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Enantioselective Synthesis of Atropisomeric Anilides via Pd(II)-Catalyzed Asymmetric C−H Olefination

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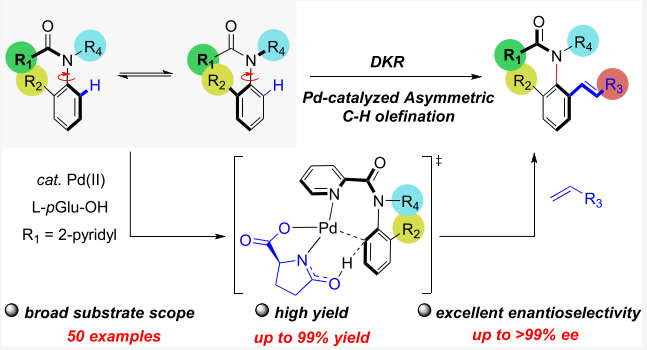
ABSTRACT: Atropisomeric anilides have received tremendous attention as a novel class of chiral compounds possessing restricted rotation around an N-aryl chiral axis. However, in sharp contrast to the well-studied synthesis of biaryl atropisomers, the catalytic asymmetric synthesis of chiral anilides remains a daunting challenge, largely due to the higher degree of rotational freedom compared to their biaryl counterparts. Here we describe a highly efficient catalytic asymmetric synthesis of atropisomeric anilides via Pd(II)-catalyzed atroposelective C−H olefination using readily available L-pyroglutamic acid as a chiral ligand. A broad range of atropisomeric anilides were prepared in high yields (up to 99% yield) and excellent stereoinduction (up to >99% ee) under mild conditions. Experimental studies indicated that the atropostability of those anilide atropisomers toward racemization relies on both steric and electronic effects. Experimental and computational studies were conducted to elucidate the reaction mechanism and rate-determining step. DFT calculations revealed that the amino acid ligand distortion is responsible for the enantioselectivity in the C−H bond activation step. The potent applications of the anilide atropisomers as a new type of chiral ligand in Rh(III)-catalyzed asymmetric conjugate addition and Lewis base catalysts in enantioselective allylation of aldehydes have been demonstrated. This strategy could provide a straightforward route to access atropisomeric anilides, one of the most challenging types of axially chiral compounds.



INTRODUCTION

In a chiral molecule, an sp^3-hybridized carbon atom connected to four different substituents is a well-recognized asymmetric element known as central chirality. Axially chiral compounds lack stereogenic centers but exist as enantiomers, due to the restricted rotation around a chiral axis, which are known as "atropisomers".[1] To date, biaryl atropisomers, a kind of stereoisomer arising from a restricted rotation around the single bond between two aromatic rings, have been extensively investigated.[2] In sharp contrast, the catalytic asymmetric synthesis of axially chiral anilides, an interesting class of atropisomeric compounds bearing an N−C chiral axis first reported by Curran,[3] has been overlooked.[4] Despite the fact that these atropisomers are becoming increasingly prevalent and important in medicinal chemistry,[5] asymmetric synthesis,[6] and peptoid chemistry (Figure 1a),[7] the main hurdle is largely due to that chiral anilides are conformationally more flexible and have a higher degree of rotational freedom compared to the biaryl counterparts (Figure 1b, multiple rotations around N−Ar and N−CO bonds vs one single rotation around the Ar−Ar bond, which also distinguish those cyclic anilides with carbonyl trapped in a rigid ring),[4a,8,9] rendering the enantiocontrol much more complicated and challenging. Catalytic asymmetric approaches to access these synthetically challenging chiral skeletons were first reported by the Curran and Taguchi groups in 2002.[9,10] Although the stereoinduction was low at that time (24−56% ee), these pioneering works inspired further efforts in this cutting-edge area,[4b] including (a) distinguishing the substituents R_2 and R_3 on aromatic rings through enantioselective N-functionalization, such as the Tsuji−Trost reaction,[11] metal-catalyzed N-arylation,[12] phase-transfer catalyzed N-alkylation,[13] and the N-allylation Morita−Baylis−Hillman reaction[14,15] (Figure 1c, I); (b) the enantioselective construction of the Ar−N axis via organocatalytic nucleophilic addition[16] (Figure 1c, II); (c) *de novo* aromatic ring formation via asymmetric [2 + 2 + 2] cycloaddition[17] (Figure 1c, III). Despite these remarkable advances, the research is still in its infancy with regard to efficiency, generality, and diversity. Therefore, further development of economic and facile strategies that can efficiently deliver highly enantiopure chiral anilides is highly warranted.

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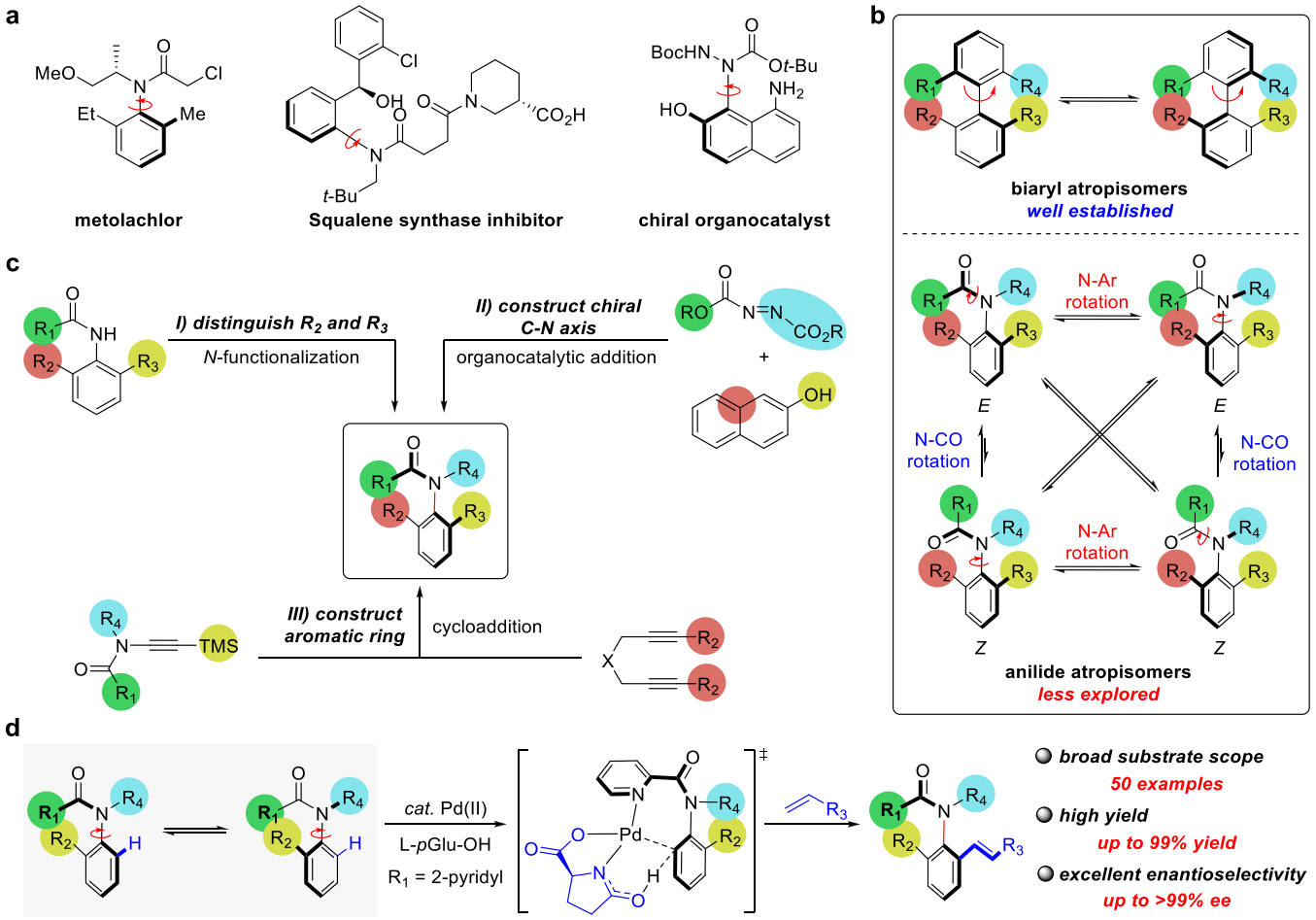

