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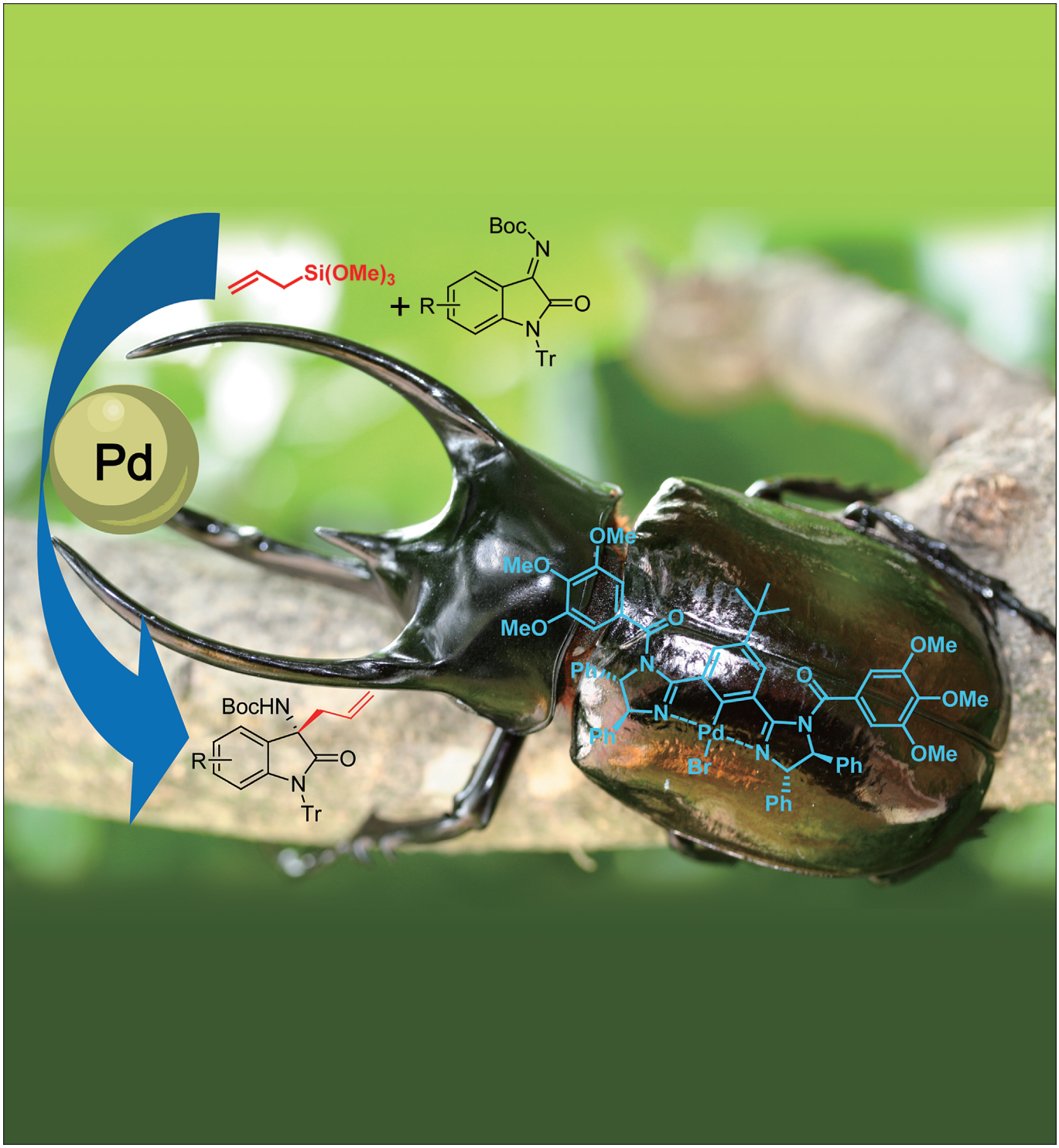
Catalytic Enantioselective Allylation of Ketimines by Using Palladium Pincer Complexes with Chiral Bis(imidazoline)s

