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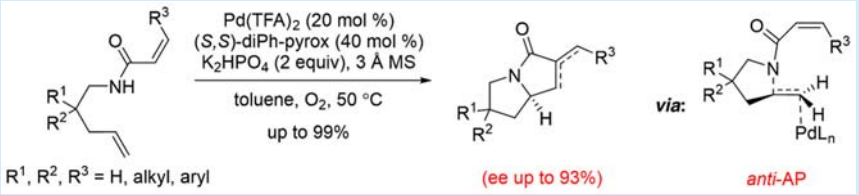
Enantioselective Palladium-Catalyzed Oxidative Cascade Cyclization of Aliphatic Alkenyl Amides

Wei Du,[†,⊥,§] Qiangshuai Gu,[†,⊥] Yang Li,[‡,∥] Zhenyang Lin,[‡] and Dan Yang*[,†]

[†]Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong SAR, China

[‡]Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

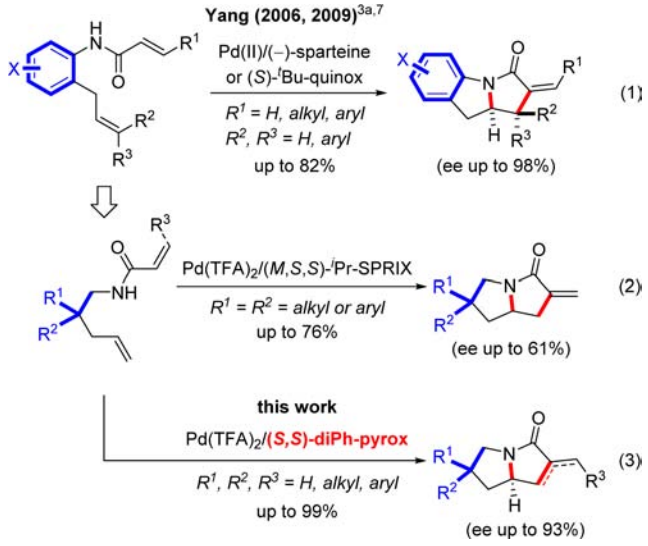
Supporting Information



ABSTRACT: The catalyst system of $Pd(TFA)_2$/(*S*,*S*)-diPh-pyrox is reported to promote the highly efficient enantioselective oxidative cascade cyclization of alkene-tethered aliphatic acrylamides under mild aerobic conditions. A series of pyrrolizidine derivatives have been synthesized in good yield and excellent enantioselectivity. Deuterium-labeling experiments have revealed that the reaction proceeded through an *anti*-aminopalladation (*anti*-AP) pathway with high selectivity. The transition states for the *anti*-AP step have been calculated to account for the observed enantioselectivity.

Palladium-catalyzed asymmetric amination of alkenes is a powerful tool for the construction of enantioenriched *N*-heterocycles, which have attracted tremendous attention for their versatile bioactivities.[1] However, enantioselective Pd-catalyzed C−N bond formation via aminopalladation (AP)[2] is inherently challenging, as the aminopalladation step, which is almost always the enantiodetermining step,[3] might proceed through two stereochemically different pathways, *syn*-AP or *anti*-AP,[4] and both pathways might impose significant effects on the enantioselectivity.[5] Thus, it is not surprising that few of such transformations have achieved high levels of enantioselectivity (ee >90%).[6] Our group previously developed an enantioselective Pd(II)-catalyzed oxidative tandem cyclization of unsaturated anilides with molecular oxygen as an oxidant, which is environmentally benign and readily available, by using either (−)-sparteine or quinox as ligand (Scheme 1, eq 1).[3a,7] However, substrates in both systems were only restricted to the alkene-tethered acrylanilides. Compared to acrylanilides with fused aryl backbones, aliphatic acrylamides possess less rigid skeletons and less acidic NH and are thus unfavorable for the desired cyclization. As reported by Sasai and co-workers,[8] low to moderate enantioselectivity (up to 61% ee) was observed on cyclization of such acrylamides substrates with the Pd(II)/spirobis(isoxazoline) (SPRIX) (Scheme 1, eq 2) system,[9] which previously exhibited excellent enantiocontrol in C−C,[10] C−O,[11] as well as C−N[3b] bond formation. We herein describe a highly enantioselective oxidative tandem cyclization of alkene-tethered aliphatic acrylamides catalyzed by $Pd(TFA)_2$/(*S*,*S*)-diPh-pyrox that affords a series of pyrrolizidines in excellent yield (up to 99%) and enantioselectivity (up to 93% ee) (Scheme 1, eq 3) under mild conditions.