Figure 1. Strategies for the enantioselective synthesis of atropisomeric anilides. (a) The importance of chiral anilides in pharmaceuticals and asymmetric synthesis. (b) Challenges of the asymmetric synthesis of chiral anilides: different modes of rotation between chiral biaryls (top, Ar−Ar rotation) and chiral anilides (bottom, N−Ar and N−CO rotations). (c) Previous approaches to the enantioselective synthesis of chiral anilides. (d) This work: a new strategy for the enantioselective synthesis of atropisomeric anilides via an atroposelective C−H olefination strategy.

In light of the unique features and significance of this structural motif, we assumed that an asymmetric C−H functionalization/dynamic kinetic resolution (DKR) strategy might enable the diverse and straightforward access of these chiral skeletons. In the past decade, transition metal-catalyzed asymmetric C−H functionalization has become one of the most efficient strategies in the construction of stereochemically complex molecules.[18] In particular, the atroposelective C−H functionalization/DKR has been realized to be a straightforward and practical tool to access axially chiral biaryls,[2d,f,19,20] showing great potential in natural products syntheses[20b,c] and ligand elaborations.[20g] However, the synthesis of chiral anilides via catalytic asymmetric C−H functionalization strategy remains an unsolved problem. We posit that the following daunting challenges need to be addressed to achieve the goal: (1) the mode of asymmetric induction during the C−H cleavage step is poorly understood due to the relatively complicated rotational freedom. (2) the C−H activation reaction has to be conducted under mild conditions in order to ensure good asymmetric induction and maintain the chirality due to the relatively low atropostability of the resulting products; thus, the judicious choice of types of substrates and transformation would be crucial for the success. Moreover, to merit the goal of high enantiocontrol and economy, the chiral ligand must be readily available and inexpensive. As a continuation of our long-standing efforts to synthesize axially chiral compounds via C−H activation,[20] herein we report the discovery of a novel catalytic system that overcomes those challenges and enables the synthesis of chiral anilides via Pd(II)-catalyzed C−H olefination/DKR using readily available L-pGlu-OH as an inexpensive chiral ligand (Figure 1d). A wide range of chiral anilides were obtained in excellent yields and enantioselectivities (50 examples, up to 99% and >99% ee). This strategy opens up a straightforward route to access chiral anilides via a highly efficient and atom-economical approach.

RESULTS AND DISCUSSION

Optimizing Reaction Conditions. Initial exploratory studies of the reaction were commenced by exploring the enantioselective C−H olefination/DKR of *N*-benzyl-*N*-(2-isopropylphenyl) picolinamide (***rac*-1a**) with methyl acrylate (**4a**). We expected that the use of pyridine-type DG would enable the challenging C−H olefination to occur under mild conditions, guaranteeing high atroposelectivity during the stereoselectivity-determining step and atropostability of the products. The presence of the bulky isopropyl group at the ortho-position ensures the configurational stability of the newly formed atropoisomers. To our delight, we found that in the presence of 10 mol % $Pd(OAc)_2$ as catalyst and 20 mol % L-*p*Glu-OH (**L1**) as the chiral ligand, the atroposelective C−H

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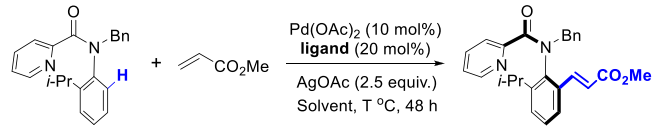
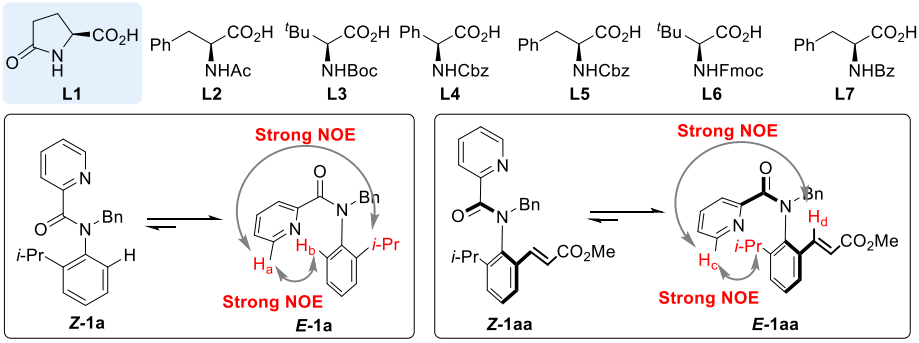
Table 1. Optimization of the Reaction Conditions[a]



rac-**1a** **4a** **1aa**

Entry	Ligand (20 mol%)	Solvent	T (°C)	Yield (%)[b]	Ee (%)[c]
1	**L1**	HFIP	80	84	53
2	**L1**	TFE	80	92	84
3	**L2**	TFE	80	87	0
4	**L3**	TFE	80	94	-5
5	**L4**	TFE	80	99	-45
6	**L5**	TFE	80	93	-23
7	**L6**	TFE	80	89	0
8	**L7**	TFE	80	84	0
9	**L1**	TFE/DME = 1/1 (v/v)	80	95	91
10	**L1**	TFE/DME = 1/1 (v/v)	70	97	94
11	**L1**	TFE/DME = 1/1 (v/v)	60	97	96
12	**L1**	**TFE/DME = 1/1(v/v)**	**50**	**98**	**97 (*E*:*Z* = 7:1)**