Shuichi Nakamura,* Kengo Hyodo, Masayuki Nakamura, Daisuke Nakane, and Hideki Masuda[a]



The development of mild, catalytic, and enantioselective versions of C–C bond-forming processes is a topic of paramount importance in modern organic chemistry. In this context, the enantioselective allylation of ketimines by using chiral catalysts attracts a great deal of interest, as it provides efficient access to chiral homoallylic amines containing a quaternary carbon center. In particular, the utilization of ketimines derived from isatins has attracted much attention, because the reaction affords chiral 3-substituted 3-amino-2-oxindole derivatives, which are an important structural motif in biologically active compounds,[1] such as AG-041R,[2] chartelline C,[3] and NITD609[4] (Figure 1). Especially, the allylation of ketimines derived from isatins affords homoallylic aminooxindole derivatives, which act as an inhibitor of HIV-1 protease.[5] Furthermore, spirocyclic aminooxindole frameworks are present in a large number of bioactive, naturally occurring alkaloids and medicinally relevant compounds.[6]

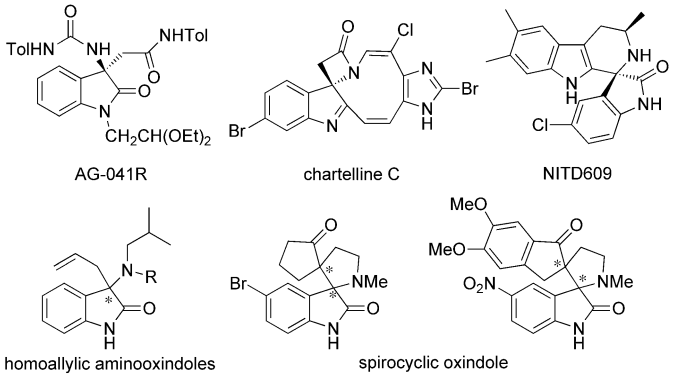


Figure 1. Biologically active 3-substituted 3-amino-2-oxindole derivatives.

However, the enantioselective allylation of ketimines is not a trivial task due to their low reactivity and the difficulty in controlling enantiofacial aspects.[7] Pioneering work on the catalytic enantioselective allylation of various ketimines has been reported by Shibasaki and co-workers in which the reaction of various acyclic ketimines with allylboronate by using {Duphos–CuF} catalyst gave products in high yield with high enantioselectivity.[7a] Recently, Lam and co-workers reported the catalytic enantioselective allylation of cyclic ketimines by using chiral rhodium complexes.[7b] Despite the fact that electron-deficient ketimines derived from isatins would constitute an elegant precursor of biologically active compounds and quaternary α-amino acids, the catalytic enantioselective allylation of such compounds has not been reported.[8,9] Recently, we reported the enantioselective decarboxylative addition of malonic acid half-thioesters (MAHTs) to ketimines derived from isatins by using bifunctional organocatalysts.[10] On the other hand, we also developed palladium pincer complexes with 1,3-bis(imidazolin-2-yl)benzene (Phebim).[11–13] Herein, our interest was extended to the enantioselective allylation of ketimines derived from isatins by using bis(imidazoline)–palladium pincer complexes (Figure 2).[14] To our knowledge, this is the first example of enantioselective allylation of ketimines derived from isatins.

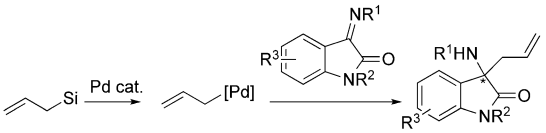
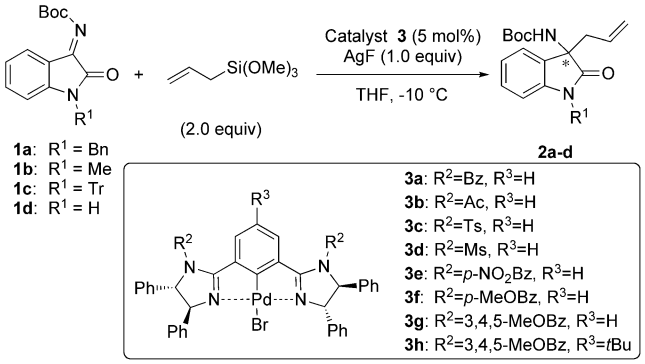


Figure 2. Enantioselective allylation of ketimines derived from isatins by using chiral palladium complexes.

