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Catalytic Enantioselective Synthesis of Planar-Chiral Cyclic Amides Based on a Pd-Catalyzed Asymmetric Allylic Substitution Reaction

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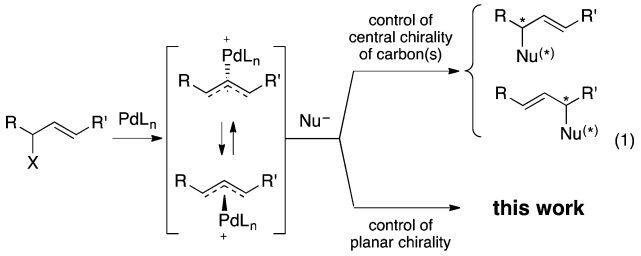
Supporting Information

ABSTRACT: The highly enantioselective synthesis of planar-chiral nine-membered cyclic amides was achieved by the Pd-catalyzed asymmetric allylic cyclization of achiral linear precursors in the presence of a catalytic amount of chiral ligand.

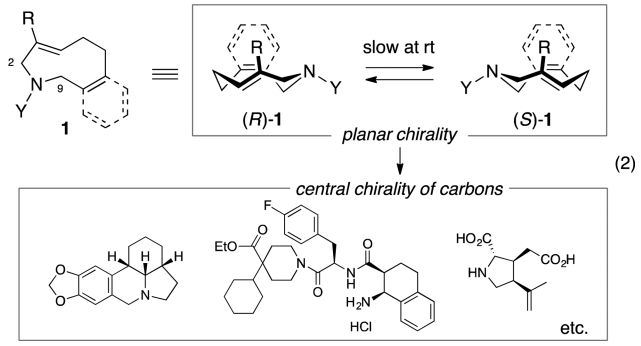
Pd-catalyzed asymmetric allylic substitution (AAS), or the so-called asymmetric Tsuji–Trost reaction, is one of the most powerful methods for asymmetric synthesis and has been intensively investigated.[1] The reaction proceeds via the formation of a planar-chiral π-allyl Pd complex and stereoselective nucleophilic substitution with Nu^-, which allows C–Nu bond formation with stereocontrol of the newly generated stereogenic center(s) C* and/or Nu* (eq 1). Therefore, the



AAS reaction has been widely used for the stereoselective construction of central chirality of carbon at the allylic and homoallylic positions. However, to the best of our knowledge, its use for stereocontrol of planar chirality has not been reported, despite the potential for such an application.

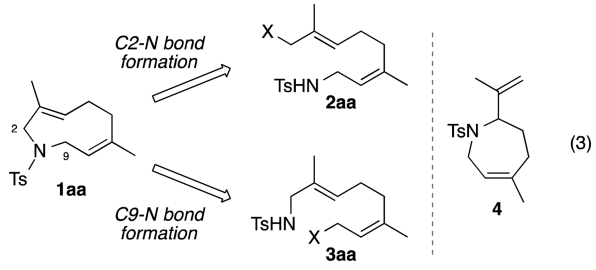
We recently reported novel organonitrogen cycles **1** with inherent planar chirality (eq 2).[2] The key features of this class of heterocycles are as follows: (i) their planar chirality is remarkably stable at ambient temperatures, and (ii) the planar chirality can be transferred to central chirality through both inter- and intramolecular transformations without loss of stereopurity. Thus, organonitrogen cycles **1** can serve as useful chiral building blocks for the synthesis of various alkaloids in a highly stereospecific manner.[2b,3]

However, despite the synthetic potential of **1**, there have been limited investigations into their asymmetric synthetic approaches.[4] To this end, we envisioned that nine-membered-ring construction of **1** with C–N bond formation through an



intramolecular Pd-catalyzed AAS reaction would be an efficient approach. This challenge was also attractive as an unprecedented example of control of planar chirality through the AAS reaction. The details of the study are provided below.