[a]Reaction conditions: ***rac*-1a** (0.10 mmol, 1.0 equiv), methyl acrylate **4a** (0.25 mmol, 2.5 equiv), ligand (20 mol %), and $Pd(OAc)_2$ (10 mol %) in solvent (1.0 mL). [b]Isolated yields. [c]The ee values were determined by chiral HPLC.

olefiantion of ***rac*-1a** affords the desired product **1aa** in 84% yield with 53% ee (Table 1, entry 1). We then screened a variety of solvents and found that TFE was the optimal (entry 2, 92%, 84% ee, see Table S2 for details). N-monoprotected α-amino acids (MPAAs) have been widely used as a class of privileged chiral ligands in Pd(II)-catalyzed enantioselective C−H activation,[21] since the groundbreaking work by Yu and co-workers.[21a] Various MPAAs were then investigated, and L-*p*Glu-OH (**L1**) proved to be the best (entries 2−8).[22] Further tuning of a mixture of solvents revealed that the ee value of **1aa** could be improved to 91% without significantly affecting the reactivity in TFE/DME (entry 9). As expected, the reaction temperature could be reduced to 50 °C, giving **1aa** in high yield and improved enantioselectivity (entry 12, 98% yield, 97% ee). Notably, both the racemic starting material ***rac*-1a** and the enantiopure product **1aa** exist as couples of *Z*/*E* rotamers as observed in ^{1}H NMR. Conformational analysis of anilides ***rac*-1a** and **1aa** by NOESY experiments in $CDCl_3$ indicated that *E*-rotamers were formed predominantly. These conclusions were also supported by ^{1}H NMR directly. In the *E*-rotamer, H_a of ***rac*-1a** is located in the shielding area of the aromatic ring, rendering the chemical shift of H_a in the *Z*-rotamer smaller than that in the *E*-rotamer. The ratio of *Z*/*E* rotamers could be determined by the integration of H_a. This similar phenomenon was also observed in **1aa** (see the Supporting Information for details).

Scoping the Substrates. With the optimal reaction conditions in hand, the scope of the anilides was examined (Table 2). We first investigated the substituents on the pyridine ring (Table 2a). Both electron-withdrawing groups (EWGs: **1ba**, 5′-NO_2; **1ca**, 5′-CF_3; **1da**, 5′-CO_2Me; **1ea**, 4′-Cl; **1fa**, 5′-F) and electron-donating groups (EDGs: **1ga**, 4′-OMe; **1ha**, 5′-OMe) were compatible and gave the desired products in excellent enantioselectivities (91% ee to >99% ee), albeit anilides with EWGs were less reactive and prolonged reaction time was needed to ensure good yields. 3′-Methyl-substituted pyridine anilide ***rac*-1i** reacted smoothly to give chiral anilide **1ia** in good yield and enantioselectivity, but with a low *E*/*Z* ratio (85%, 91% ee, *E*:*Z* = 2.3:1), largely due to the steric repulsion between Me and 2,6-substituents on the aryl ring (*i*-Pr and olefin). Control experiments using **1k−1m** as substrates revealed that (1) pyridine rather than carbonyl group acted as the coordinating site; (2) the coordination of palladium is very sensitive to steric hindrance, as 6′-Me and even 6′-F could prevent the coordination.

Then we investigated the substituents on the aryl ring (Table 2b). The steric hindrance of ortho-substituents is important for

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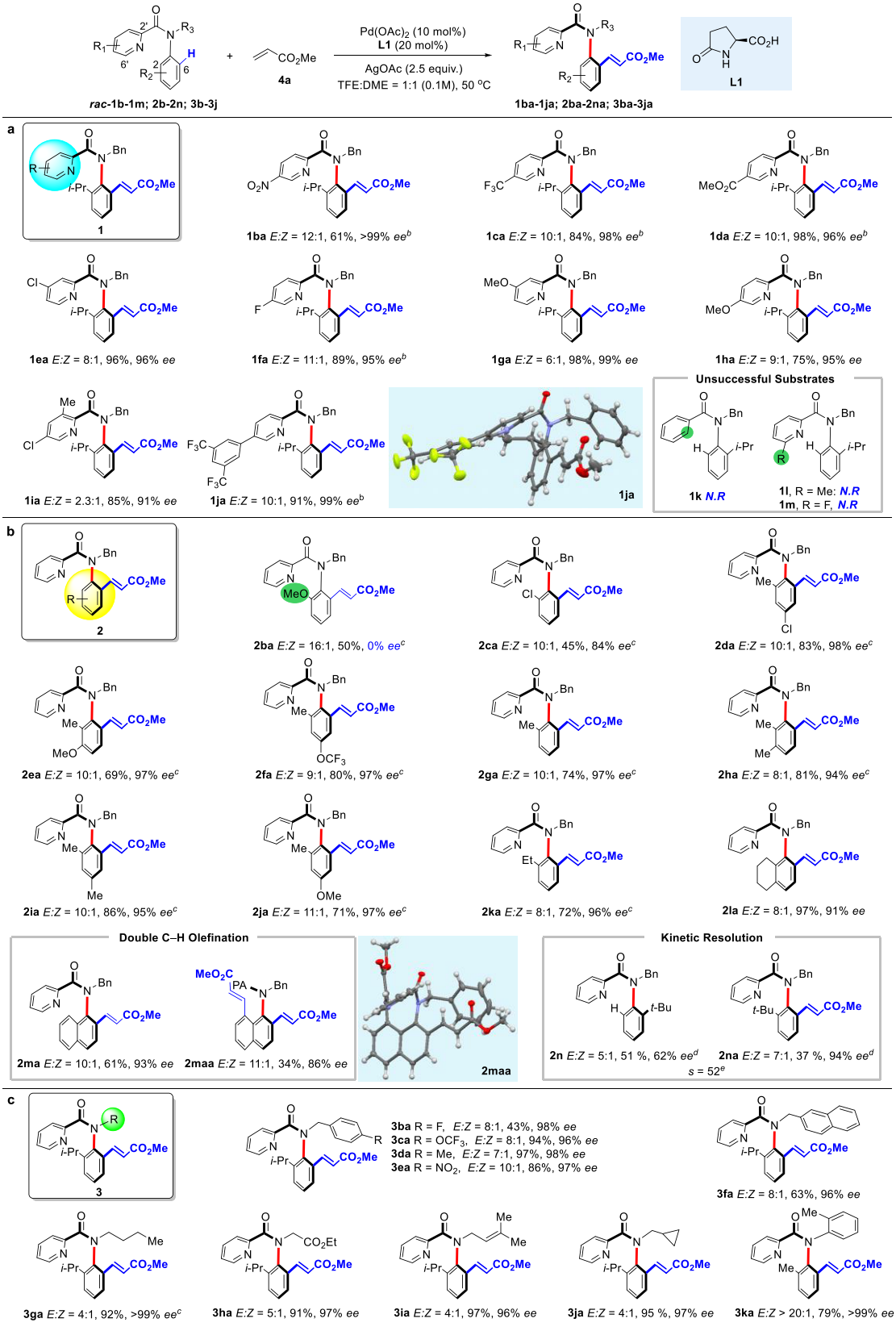
Table 2. Substrate Scope of Atropoisomeric Anilides[a]