We first examined the reaction of ketimine **1a** derived from *N*-benzylisatin with allyltrimethoxysilane as an allylating reagent in the presence of 5 mol% of various chiral catalysts **3a–h** and silver fluoride (1.0 equiv) in THF. The results are shown in Table 1.

Table 1. Enantioselective allylation of ketimines **1a–d** derived from *N*-benzylisatins using **3a–h**.



Entry	**1**	Catalyst	*t* [h]	Yield [%]	*ee* [%][a]
1	**1a**	**3a**	36	91	71 (*S*)
2	**1a**	**3b**	36	87	7 (*S*)
3	**1a**	**3c**	24	90	57 (*R*)
4	**1a**	**3d**	36	92	62 (*R*)
5	**1a**	**3e**	72	82	7 (*R*)
6	**1a**	**3f**	36	92	72 (*S*)
7	**1a**	**3g**	24	93	78 (*S*)
8	**1a**	**3h**	24	92	85 (*S*)
9	**1b**	**3h**	24	93	81 (*S*)
10	**1c**	**3h**	24	91	92 (*S*)
11	**1d**	**3h**	24	88	0
12[b]	**1c**	**3h**	72	68	66 (*S*)
13[c]	**1c**	**3h**	36	92	94 (*S*)
14[d]	**1c**	**3h**	54	93	90 (*S*)

[a] The absolute configuration of **2** is provided in parentheses. [b] Allyltrimethylsilane was used. [c] The reaction was carried out at −30 °C. [d] Catalyst (1 mol%) was used.

[a] Prof. S. Nakamura, K. Hyodo, M. Nakamura, Dr. D. Nakane, Prof. H. Masuda
Department of Frontier Materials, Graduate School of Engineering
Nagoya Institute of Technology
Gokiso, Showa-ku, Nagoya 466-8555 (Japan)
Fax: (+81) 52-735-5245
E-mail: snakamur@nitech.ac.jp

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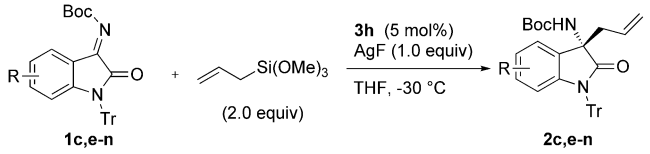
The reaction of ketimine **1a** derived from *N*-benzylisatin with allyltrimethoxysilane by using N-benzoylated palladium pincer-type catalyst **3a** afforded product **2a** in high yield with moderate enantioselectivity (Table 1, entry 1).[15] Encouraged by this result, we next investigated the effect of the catalyst structure on stereoselectivity. The reaction of **1a** with allylsilane by using acetylated catalyst **3b** gave product **2a** as an almost racemic product (entry 2). Interestingly, the reaction using sulfonylated catalysts **3c** and **3d** afforded **2a** containing a stereochemistry opposite that obtained in the reaction using **3a** (entries 3 and 4). The reaction using catalysts **3f**,**g** containing electron-donating groups on the benzoyl group afforded product **2a** with high enantioselectivity (entries 6 and 7). When catalyst **3h**, containing a *tert*-butyl group on the phenylene linker, was used, to our delight, good enantioselectivity was obtained (entry 8). To improve enantioselectivity, we optimized the structure of ketimines derived from isatins containing various protecting groups on the nitrogen atom (entries 9–11). When the reaction with ketimine **1c**, containing a triphenylmethyl group (trityl group: Tr), was carried out, enantioselectivity could be improved (entry 10). The reaction of **1c** with allyltrimethylsilane as an allylating reagent afforded the product **2c** in moderate yield with moderate enantioselectivity (entry 12). The reaction at lower temperature (−30 °C) allowed for even more rigorous enantiofacial control (entry 13). Even 1 mol % of **3h** worked efficiently (entry 14).