At the outset, we examined the racemic synthesis of the model compound **1aa** under achiral conditions to determine the effectiveness of the approach. Retrosynthetic cleavage of the C2–N or C9–N bond in **1aa** furnished **2aa** or **3aa**, respectively, as a precursor (eq 3).[5] Of these, **2aa** was found



to be a suitable substrate for the Pd-catalyzed allylic substitution reaction because the reaction of **2aa** (X = MeOCOO) with 5 mol % $Pd(PPh_3)_4$ in toluene at rt for 1 day provided **1aa** in good yield (86%) along with a small amount of the seven-membered cyclized product **4** (6%). In contrast, a similar reaction of **3aa** (X = MeOCOO) afforded no **1aa**, and **3aa** was recovered in 84% yield.[6]

On the basis of these results, we then examined the catalytic enantioselective cyclization of **2aa**. We evaluated a number of

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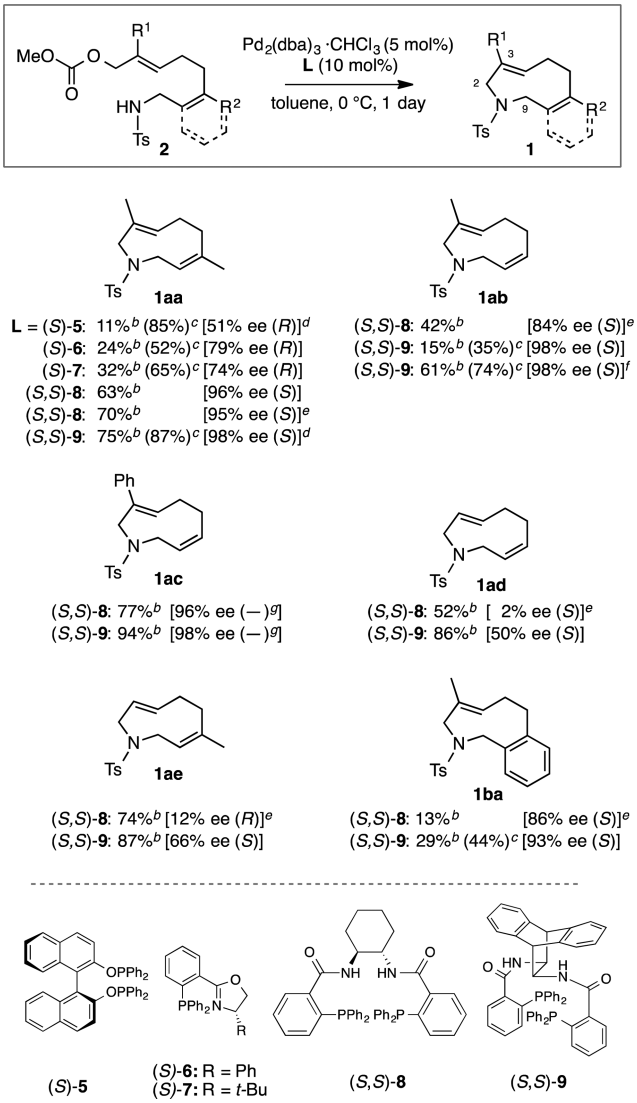
chiral phosphine ligands and found the DACH-phenyl and ANDEN-phenyl Trost ligands (**8** and **9**, respectively) to be the ligands of choice.[7] The reaction was performed with 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol % phosphine ligand in toluene at 0 °C. As shown in Scheme 1, reactions with BINAPO [(*S*)-**5**][8]

Scheme 1. Catalytic Enantioselective Synthesis of Planar-Chiral Cyclic Amides[a]

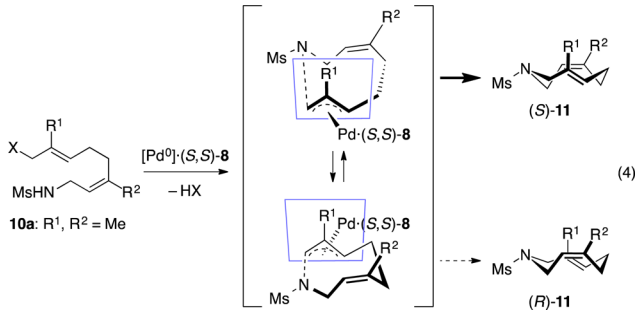


[a]Unless otherwise noted, the reactions were performed with 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol % phosphine ligand in toluene at 0 °C for 1 day. [b]Yield determined by ^{1}H NMR analysis. [c]Yield based on recovered **2**. [d]The reaction was carried out over 3 days. [e]The reaction was performed with 2.0 equiv of *t*-BuOH. [f]The reaction was performed with 10 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 20 mol % phosphine ligand. [g]Sign of $[\alpha]_D$ ($CHCl_3$). The absolute stereochemistry has not yet been determined.

and the PHOX ligands (*S*)-**6** and (*S*)-**7**[9] gave **1aa** in low to moderate yields (11−32%) in enantioenriched form [51−79% ee (*R*)]. The yield and enantioselectivity were improved significantly to 63% and 96% ee, respectively, with the use of (*S*,*S*)-**8** as the ligand. Interestingly, the addition of 2 equiv of *t*-BuOH improved the yield (70%) while retaining high enantioselectivity [95% ee (*S*)].[10] A similar good result was obtained with (*S*,*S*)-**9** [75%, 98% ee (*S*)].