[a]Standard reaction conditions: anilides ***rac*-1**, ***rac*-2**, or ***rac*-3** (0.1 mmol), methyl acrylate **4a** (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), **L1** (0.02 mmol), AgOAc (0.25 mmol), TFE/DME (1/1, 1 mL), 50 °C, 48 h. Isolated yields. Ees were determined by chiral HPLC analysis. [b]72 h. [c]40 °C. [d]96 h. $s = \ln[(1 - C)(1 - ee_{2n})]/\ln[(1 - C)(1 + ee_{2n})]$, $C = ee_{2n}/(ee_{2n} + ee_{2na})$. PA = picolinoyl.

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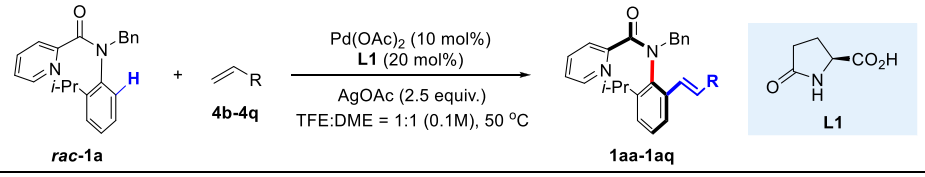
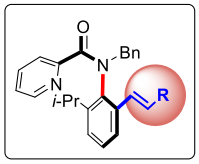
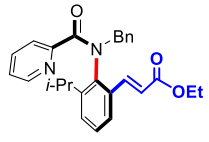
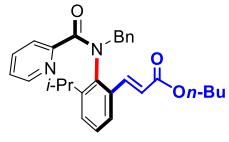
Table 3. Substrate Scope of Olefins[a]



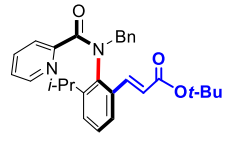




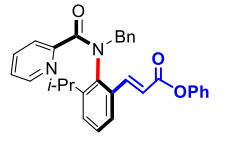
1ab *E*:*Z* = 6:1, 88%, 97% *ee*



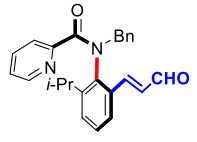
1ac *E*:*Z* = 6:1, 96%, 97% *ee*



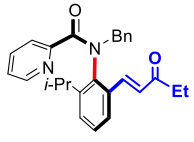
1ad *E*:*Z* = 6:1, >99%, 97% *ee*



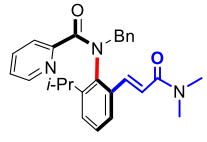
1ae *E*:*Z* = 6:1, 83%, 98% *ee*



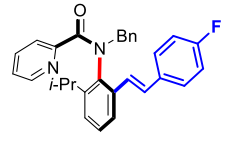
1af *E*:*Z* = 10:1, 60%, 97% *ee*



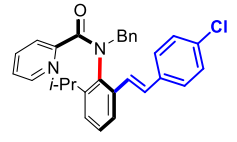
1ag *E*:*Z* = 9:1, 92%, 96% *ee*



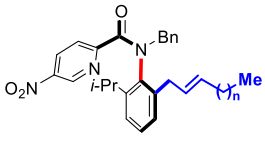
1ah *E*:*Z* = 5:1, 79%, >99% *ee*



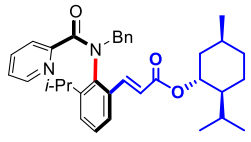
1ai *E*:*Z* = 10:1, >99%, 97% *ee*



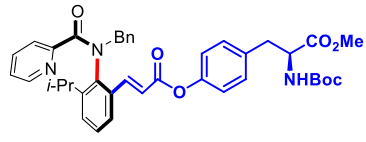
1aj *E*:*Z* = 11:1, >99%, 96% *ee*



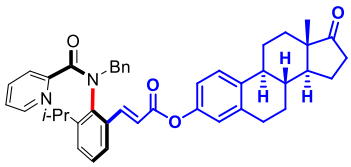
1bk n = 2, *E*:*Z* = 12:1, 41%, 91% *ee*[b]
1bl n = 5, *E*:*Z* = 12:1, 42%, 92% *ee*[b]



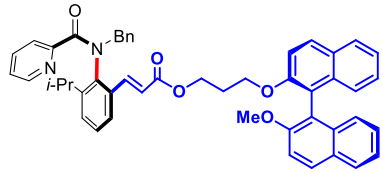
1am *E*:*Z* = 6:1, 90%, >99% *de*[c]



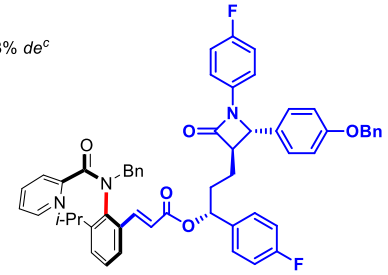
1an *E*:*Z* = 6:1, 82%, 98% *de*[c]



1ao *E*:*Z* = 6:1, 92%, 98% *de*[c]



1ap *E*:*Z* = 7:1, 87%, 96% *de*[c]