With these optimized conditions, the allylation of a series of ketimines **1c**,**e**–**n** with **3h** and AgF was examined (Table 2). Ketimines **1e**–**n** carrying either electron-donating or -withdrawing substituents gave products **3e**–**n** in good yield with high enantioselectivity (entries 2–10).

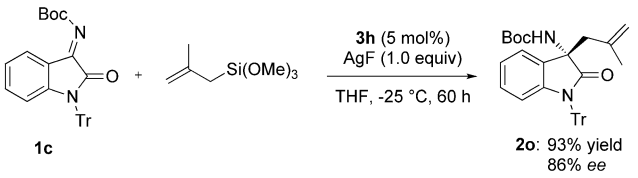
Table 2. Enantioselective allylation of ketimines **1c**,**e**–**n** by using **3h**.



Entry	R	2	*t* [h]	Yield [%]	*ee* [%]
1[a]	H (**1c**)	**2c**	72	92	95
2	5-Me (**1e**)	**2e**	36	91	94
3	5-MeO (**1f**)	**2f**	48	92	90
4	5-F (**1g**)	**2g**	60	92	91
5	5-Cl (**1h**)	**2h**	48	96	85
6	5-Br (**1i**)	**2i**	72	84	82
7[a]	4-Br (**1j**)	**2j**	24	94	85
8	6-Br (**1k**)	**2k**	48	93	93
9	6-Cl (**1l**)	**2l**	36	93	93
10	7-F (**1m**)	**2m**	48	95	93
11	4,6-Me (**1n**)	**2n**	48	90	87

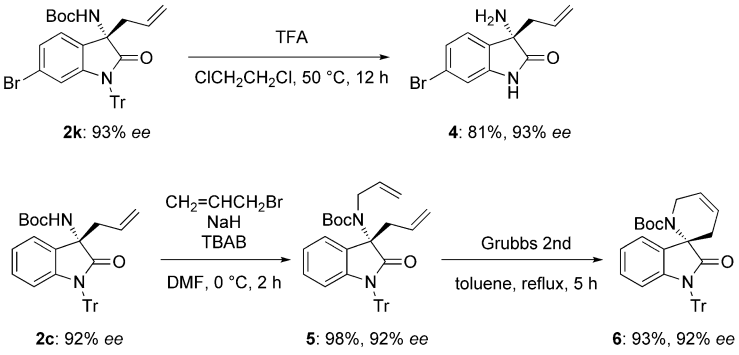
[a] The reaction was carried out at −40 °C.

We also examined the reaction with 2-substituted allyltrimethoxysilane. The reaction afforded product **2o** in high yield with good enantioselectivity (Scheme 1).



Scheme 1. Reaction of ketimine **1c** with 2-substituted allylsilane.

We next examined the synthesis of optically active homoallylamine **4** from *N*-*tert*-butoxycarbonyl-*N*′-trityl-protected amide **2k** (Scheme 2). Deprotection of both the *tert*-butoxycarbonyl (Boc) and trityl (Tr) group from 93 % *ee* of **2k** by using trifluoroacetic acid in 1,2-dichloroethane at 50 °C afforded homoallylic amine **4** in high yield without a loss of enantiopurity. The absolute configuration of **4** was assigned as *S* by X-ray crystallographic analysis, and the configuration of other products was tentatively assumed by analogy. We next examined the formation of a spirocyclic compound from the product. The N-allylation of **2c** by using allylbromide, sodium hydride, and tetrabutylammonium bromide (TBAB) in DMF afforded *N*-allyl-*N*-Boc product **5** in high yield. The ring-closing metathesis of **5** by using a second generation of Grubbs catalyst in toluene gave spirocyclic amine **6** in high yield.



Scheme 2. Transformation of products to chiral homoallylic amines or a spiroamine.