The present enantioselective cyclization has a broad substrate scope. For the reaction of **2ab** (R^1 = Me, R^2 = H), both (*S*,*S*)-**8** and (*S*,*S*)-**9** were efficient; the reactions proceeded with good to excellent enantioselectivity (84−98% ee), albeit in poor yields (15−42%). The yield of (*S*)-**1ab** improved to 61% when the reagents were doubled. Similarly, highly enantioenriched **1ac** (R^1 = Ph, R^2 = H) was obtained through the use of (*S*,*S*)-**8** (77%, 96% ee) or (*S*,*S*)-**9** (94%, 98% ee). Interestingly, a similar reaction of a C3-nonsubstituted system (R^1 = H) gave rather different results, that is, the reaction of **2ad** (R^1 = H, R^2 = H) with (*S*,*S*)-**8** gave nearly racemic **1ad** [2% ee (*S*)]. In contrast, the reaction with (*S*,*S*)-**9** afforded (*S*)-**1ad** with moderate enantioselectivity (50% ee). Substantially different efficiencies for ligands **8** and **9** were also observed in the reaction of **2ae** (R^1 = H, R^2 = Me): the reaction with (*S*,*S*)-**8** afforded (*R*)-**1ae** with low enantioselectivity (12% ee), while (*S*,*S*)-**9** afforded the antipode (*S*)-**1ae** with moderate enantioselectivity (66% ee). The AAS reaction using ligand **9** was also efficient for planar-chiral orthocyclophenes, as **1ba** was obtained with excellent enantioselectivity (93% ee).

To gain insight into the enantioselectivity of these AAS reactions, we performed theoretical studies of the transition-state models using density functional theory (DFT) calculations with the simplified substrate **10**, in which the tosyl group of **2** was replaced by a mesyl group to reduce the calculation cost (eq 4).



(4)

In regard to transition-state models for the AAS reaction using ligand **8**, Lloyd-Jones and Norrby studied intermolecular reactions of alkenyl esters in great detail and proposed that hydrogen bonding between the amide proton of **8** and the heteroatom on the nucleophile stabilize the transition state.[11] On the basis of the model of Lloyd-Jones and Norrby, we surveyed transition-state models for the AAS reaction of **10a** (R^1, R^2 = Me), a simplified model of **2aa**, with (*S*,*S*)-**8** at the B3PW91/3-21G* level of theory, and eight appropriate models involving hydrogen bonding between the amide proton of **8** and a sulfonamide oxygen of **10a** were obtained.[12−14] Among these, $\mathbf{TS_a}$-(*S*) and $\mathbf{TS_a}$-(*R*) were found to be the most favorable transition-state models for (*S*)-**11a** and (*R*)-**11a**, respectively (Scheme 2). The potential energy of $\mathbf{TS_a}$-(*R*) was found to be 7.3 kcal mol^{-1} higher than that of $\mathbf{TS_a}$-(*S*),[15] consistent with the observation that the AAS reaction of **2aa** with (*S*,*S*)-**8** provided (*S*)-**1aa** as the primary product with high stereoselectivity (96% ee).[16] The higher potential energy of $\mathbf{TS_a}$-(*R*) was likely caused by strong steric repulsion between the methyl group (R^1) of the (*E*)-alkene moiety and the cyclohexane ring of (*S*,*S*)-**8**, which is indicated by the purple double arrow in Scheme 2. In contrast, a similar DFT calculation for **10d** (R^1, R^2 = H), a simplified model of the weakly enantioselective substrate **2ad**, provided $\mathbf{TS_d}$-(*S*) and