1aq *E*:*Z* = 6:1 , 79%, 95% *de*[c]

[a]Reaction conditions: **1a** (0.1 mmol), **4** (0.3 mmol), $Pd(OAc)_2$ (0.01 mmol), **L1** (0.02 mol), AgOAc (0.25 mmol), TFE/DME (1/1) (1 mL), 50 °C, 48 h. Yields are based on **1a**, Isolated yields. Enantiomeric excess (ee) were determined by chiral HPLC analysis. [b]Reaction performed for 60 h. [c]Reaction performed with 1.1 equiv of olefin (0.11 mmol). Boc, *tert*-butyloxycarbonyl.

the atropostability, and as a result, ***rac*-2b** with a smaller methoxy group led to completely racemized product **2ba** even at reduced temperature (40 °C), while those with larger substituents, such as chloro (*rac*-**2c**), methyl (***rac*-2d-2j**), ethyl (***rac*-2k**), tetrahydronaphthyl (***rac*-2l**), and naphthyl (***rac*-2m**), gave the corresponding products in good yields and enantioselectivities. Interestingly, olefination of 1-naphthylamine-derived ***rac*-2m** occurred at both 2- and 8-positions, affording the mono- and diolefination products (**2ma**, 61%, 93% ee; **2maa**, 34%, 86% ee). Notably, ***rac*-2n** bearing sterically more demanding *tert*-butyl substituent at the 6-position was configurationally stable and cannot quickly racemize under 50 °C, just enabling a kinetic resolution reaction. The reaction of ***rac*-2n** with methyl acrylate for 96 h, affording **2na** in 37% yield with 94% ee and the starting martial **2n**, was recovered in 51% yield with 61% ee (*s*-factor = 52). Moreover, a variety of substituents on nitrogen, including substituted benzyl (**3ba**−**3fa**), alkyl (**3ga**), acetate (**3ha**), isopentenyl (**3ia**), cyclopropylmethyl (**3ja**), and aryl (**3ka**), were well tolerated, giving the products in excellent enantiocontrol (**3ba**−**3ka**, 96% to >99% ee). The absolute configuration of olefination products **1ja** and **2maa** was determined by X-ray diffraction analysis, and those of the others were assigned by analogy.

The scope of the other coupling partner, olefins, was then evaluated (Table 3). A wide range of electronically biased olefins, such as acrylates (**4b**−**4e**), acrylaldehyde (**4f**), *α*,*β*-unsaturated ketone (**4g**), acrylamide (**4h**), and styrenes (**4i** and **4j**), all worked well to give the desired products with good results (Table 3, **1ab**−**1aj**, 60−99% yield and 96 → 99% ee). Notably, when using ***rac*-1b** as a mode substrate, unactivated simple aliphatic olefins (**4k**, 1-hexene and **4l**, 1-nonene) also reacted smoothly, affording the formal C−H allylation products in moderate yield and high ee (**1bk**, 41%, 91% ee; **1bl**, 42%, 92% ee). To further demonstrate the utility of this protocol, we further examined the atroposelective C−H olefination with olefins derived from the core structures of natural products (l-menthol, **4m**; tyrosine, **4n**; estrone, **4o**), chiral skeleton (BINOL, **4p**), and drug molecule (**4q**). All of the desired olefinated products were obtained in good yield with high diastereomeric excess (79−92% yield and 95 → 99% de), irrespective of the existing chiral centers and complexity.

Based on the experimental kinetic isotope effects (Scheme S1) and previous mechanistic studies of Pd-catalyzed asymmetric C−H bond functionalizations,[22,23] we next explored the reaction mechanism with density functional theory (DFT) calculations, using experimental amide substrate ***rac*-1a** and methyl acrylate (**2a**) as the model compounds.[24] The DFT-

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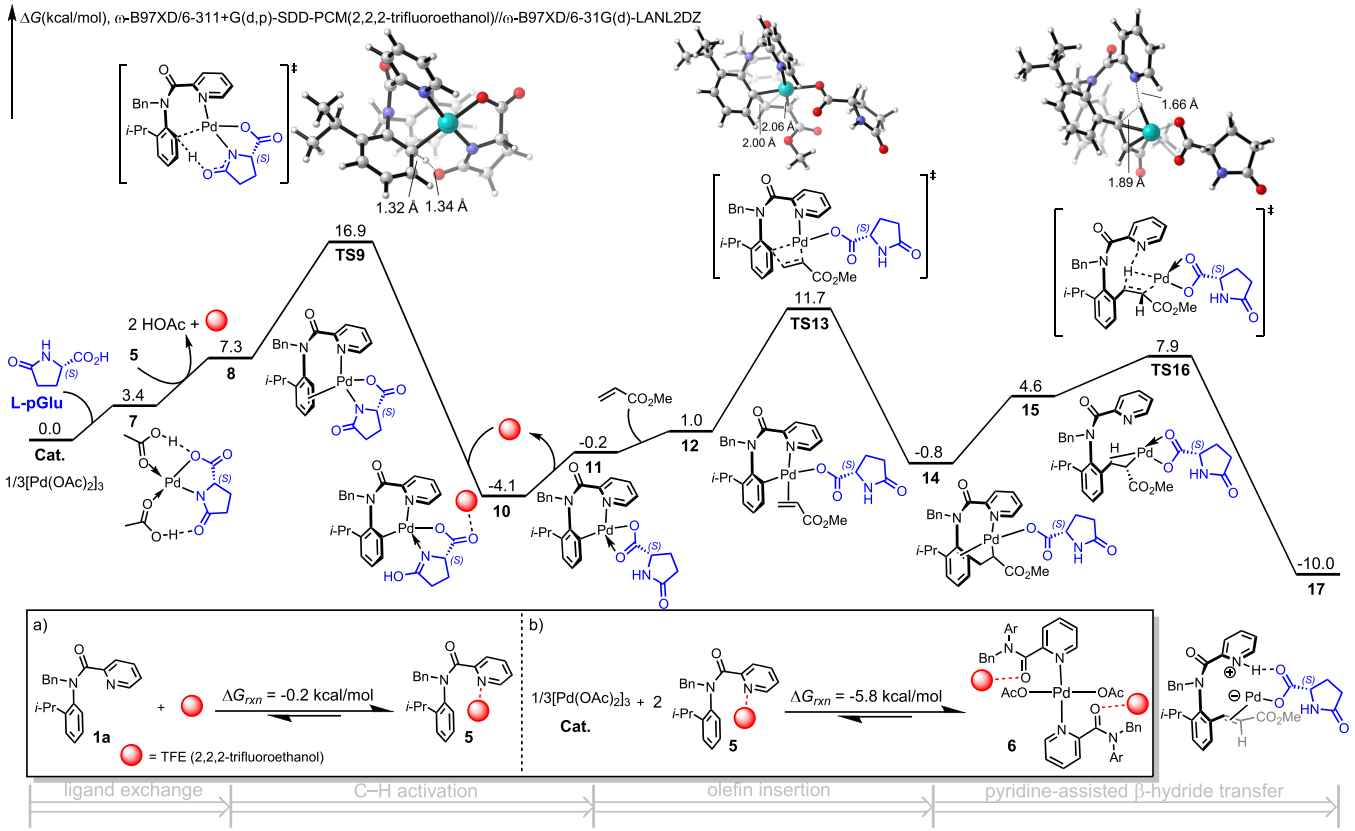