Scheme 1. Background of this Work



We initiated reaction condition screening with our previous $Pd(TFA)_2$/(−)-sparteine system and later identified bidentate oxazoline-containing ligands as promising candidates (for detailed screening results, see the Supporting Information). Upon further ligand screening and reaction condition optimization, optimal conditions were found as follows: substrate **1** (0.5 mmol), $Pd(TFA)_2$ (20 mol %), (*S*,*S*)-diPh-

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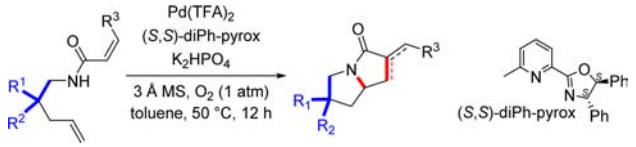
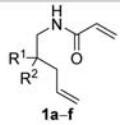
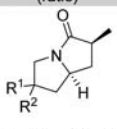
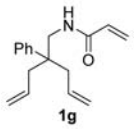
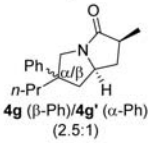
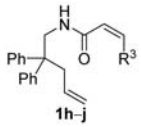
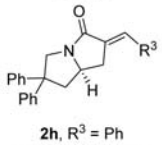
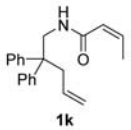
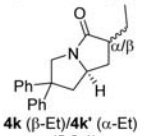
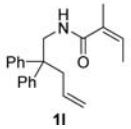
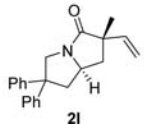
Table 1. Pd(II)-Catalyzed Enantioselective Tandem Cyclization of Various Substrates[a]



entry	substrate	product (ratio)	yield (%)[b]	ee (%)[c]
	 1a–f			
1[d,e]		**4a**, $R^1 = R^2$ = H	72	89
2[d,e]		**4b**, $R^1 = R^2$ = Me	84	83
3[d,e]		**4c**, R^1,R^2 = –$(CH_2)_4$–	88	83
4[d,e,f]		**4d**, R^1,R^2 = –$(CH_2)_5$–	82	86
5[d,e]		**4e**, $R^1 = R^2$ = Ph	99	90
6[d,g,h]		**4f** (β-Ph)/**4f'** (α-Ph) (1.4:1) R^1 = H, R^2 = Ph	77	43 (92)[n]
7[d,h,i]	 1g	 **4g** (β-Ph)/**4g'** (α-Ph) (2.5:1)	88	88 (85)[n]
	 1h–j			
8[j]		**2h**, R^3 = Ph	73	93
9		**2i**, R^3= *p*-$OMeC_6H_5$	74	92
10		**2j**, R^3 = *p*-ClC_6H_5	76	92
11[d,k,l]	 1k	 **4k** (β-Et)/**4k'** (α-Et) (5.8:1)	68	86 (89)[n]
12[e,m]	 1l	 2l	69	82

