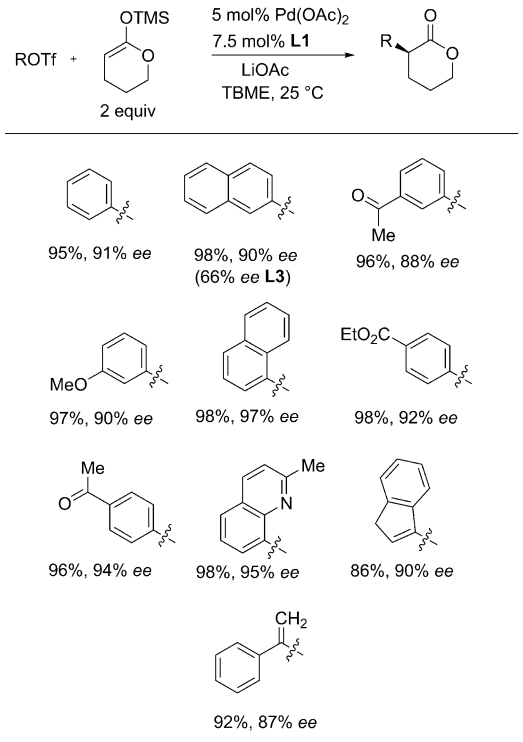
A single crystal of the *p*-chlorophenyl product was obtained and its absolute configuration was determined to be *S*, based on X-ray diffraction.[12] The high-resolution diffraction data was collected at −170 °C using Mo-K radiation. In this case, chlorine was sufficient to serve as a heavy atom for assignment of the absolute configuration.[13]



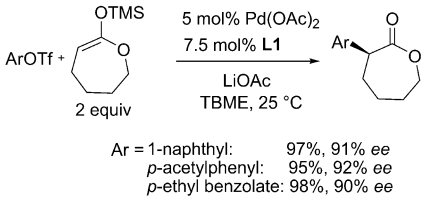
Scheme 5. Couplings of substituted γ-butyrolactones.

Lactone enolates having ring-substituents also coupled to give the *trans*-isomers predominantly (Scheme 5). Notably, β-substituted lactones gave only the *trans* isomers in greater than 90% *ee*, when 3 equivalents of the racemic enolate was used. If a substituent was present at the γ-position, the *trans* selectivity fell to 3:1. The diastereomeric pairs can be separated by silica gel flash chromatography and the major isomers have the *trans* configurations, based on X-ray diffractional analysis.[12]

In couplings of δ-valerolactone, **L1** proved to be more selective than **L3** (Scheme 6). This selectivity may have something to do with the conformational difference of the rings. Heteroaryl and vinyl electrophiles also worked well and the seven-membered caprolactone reacted smoothly (Scheme 7). The coupling procedure can be used for the

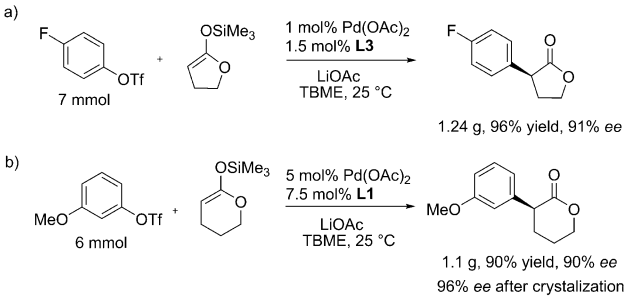


Scheme 6. Coupling of δ-valerolactone.



Scheme 7. Coupling of ε-caprolactone.

gram-scale synthesis of 2-aryllactones, wherein the palladium catalyst loading can be as low as 1 mol% (Scheme 8a), and a simple crystallization can give 96% ee (Scheme 8b).