Figure 2. DFT-computed free energy profile of the most favorable pathway for the Pd/L-pGlu-catalyzed atroposelective C−H alkenylation.

computed free energy changes of the most favorable pathway for the Pd(II)/L-pGlu-catalyzed atroposelective C−H alkenylation are shown in Figure 2. The pyridine substrate can form a hydrogen-bonding complex with TFE solvent, and this complex would coordinate to palladium to create an off-cycle resting state **6**.[25] The catalytically active palladium acetate monomer complexes with L-pGlu to form intermediate **7**.[26] Subsequent substrate coordination generates intermediate **8**, and **8** undergoes the enantioselective concerted-metalation deprotonation (CMD) step via **TS9** to form the arylpalladium species **10**. From **10**, the alkene coordination and subsequent insertion via **TS13** generates the alkylpalladium intermediate **14**.[27] **14** then undergoes a facile intramolecular pyridine-assisted *β*-hydride transfer through **TS16**, leading to the reduced palladium(0) complex **17** with product coordination.[28] **17** would be oxidized to regenerate the palladium(II) active catalyst and liberate the product. Based on the DFT-computed free energy profile, the rate-determining step is the CMD step via **TS9**, with an overall barrier of 22.7 kcal/mol, which is consistent with the experimental result (KIE = 2.3). We also confirmed that the racemization of the axial chirality of the organopalladium species is not feasible after the C−H bond activation step (Figure S10).

To reveal the origins of enantioselectivity, Figure 3a shows the optimized structures and relative energies of the two competing stereoselectivity-determining CMD transition states. **TS9** is 1.7 kcal/mol more favorable than **TS18**, which corroborated the observed enantioselectivitiy (Table 1, entry 2, TFE as solvent). The comparison between the experimental substrate ***rac*-1a** and the truncated model indicated that the *i*Pr substituent is not responsible for the enantioselectivity (Figure 3a vs b). Further analysis revealed that the distortion of amino acid leads to the chiral induction in the C−H bond activation. The DFT-computed transition state **TS21** for the Pd/L-pGlu-OH-catalyzed C−H bond activation of benzene suggested that this process intrinsically prefers to occur in the fourth quadrant (Figure 3c) due to the chirality of amino acid. The geometries of the benzene and pyridine fragments match well with the axial chirality of the favored transition state **TS9** when the amide tether links the two fragments in substrate ***rac*-1a**. In contrast, chirality mismatch exists in the disfavored transition state **TS18**. Thus, significant distortion of the amino acid ligand is required to force the C−H bond activation occurring in the fourth quadrant. The pyramidalization angle of the amino acid nitrogen in **TS18** is only 11.0°, suggesting that the amino acid nitrogen is much more planar as compared to that in **TS9** or **TS21** (28.7°, 26.3°, respectively). The 2.0 kcal/mol energy difference of the Pd(L-pGlu-OH) fragment in **TS9** and **TS18** further supported the hypothesis that the amino acid ligand distortion is responsible for the enantioselectivity in the C−H bond activation step. This chiral induction rationale provides a useful mechanistic model for future designs of Pd/L-pGlu-OH-catalyzed asymmetric C−H bond activation.

In order to investigate the relationship of the conformational stability of these axially chiral anilides with the electronic effect, we measured the N−Ar rotational barriers (Δ*G*‡) of a series of chiral anilides with similar steric circumstances. We found that substituents on the aryl ring with high Hammett constant values (*σ*) lower the barriers (Figure 4a). This is consistent with a bigger Hammett constant (more electron-withdrawing substituents) making the conjugation of the lone pair on the nitrogen atom with carbonyl more difficult, causing the N atom to tend to pyramidalize. Since Hammett constants are not suitable to represent the electronic property of the pyridyl ring, we considered that the ^{13}C NMR chemical shift of carbonyl