[a]Reaction conditions: substrate **1** (0.5 mmol), $Pd(TFA)_2$ (20 mol %), (*S,S*)-diPh-pyrox (40 mol %), K_2HPO_4 (2 equiv), and 3 Å MS (1 g/mmol substrate) in toluene (10.0 mL/mmol substrate) at 50 °C under O_2 for 12 h or as otherwise indicated. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]The products were reduced by H_2 in the presence of Pd/C catalyst. [e]Only a single diastereomer was obtained. [j]Substrate **1d** (0.2 mmol), (*S*)-Ph-pyrox (**L10** in the Supporting Information, 40 mol %), 24 h. [g]Substrate **1f** (0.3 mmol). [h]The dr ratio was determined by ^1H NMR spectrum of the crude product. [i]Substrate **1g** (0.3 mmol). [j]Substrate **1h** (0.2 mmol), 19 h. [k]15 h. [l]The dr ratio was calculated based on the isolated yields of the two diastereomers. [m]Substrate **1l** (0.30 mmol), 36 h, 89% conversion. [n]Enantiomeric excess of the minor diastereomer.

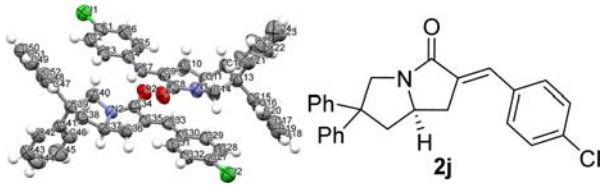
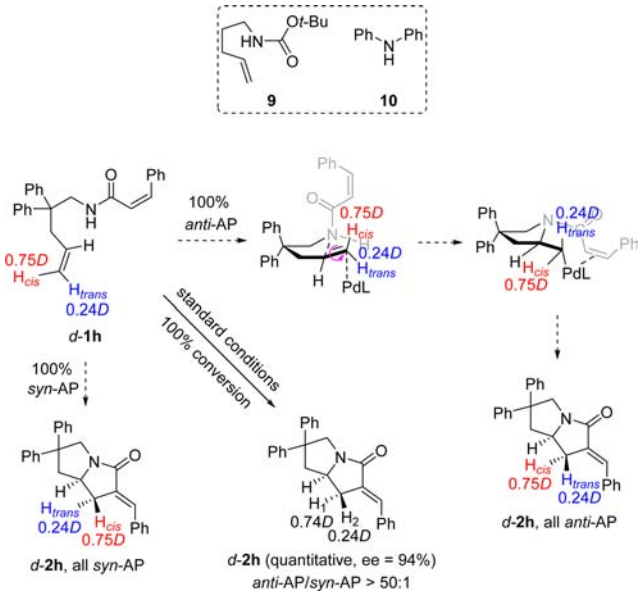


Figure 1. X-ray diffraction analysis of chiral compound **2j**.

Scheme 2. Deuterium-Labeling Experiment on the Enantiodetermining Aminopalladation Step