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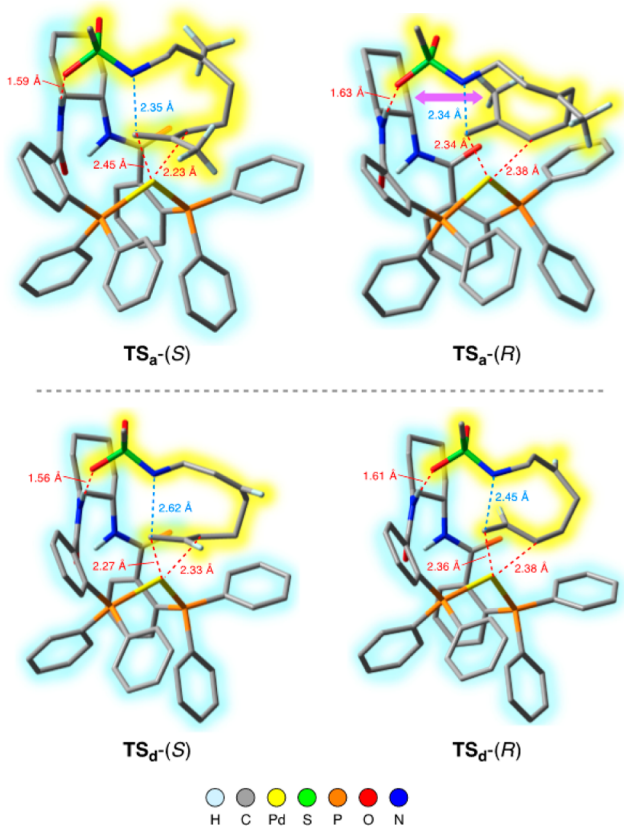
Scheme 2. Transition-State Models for the AAS Reactions of 10a and 10d with Ligand (*S,S*)-8[a]



[a]For clarity, hydrogens have been omitted from the transition-state models, except for the amide protons of (*S,S*)-**8** and the hydrogens in the R^1 and R^2 groups (Me in **TS$_a$**; H in **TS$_d$**). The substrate and catalyst units are highlighted by yellow and blue background colors, respectively.

TS$_d$-(*R*) as the most favorable transition-state models for (*S*)-**11d** and (*R*)-**11d**, respectively. Their energy difference (1.9 kcal mol^{-1}) is substantially smaller than that between **TS$_a$**-(*S*) and **TS$_a$**-(*R*).[15−17] These results demonstrate that the enantiotopic faces of the (*E*)-alkene moiety were well-discriminated by the steric effect of the R^1 group in enantioselective cyclization.

In summary, we have developed an efficient asymmetric approach to planar-chiral cyclic amides in which the intramolecular Pd-catalyzed AAS reaction proceeds with discrimination of the enantiotopic faces of the π-allyl Pd complex intermediate derived from achiral linear precursors. This result is noteworthy not only as an advancement in the chemistry of planar-chiral heterocycles but also as a demonstration of novel possibilities for Pd-catalyzed AAS reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04340.

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Notes

The authors declare no competing financial interest.

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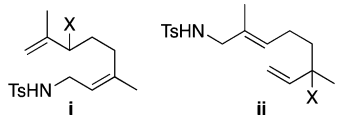
(4) We previously reported the stoichiometric chiral-alkoxide-mediated enantioselective synthesis of **1aa** and **1ae**. See: Tomooka, K.; Uehara, K.; Nishikawa, R.; Suzuki, M.; Igawa, K. *J. Am. Chem. Soc.* **2010**, *132*, 9232−9233.

(5) **i** and **ii** were also considered as potential precursors for **1aa**. However, a similar reaction of **i** (X = OBoc) gave **1aa** in rather low yield (20%). Furthermore, our attempt to prepare **ii** failed. Thus, we selected **2aa** as the most promising precursor.



(6) We also found that C9−N bond formation in **3aa** through intramolecular Mitsunobu reactions (X = OH) and base-promoted alkylation reactions (X = Br) afforded poor yields of **1aa**.

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(10) Several protic additives improved the reaction yields, among which *t*-BuOH produced the best results.

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(12) Calculations were performed with the Gaussian 09 program on a TATARA system at Kyushu University; see the Supporting Information.

(13) For a more detailed discussion in the origin of the enantioselectivity of **1**, other possibilities should be considered, such as (i) enantioselective formation of π-allyl complexes by enantioface-selective oxidative addition and (ii) thermodynamically controlled isomerization of enantiomers of the π-allyl complex. Further mechanistic studies are in progress.

(14) We also performed calculations on transition-state models without hydrogen bonding, which gave substantially higher potential energies; see the Supporting Information for details.

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(15) The relative energy values were calculated with zero-point energy corrections.
(16) The calculated energy difference between the transition states was larger than expected on the basis of the observed enantioselectivity. This may be due to simplifications of the model and/or the low level of theory in the calculations.
(17) The initial conformations for the DFT calculations on **10d** were prepared from the eight optimized structures obtained from the calculations on **10a**; see the Supporting Information for details.

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