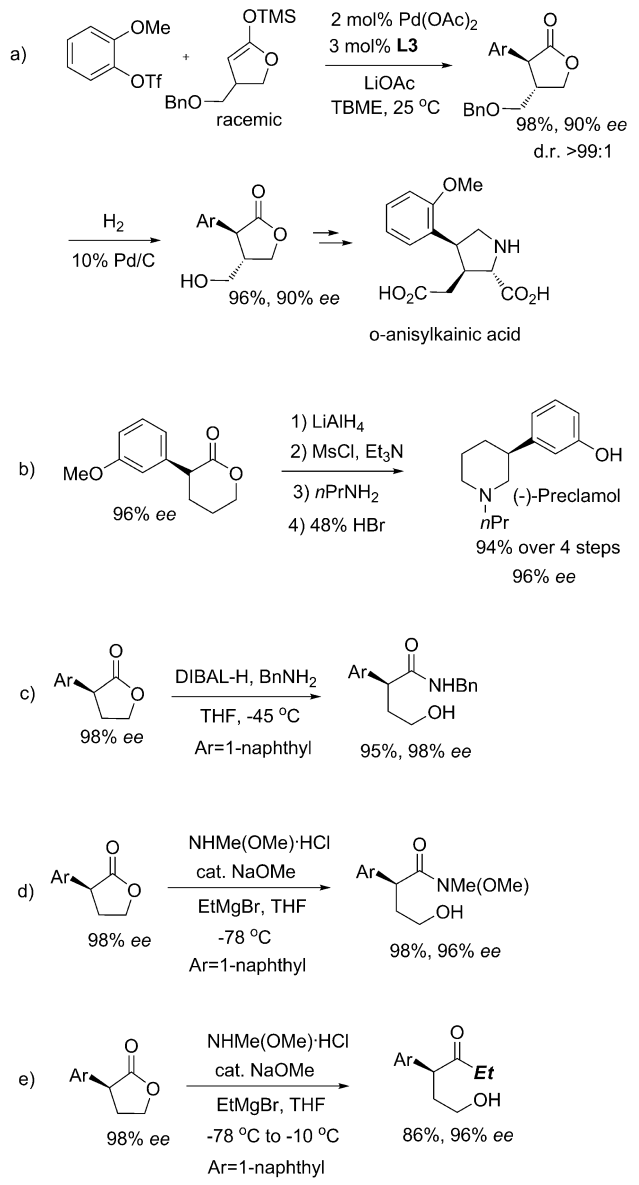


Scheme 8. Gram-scale coupling.

We have synthesized two drug candidates to demonstrate the utility of our method. For example, the diastereoselective arylation of a racemic enolate can give an alcohol in 90% *ee* and d.r. value greater than 99:1 (Scheme 9a). After debenzylation and alcohol oxidation, the resulting aldehyde can be used as a key intermediate in the synthesis of arylkainic acid analogues reported by Kan and co-workers.[14] The same aldehyde required a seven-step synthesis as reported by Kan and co-workers, and featured a rhodium-catalyzed diastereoselective carbene insertion. *o*-Anisylkainic acid is a potent ligand for ionotropic glutamate receptors, which are involved in memory and learning processes.[15]

The second example is (−)-preclamol, a potential drug for the treatment of neurological disorders such as Parkinson's disease, schizophrenia, drug addiction, and depression.[16] The aryllactone was converted to (−)-preclamol in four steps (Scheme 9b). After optimization of the reaction conditions, each step was high yielding and only one purification was needed after last step to isolate (−)-precamol in 94% yield. This route offers the opportunity to introduce other aryl and alkyl amine groups for analogue synthesis.

The α-aryl-γ-butyrolactone can also undergo lactone opening in the presence of DIBAL-H, and the product can be mapped onto a nanomolar CC chemokine receptor antagonist for potential treatment of arthritis and sclerosis (Scheme 9c).[17,18] Alternatively, it can be converted into the Weinreb amide at −78 °C (Scheme 9d). At −10 °C, Grignard addition occurred to allow quick access to acyclic α-aryl-ketones, which were difficult to obtain using other methods (Scheme 9e).[19]



Scheme 9. Synthetic applications. DIBAL-H = diisobutylaluminum hydride, Ms = methanesulfonyl.

We have conducted DFT calculations on the C–C reductive elimination to understand the role of the 2-naphthyl group in **L1** (Scheme 2). The B3LYP functional was used with Lanl2dz ECP basis set for palladium and 6-31G* basis set for the other atoms. The solvent effect (*tert*-butyl methyl ether) was also taken into account by using IEFPCM method. First, we examined all possible isomers of the [(**L1**)Pd(Ar)-(enolate)] complexes (Figure 1). We found that the Pd^{II} centers preferentially interact with the *ipso* carbon atom of the lower ring of **L1**. The Pd–arene interaction in the biarylphosphine complexes was previously revealed by Kočovský, Buchwald, Pregosin, and others.[20] The palladium complexes having a Pd–O(ether) interaction were 4–6 kcal mol^{-1} less stable, and structural rearrangement from the latter to the former was almost barrierless. Thus, we focused on enolate complexes having Pd–arene interactions in subsequent calculations.