The proposed catalytic cycle for the allylation of ketimines derived from isatins is shown in Figure 3. The addition of AgF causes the exchange reaction of bromide in **3** to fluoride (complex **A**). The fluoride on palladium reacts with allylsilane to give an η^1-allyl coordinated pincer species (complex **B**). The next step is the nucleophilic reaction of allyl-palladium species with ketimines to give complex **C**, which subsequently undergoes transmetallation with silver fluoride giving product **2**.[16] To clarify the assumed catalytic cycle, we conducted spectroscopic analysis. The ESI mass spectrometric analysis of the mixture of **3b**, AgF, and allyltrimethoxysilane in a 1:1:1 ratio in THF showed complex **B** (cation mode, calcd for $C_{53}H_{43}N_4O_2Pd$ as complex **B**+H^+: 873.2; found: 873.0, see the Supporting Information). These signals support our proposed catalytic cycle.

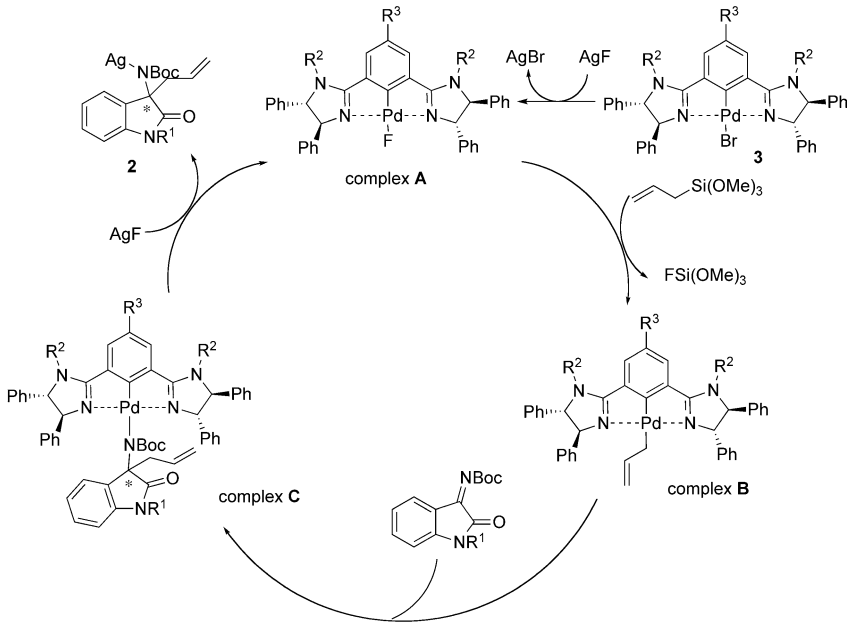


Figure 3. Plausible catalytic cycle for the reaction.

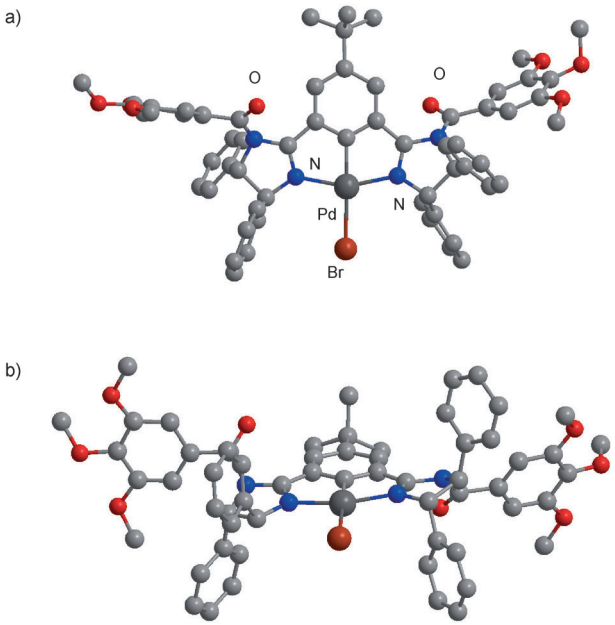


Figure 4. X-ray crystal structure of **3h**·$CHCl_3$ (top view (a), side view (b)). H atoms and chloroform have been omitted for clarity.