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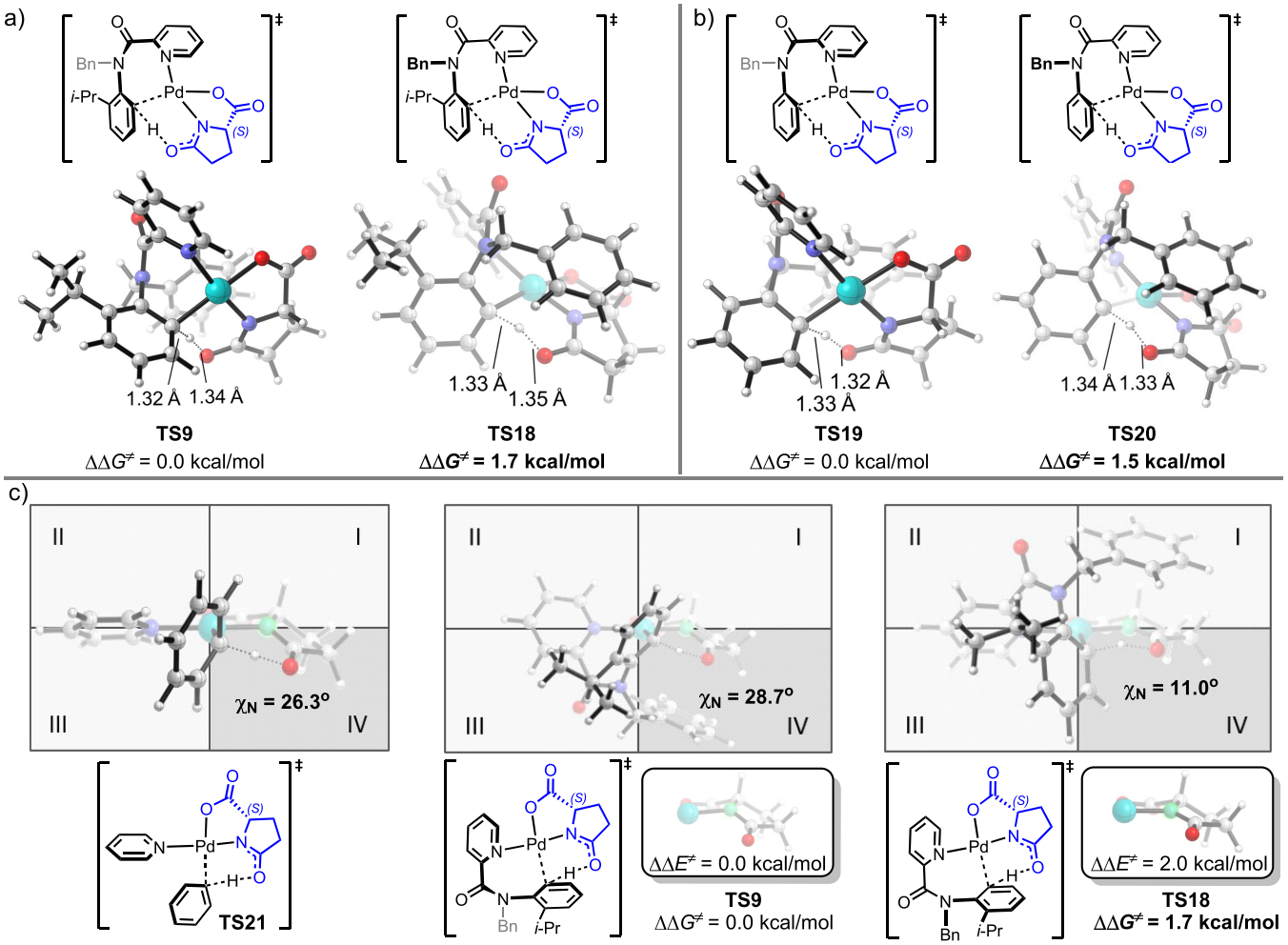

Figure 3. Origins of enantioselectivity in Pd/L-pGlu-OH-catalyzed asymmetric C−H olefination. (a) Enantioselectivity-determining C−H activation transition states with experimental substrate ***rac*-1a**. (b) Enantioselectivity-determining C−H activation transition states with truncated model ***rac*-1a**. (c) Mechanistic model of chiral induction.

(δ_{CO}) would be a useful parameter to describe the electronic property of picolinamide DG (vide infra). A negative correlation between δ_{CO} and the rotational barriers was also observed (Figure 4b). Those results are consistent with the idea that pyramidalization of the nitrogen atom significantly affects the N−Ar bond rotation.[29] Therefore, the atropostability of chiral anilides is governed by both steric and electronic effects.[30]

Finally, to demonstrate the potential applications of the chiral anilides in asymmetric catalysis, we investigated the applications in several catalytic asymmetric reactions. Inspired by the recent success of chiral olefin ligands in asymmetric catalysis,[31] we reasoned that the resulting products might act as a novel type of olefin-pyridine ligand with an unusual N−C axial chirality. When using the olefination product **L8** (**1ga**) as a chiral ligand in rhodium-catalyzed conjugate addition of phenylboronic acid to cyclohexanone, promising enantioselectivity was afforded (Scheme 1a, 53% yield, 30% ee).[32] In contrast, the analogous axially chiral styrene ligand **L9**[22b] could not introduce any enantioselectivity to this reaction, and no product was observed when using axially chiral biaryl ligand **L10**.[20f] The preliminary results demonstrated that the anilide atropisomers were superior to the analogous styrene and biaryl atropisomers in controlling the enantioselectivity of the conjugate addition and encouraged us to further investigate other chiral anilides. We decided to test styrene-derived chiral anilides that synthesized by enantioselective C−H olefination with styrenes, due to it being much easier to tune the electronic effect of the olefin part. A significant improvement in enantiocontrol was obtained when using the new styrene-derived chiral olefin-pyridine ligands (**L11**−**L13**). Gratifyingly, the use of *p*-methoxy-substituted ligand **L13** gave **18** in 69% yield with 87% ee.

The enantioselective addition of allylic silanes to carbonyl compounds to produce chiral homoallylic alcohols represents an important transformation in asymmetric synthesis.[33] We then investigated the use of the resulting chiral anilides as a new type of chiral Lewis base to catalyze the asymmetric allylation of aldehyde. To our delight, chiral product **19** was obtained in 47% yield with 88% ee when using **1ah** as a chiral catalyst (Scheme 1b). There results demonstrate that these anilide atropisomers hold great potential as a new type of chiral ligand/catalyst in asymmetric catalysis.

CONCLUSION

In summary, we have reported a novel strategy for the synthesis of chiral anilides via Pd(II)-catalyzed atroposelective C−H olefination. A broad range of axially chiral anilides were prepared in good yields (up to 99% yield) and excellent enantioselectivities (up to >99% ee) using commercially available L-pGlu-OH as an inexpensive and catalytic chiral ligand. This protocol is also compatible with various alkenes bearing core structures of

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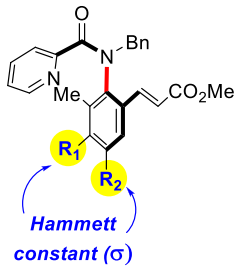
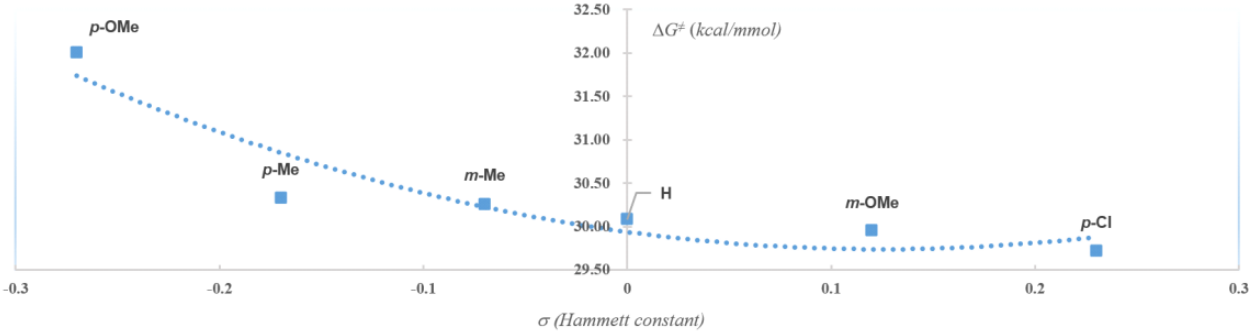
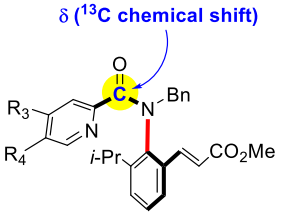
a