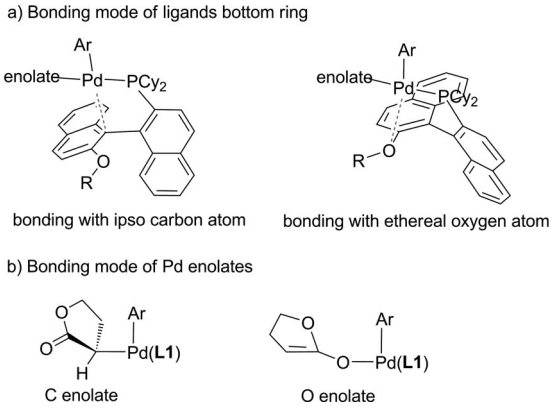


Figure 1. Bonding modes between Pd and the lower ring of **L1**, and stereoisomers of palladium-bound C- and O-enolate complexes.

We first explored the possibility of direct C–C reductive elimination from the O-enolate complexes.[21] We found that an abrupt "jumping" of atoms at a certain C-C distance. Also, isomerization of the O-enolate complexes to more stable C-enolates had low barriers of about 15 kcal mol^{-1}.

In contrast, direct C–C reductive elimination from the C-enolate complexes proceeded smoothly (Figure 2). The corresponding barriers for C–C bond formation were only 12 and 14 kcal mol^{-1}. In the major-product pathway, the ground state (Int1a) and transition state (TS1a) were more stable by 4.2 and 2.1 kcal mol^{-1}, respectively, than those in the minor-product pathway. The origin of stabilization was the double CH···O hydrogen bond between naphthyl C–H bonds and the palladium-bound C-enolate. In the minor-product pathway,

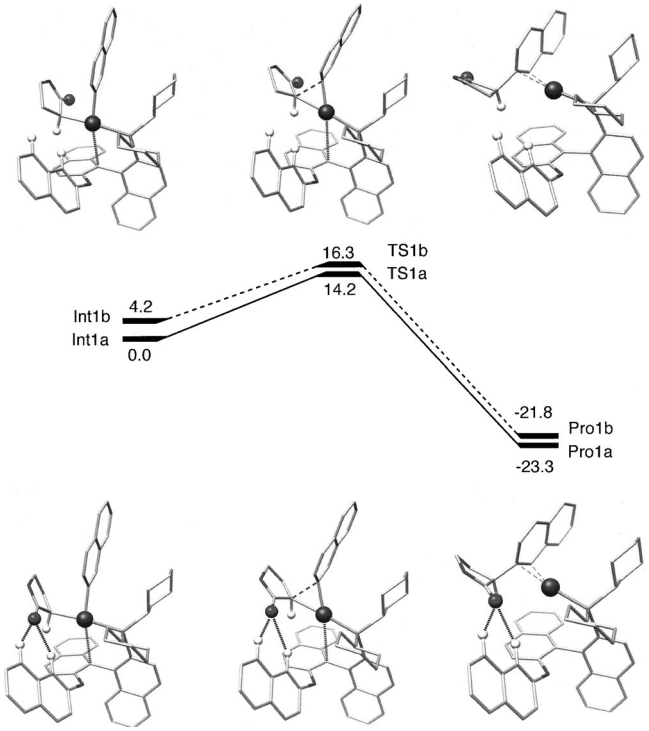


Figure 2. Reaction pathway of C–C reductive elimination from C-enolate complexes of **L1**.

the carbonyl group pointed away and hydrogen bonds were lost. Conformational scanning was performed on the complex Int1a by rotating two C–O bonds in the diaryl ether moiety. The specific conformation which supported the hydrogen bonding proved to be more stable than other conformers by a few kcal mol^{-1} (see the Supporting Information).