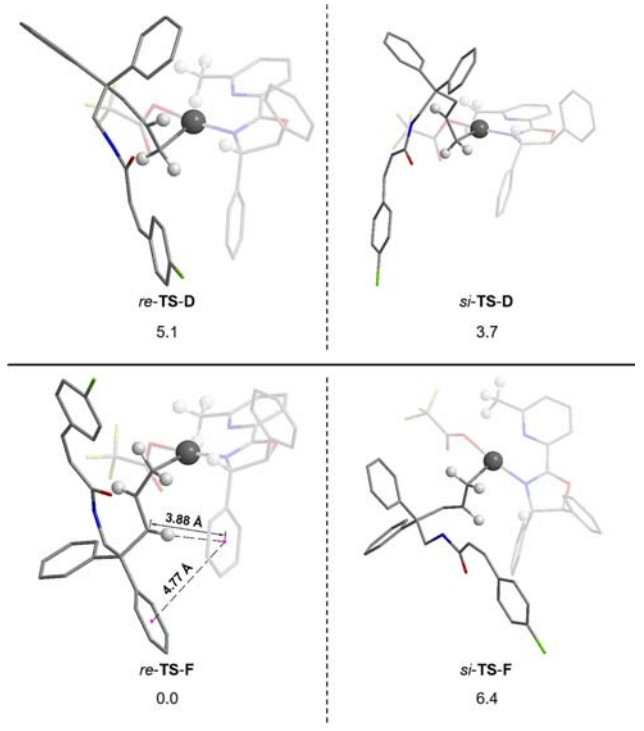


Figure 2. Computed transition states in the *anti*-AP step (relative energies were given in kcal/mol). Structures are depicted in a mixed ball-and-stick model. Most hydrogens except for selected important ones have been omitted, and the color of ligand (*S,S*)-diPh-pyrox and trifluoroacetate has been deliberately faded to some extent for clarity.

pyrox (40 mol %), K_2HPO_4 (2 equiv), and 3 Å MS (1 g/mmol substrate) in toluene (5.0 mL) at 50 °C under O_2 (1 atm) for 12 h. We subsequently examined a variety of aliphatic alkenyl acrylamides, as shown in Table 1. To simplify product analysis, the C=C double bonds of some cyclized products were hydrogenated to avoid the problem of regioisomers (Table 1, entries 1−7 and 11). Substrates with *gem* disubstituents gave higher yields than that without backbone substitution (Table 1,

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entries 1−5), and all of them afforded the desired products as single diastereomers with good to excellent ee. In particular, substrate **1e** with sterically bulky *gem*-diphenyl groups delivered **4e** in quantitative yield and 90% ee (Table 1, entry 5). Racemic monosubstituted substrate **1f** gave rise to **4f** (43% ee) and **4f′** (92% ee) after hydrogenation in 77% overall yield with a dr ratio of 1.4:1 (Table 1, entry 6). Symmetrically substituted diene **1g** afforded the desymmetrized products with very good ee and moderate diastereoselectivity after the hydrogenation step (Table 1, entry 7). Notably, *Z*-cinnamide substrates **1h−j** afforded products **2h−j** in the *E*-configuration exclusively[12] with excellent enantioselectivity (92−93% ee; Table 1, entries 8−10), which is consistent with our previous results.[3a,7,13] In addition, X-ray crystallographic analysis of product **2j** revealed the absolute configuration of the angular carbon center as *R* (Figure 1).[14] However, *Z*-crotonamide **1k** led to more complicated results, with several regioisomeric alkenes formed under the standard conditions due to reversible *β*-hydride elimination (Table 1, entry 11).[15] After hydrogenation, enantioenriched diastereomers **4k** (86% ee) and **4k′** (89% ee) were delivered in 68% overall yield with a ratio of 5.8:1. When trisubstituted acrylamide **1l** was applied to the reaction, **2l** bearing a new quaternary carbon center was obtained as a single diastereomer in 82% ee (Table 1, entries 12). A longer reaction time (36 h) was required, suggesting that the steric crowdedness of the acrylamide double bond has an inhibitory effect on the reactivity.

Only a handful of reversible amino-palladation reactions have been disclosed so far either under acidic conditions[16] or with substrates containing acidic N−H bonds,[3l,16g,17] where fast *β*-heteroatom elimination, i.e., the reverse reaction of amino-palladation, is rendered practicably observable. Our acrylamide substrates are supposed to be less acidic than carbamate **9**[3j] and slightly more acidic than diphenylamine **10**,[18] both of which (Scheme 2) have been reported to undergo irreversible aminopalladation under basic conditions. Under our optimized conditions, external base K_2HPO_4 and an excess amount of basic pyrox ligand (relative to the Pd catalyst) were added, both of which ensure an essentially basic environment. It then becomes reasonable for us to presume that the amino-palladation step is irreversible and thus determines the final enantioselectivity. Accordingly, we prepared substrate *d*-**1h** with 75% and 24% deuterium incorporated into the H_{cis} and the H_{trans} positions,[19] respectively, to examine the stereochemistry of the aminopalladation step (Scheme 2). The ratio of *anti*-AP/*syn*-AP can be estimated on the basis of the deuterium distribution patterns in the H_1 and H_2 positions of product *d*-**2h**. Thus, under the optimized conditions, product *d*-**2h** was obtained with 74% and 24% deuterium incorporated into the H_1 and H_2 positions,[20] respectively, indicating a high *anti*-AP selectivity.