Compound	Substituents	σ	$t_{1/2}$ (h)	$\Delta G^{\neq}$ (kcal/mol)[a]
	**2da** R_1 = H, R_2 = Cl	0.23	6.2	29.72
	2ea R_1 = OMe, R_2 = H	0.12	8.7	29.95
	2ga R_1 = H, R_2 = H	0.00	10.4	30.08
	2ha R_1 = Me, R_2 = H	-0.07	13.6	30.27
	2ia R_1 = H, R_2 = Me	-0.17	15.0	30.34
	2ja R_1 = H, R_2 = OMe	-0.27	162.0	32.01



b

Compound	Substituents	δ (ppm)	$t_{1/2}$ (h)	$\Delta G^{\neq}$ (kcal/mol)[b]
	**1ba** R_3 = H, R_4 = NO_2	166.626	284.3	33.47
	1ca R_3 = H, R_4 = CF_3	166.735	120.2	32.81
	1da R_3 = H, R_4 = CO_2Me	166.753	79.5	32.49
	1ea R_3 = Cl, R_4 = H	166.768	69.2	32.39
	1fa R_3 = H, R_4 = F	166.795	49.0	32.13
	1ga R_3 = OMe, R_4 = H	166.847	42.8	32.02
	1aa R_3 = H, R_4 = H	166.854	39.3	31.96
	1ha R_3 = H, R_4 = OMe	166.968	25.4	31.62

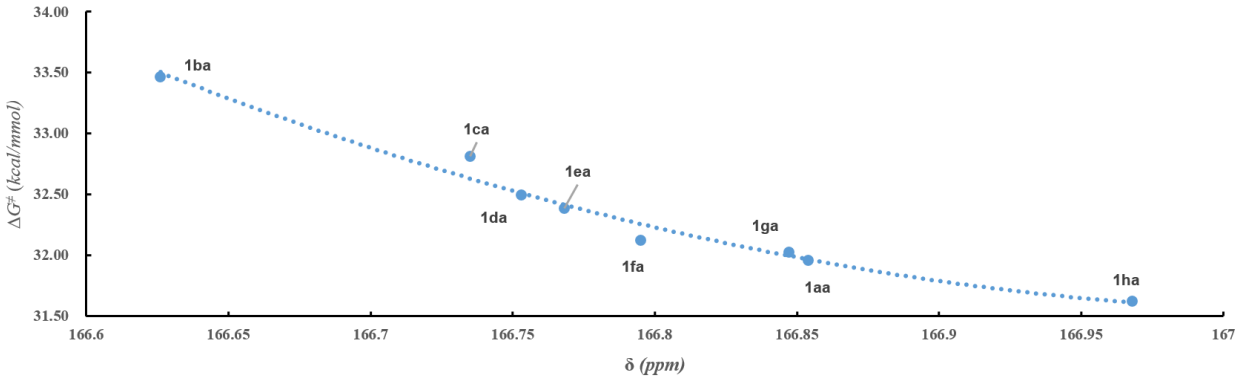


Figure 4. Relationship of the conformational stability of chiral anilides with the electronic effect. (a) Negative correlation between Hammett substituent constants (σ) of the aryl ring with rotational barriers ($\Delta G\ddagger$). (b) Negative correlation between ^{13}C chemical shifts of carbonyl (δ_{CO}) with half-lives and rotational barriers ($\Delta G\ddagger$). [a]Measured at 80 °C in isopropyl alcohol. [b]Measured at 110 °C in isopropyl alcohol. See the Supporting Information for details.

natural products, chiral skeleton, and drug molecule. Experimental studies revealed that the atropostability of those anilide atropisomers toward racemization relies on the electronic effects of both the picolinamide and aromatic ring. Computational studies were conducted to elucidate the reaction mechanism and the chiral induction model of the atroposelective C−H olefination. Moreover, the chiral anilide atropisomers hold great promise as chiral ligands/catalysts in asymmetric synthesis. We anticipate that this study will boost the use of an asymmetric C−H functionalization strategy to construct other types of chiral

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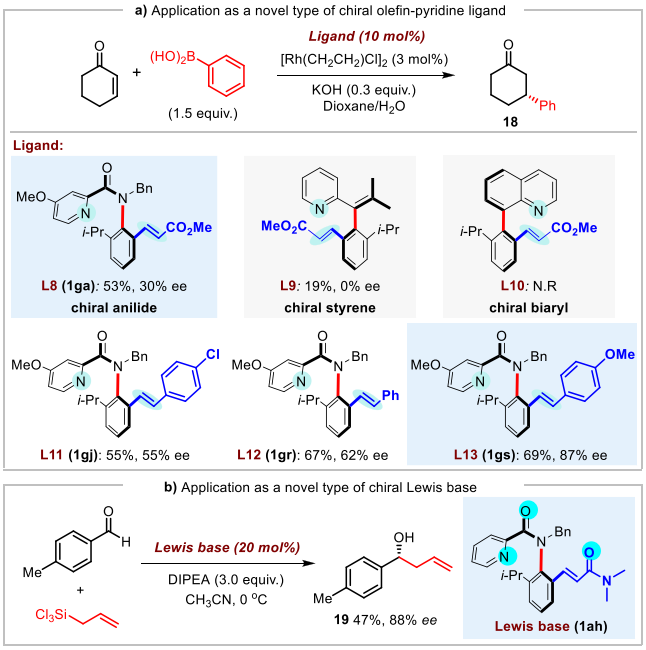
Scheme 1. Applications of Axially Chiral Anilides. (a) Olefin-Pyridine Type Ligand with N−C Axial Chirality in Rh-Catalyzed Asymmetric Conjugate Addition. (b) Application o f Chiral Anilides as Chiral Lewis Base Catalyst in the Asymmetric Allylation of Aldehydes



skeletons. Further synthetic applications of the axially chiral anilides in the synthesis of bioactive molecules and asymmetric reactions are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09400.

Experimental procedures, spectral data for all new compounds (PDF)

X-ray crystal structure for **1ja** (CCDC 1975637) (CIF)

X-ray crystal structure for **2maa** (CCDC 19675642) (CIF)

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Notes

The authors declare no competing financial interest.

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