Close contact between the CH bonds and oxygen atoms has been identified in organic crystals and enzymes. They are accepted as weak hydrogen bonds with a stabilization energy of 0.5–4 kcal mol^{-1} and the magnitude of stabilization depending upon the acidity of the CH bonds and the topology of donors and acceptors.[22] In our optimized structures of Int1a (Figure 2), the CH···O hydrogen-bond angles and lengths fell into the prescribed range. No other chiral metal catalyst was reported to use the arene CH···O interaction to induce chirality.[23]

Hydrogen bonding between other types of CH bonds and oxygen atoms were implicated in asymmetric catalysis, for example, formyl CH···O hydrogen bonds between aldehydes and Lewis-acid catalysts derived from B, Ti, and Al. This proposal of Corey has gained computational support recently.[24] Later, he proposed a similar role for both vinylic and methyl CH bonds of ketones.[25] CH bonds that were acidified by α-substitution have also been seen in a CH···O-type of interaction in the asymmetric Pauson–Khand reaction[26] and in copper-catalyzed asymmetric allylation of ketones.[27]

We also examined reductive elimination of C-enolate complexes supported by **L2**, which carries an NH_2 group (Figure 3). As expected, in the major-product pathway, both the ground-state Int2a and transition-state TS2a were stabilized by a single NH···O(carbonyl) hydrogen bond. In the minor-product pathway, hydrogen bonds were absent.

N-Methyl-2-pyrrolidone (NMP) can disrupt hydrogen bonding. Indeed, in the model reaction (Scheme 2), inclusion of 3 equivalents of NMP led to significant loss of enantioselectivity: 84 %→46 % *ee* with **L1** and 93 %→9 % *ee* with **L3**. Notably, the catalytic activity was not affected and product racemization did not occur. In another experiment, inclusion of $ZnCl_2$ also led to loss in *ee* value in the model reaction.

We also conducted calculations on transmetalation and were surprised to find that transmetaltion did not produce O-enolates. This data is contrary to common belief. The abnormality in our reaction may be attributed to coordination saturation of the palladium center by the lower ring of the biarylphosphine ligand. When starting from [(**L1**)Pd(Ar)-(κ_2-OAc)] complexes, a relatively high barrier (> 15 kcal mol^{-1}) was found in the acetate-assisted enolate transfer, thus leading to either O- or C-enolates. If starting from cationic complexes of [(**L1**)Pd(Ar)(silyl enolate)], the silyl enolate was bound to palladium through its β-carbon atom, and acted like an electron-rich olefin. External attack of the OAc anion on silicon triggered facile enolate transfer with barriers of less than 10 kcal mol^{-1}. No O-enolates were produced.

In summary, we disclosed the first general method for asymmetric arylation of lactones, thus forming tertiary centers with high *ee* values. Importantly, we found **L1** participates in arene CH···O hydrogen bonding with palladium enolates to control stereochemistry of the new stereocenters. **L3** was capable of forming NH···O hydrogen bonds. In our previously reported arylation of acyclic esters (Scheme 1 c),[7] the ligand **L** cannot support hydrogen bonding as determined by our calculations.

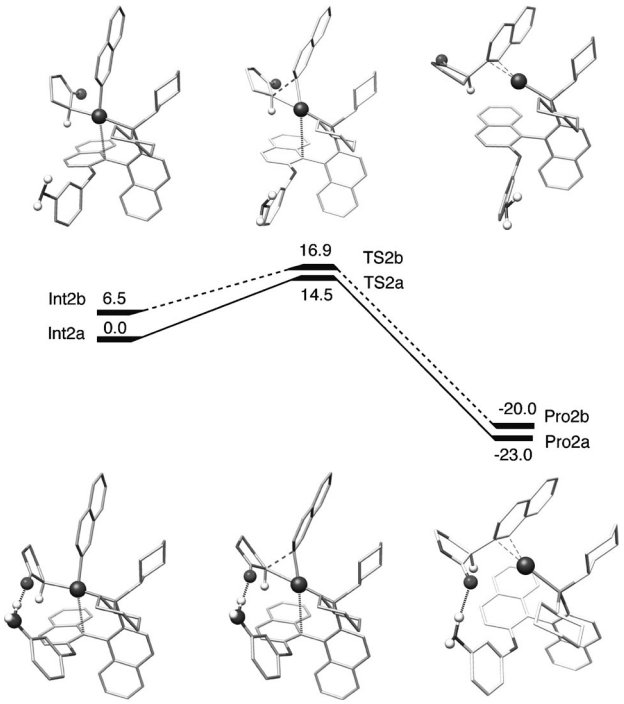


Figure 3. Reaction pathway of C–C reductive elimination from C-enolate complexes of **L2**.

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