To gain insight into the origin of enantioselectivity, we then resorted to computational calculations to obtain the transition states within the *anti*-AP step. In total, eight transition states for substrate **1j** were located, originating from different *si*- and *re*-face olefin attacks and orientations of ligand (*S*,*S*)-diPh-pyrox relative to the substrate backbone.[21] Four of them, *re*/*si*-**TS-E**/**G** (Figure S9-1) with the olefin being attacked *trans* to the oxazoline moiety of (*S*,*S*)-diPh-pyrox, were found to be noticeably less stable than the other four (*re*/*si*-**TS-D**/**F**, Figure 2). For the energetically favorable transition states *re*/*si*-**TS-D**/**F**, *re*-**TS-F** and *si*-**TS-D** were found to be the lowest and have a 3.7 kcal/mol energy difference (roughly 2.0 kcal/mol for an ee value of 92%, in theory),[22] favoring the *re* face attack of the isolated C=C double bond. This result is in accordance with the observed absolute configuration of product **2j** (Figure 1). In general, the major influential steric substrate−ligand interaction is between the protruding acrylamide moiety and the C4-phenyl group on the oxazoline ring among these four transition states. Interestingly, cooperatively stabilizing noncovalent CH/*π* and arene−arene interactions[23] have been identified only in *re*-**TS-F** (Figure 2). These interactions may account for both the favorable stability of this transition state to some extent and the slightly better enantioselectivity for substrates bearing gem-diphenyl substituents on their backbones.

In summary, the $Pd(TFA)_2$/(*S*,*S*)-diPh-pyrox system we have developed provides a robust and convenient access to a series of pyrrolizidine derivatives with high enantioselectivity. Both experimental and theoretical mechanistic studies support a highly selective *anti*-AP preference for our enantioselective transformation, reemphasizing the importance of high stereoselectivity in aminopalladation for achieving high asymmetric induction. Further mechanistic study is currently underway and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03410.

Preparation and characterization of **1**, **2**, **4**, and (*S*,*S*)-diPh-pyrox; HPLC analysis of chiral products **2** and **4**; X-ray structural analysis of **2j** containing tables of atomic coordinates and geometry parameters; details of theoretical calculations containing Cartesian coordinates and relative total energies of *re*/*si*-**TS-D**−**G** optimized using B3LYP (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yangdan@hku.hk.

ORCID

Zhenyang Lin: 0000-0003-4104-8767

Dan Yang: 0000-0002-1726-9335

Present Addresses

[§]West China School of Pharmacy, Sichuan University, Chengdu 610041, China.

[∥]School of Petroleum and Chemical Engineering, Dalian University of Technology, Panjin 124221, China.

Author Contributions

[⊥]W.D. and Q.G. contributed equally.

Notes

The authors declare no competing financial interest.

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(12) This observation confirmed that the alkene insertion proceeded in a *syn* fashion.

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(14) CCDC 1498280 (for **2j**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

(15) The proposed pathways for the formation of **4k** and **4k′** are shown in section 6 in the Supporting Information.

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(19) For details on deuterium incorporation, see section 7 in the Supporting Information.

(20) No obvious deuterium scrambling for both unreacted *d*-**1h** recovered and product *d*-**2h** was observed when the reaction was quenched before completion based on the ^{1}H NMR spectrum analysis.

(21) For details on theoretical calculation, see section 9 in the Supporting Information.

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