We also confirmed the structures of the palladium pincer complex **3h** by X-ray crystallographic analysis (Figure 4). The bis(imidazoline) ligand is coordinated to the Pd^{II} center by two nitrogen atoms in imidazoline and one carbon atom in the aryl group in a tridentate manner. Complex **3h** features a nearly square-planar Pd^{II} center in which the five rings include two imidazolines, two palladacycles, and benzene, which are approximately coplanar.

Based on a previous DFT study on the achiral pincer-complex-catalyzed allylation of sulfonylimines,[14kl,m] the η^1-allyl group on palladium attacks imines at the γ-position of the allyl moiety without coordination to sulfonylimines. Therefore, we tried to check the structure of allylpalladium complex **B** by the MO calculation by using Gaussian 09[17] B3LYP/LANL2DZ level[18] (Figure 5). To simplify the calculation, bis(imidazoline) **3a** was used to optimize the complex. The allyl moiety coordinates to palladium avoiding steric repulsion with the bulky phenyl groups in **3a**. Based on the structure of the palladium pincer complexes and the absolute configuration of products, Figure 5 shows a proposed transition state for the enantioselective allylation of imine by using **3a**. Imine **1** approaches from the opposite side of the Pd–C bond. Avoiding steric repulsion of the trityl group in ketimines with the phenyl group in chiral bis(imidazoline) and electrostatic repulsion of the allyl group on palladium with carbonyl and imino groups in ketimine, the *Re* face of ketimine reacts with allylpalladium to give the *S* isomer. Further studies are required to fully elucidate the mechanistic detail of the allylation of imines.[19,20]

In conclusion, we developed an enantioselective allylation of ketimines derived from isatins by using chiral palladium pincer complexes between 1,3-bis(imidazolin-2-yl)benzene to give products with good enantioselectivity. This process offers a simple and efficient route for the synthesis of a homoallylic amine containing a tetrasubstituted stereocenter and its derivatives. Further experiments are in progress to study the scope of this process and the potential application of the bis(imidazoline)–palladium pincer catalyst to other reactions.

Experimental Section

Typical procedure for allylation of ketimines catalyzed by chiral Phebim–Pd^{II} complexes

tert-*Butyl 3-(2-propenyl)-1-(triphenylmethyl)-2-oxoindolin-3-ylcarbamate* (***2c***): A mixture of **3h** (4.5 mg, 3.9 μmol), and AgF (10.0 mg, 0.079 mmol) was stirred in THF for 1 h. After the addition of **1c** (38.5 mg, 0.079 mmol), the reaction mixture was cooled to −30 °C. Then, allyltrimethoxysilane (26.6 μL, 0.158 mmol) was added. After the disappearance of **1c** in the reaction mixture on TLC, water (0.5 mL) was added. The mixture was filtered through Celite to remove silver salts and the filtrate was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4. Removal of solvent under reduced pressure gave a residue, which was purified by column chromatography (hexane/ethyl acetate 90:10) to give (*S*)-**2c** (38.5 mg, 92 %) as a white solid.

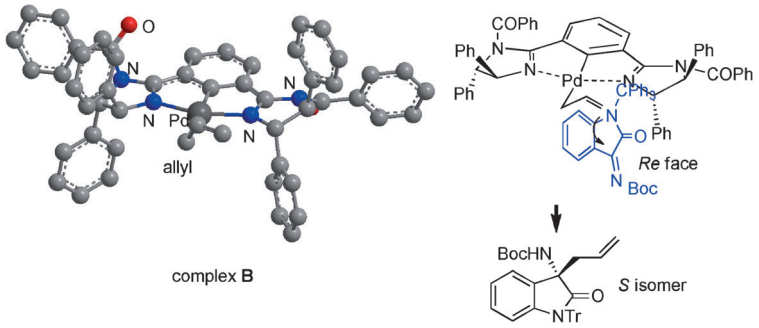


Figure 5. Optimized structure of complex **B** by Gaussian 09 B3LYP/LANL2DZ and the assumed transition state for the addition reaction of ketimines **1** derived from isatins.

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Keywords: allylation · asymmetric catalysis · ketimines · palladium · pincer complexes

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