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Enantioselective Intramolecular Oxidative Aminocarbonylation of Alkenylureas Catalyzed by Palladium−Spiro Bis(isoxazoline) Complexes

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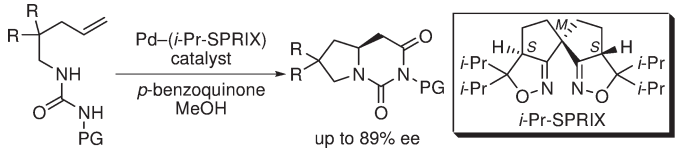

An enantioselective synthesis of tetrahydropyrrolo[1,2-*c*]pyrimidine-1,3-diones via a palladium-catalyzed intramolecular oxidative aminocarbonylation is described. The carbon−carbon double bond of alkenylurea substrates has been shown to react intramolecularly with a nitrogen nucleophile in the presence of a palladium catalyst under a carbon monoxide atmosphere. The use of a chiral spiro bis(isoxazoline) ligand (SPRIX) is essential to obtain the desired products in optically active forms. In comparison with the coordination ability of other known ligands, this peculiar character of SPRIX originates from two structural characteristics: low σ-donor ability of the isoxazoline coordination site and rigidity of the spiro skeleton.

Introduction

The development of novel chiral ligands is one of the most important tasks in the area of asymmetric catalysis. The spirocyclic framework has received considerable attention as a promising chiral skeleton because ligands containing such a unique backbone are expected to exhibit unusual reactivity and selectivity.[1,2] In 1999, we developed spiro bis(isoxazoline) ligands (SPRIXs),[3,4] which have a chiral spiro backbone and isoxazoline units. On the basis of the good affinity of SPRIXs for Pd^{II} salts and the stability of SPRIXs under oxidative conditions, we demonstrated the first example of the enantioselective Wacker-type cyclization of alkenyl alcohols mediated by the Pd−SPRIX complex and a unique catalytic asymmetric tandem cyclization of dialkenyl alcohols via oxypalladation.[4b] In addition, the Pd−SPRIX catalyst has been found to be efficient in several enantioselective reactions such as the cyclization of enyne derivatives to give α-methylene-γ-butyrolactones,[4c] and the synthesis of polyketones through alternating copolymerization of CO with styrene derivatives.[4e] Recently, the first asymmetric Pd^{II}/Pd^{IV} catalysis was achieved by employing a combination of a hypervalent iodine reagent and SPRIX.[4f] Enantioselective cyclization of enyne derivatives catalyzed by the Pd−SPRIX complex

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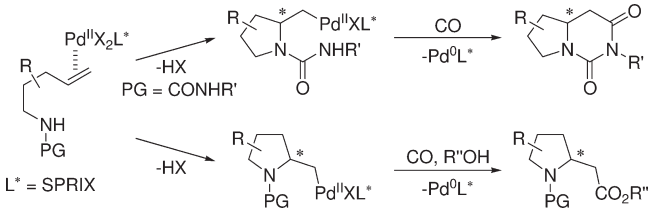
SCHEME 1. Pd^{II}−Catalyzed Intramolecular Oxidative Aminocarbonylation of Alkenyl Amide Derivatives



furnished lactones bearing a bicyclo[3.1.0]hexane skeleton with high enantioselectivity. Being encouraged by these findings, we envisioned a palladium-catalyzed enantioselective intramolecular oxidative aminocarbonylation of alkenyl amides producing optically active cyclic β-amino acid derivatives, in which both the chiral center and the pyrrolidine framework were constructed in a single step (Scheme 1).[5−7] If this reaction could be promoted enantioselectively, it is expected to be an efficient synthetic method for preparation of optically active cyclic β-amino acid derivatives. According to our initial study, the use of SPRIXs was found to be required for obtaining enantioselectivity in the catalytic cyclization.[8] However, despite the unique benefits of the Pd−SPRIX catalyst, the enantioselectivity of the intramolecular oxidative aminocarbonylation was moderate. We therefore decided to reinvestigate the reaction conditions in order to attain highly enantioselective formation of optically active cyclic β-amino acid derivatives. Herein we report a detailed investigation of the enantioselective intramolecular oxidative aminocarbonylation of alkenylureas catalyzed by a Pd−SPRIX complex as well as the intriguing properties of SPRIXs.

Results and Discussion

Establishment of Reaction Conditions. We previously reported the high utility of SPRIXs **3** for the Pd-catalyzed enantioselective cyclizations of alkenyl alcohols[4b] and aminocarbonylation of alkenylamides.[8] The alkene moiety of the substrates was efficiently activated toward intramolecular attack of the nucleophile through coordination to the Pd−SPRIX catalyst. It was therefore anticipated that SPRIXs would also exhibit an acceleration effect in enantioselective intramolecular oxidative aminocarbonylation of alkenylurea **1**.[9] To our delight, the reaction of *N*-2,2-dimethylpent-4-enyl-*N*′-*p*-toluenesulfonylurea (**1a**) proceeded enantioselectively in the presence of a catalytic amount of (*P*,*R*,*R*)-*i*-Pr-SPRIX **3a**. Thus, **1a** was treated with 10 mol % of $[Pd(MeCN)_4](BF_4)_2$, 11 mol % of **3a**, and 2 equiv of *p*-benzoquinone in MeOH at 0 °C under a carbon monoxide atmosphere to give 66% ee of the desired cyclic β-amino acid derivative **2a** in 94% yield (Table 1, entry 1).[10] When (*P*,*R*,*R*)-**3b** and (*P*,*R*,*R*)-**3c** bearing smaller substituents on the isoxazoline rings were employed as the chiral ligands, **2a** was obtained quantitatively with 25% ee and 15% ee, respectively (entries 2 and 3). The reaction with (*P*,*R*,*R*)-H-SPRIX **3d** also produced **2a** in 41% yield, albeit with lower stereoselectivity (entry 4).[11] Axially chiral bis(isoxazoline) ligand (*R*)-**4** developed by our group[12] turned out to be ineffective (entry 5). It should be noted that Pd complexes with other known chiral ligands such as (*R*)-BINAP, (−)-sparteine, (*S*,*S*)-*t*-Bu-BOX, and (*S*,*S*)-*i*-Pr-BOXAX did not promote the aminocarbonylation of **1a** at all even at 25 °C (entries 6−9).[13] Background reactions were minimal under conditions without ligand, resulting in only a trace amount of **2a** (entry 10). Furthermore, chiral Pd complex **5**, which is known to be an effective catalyst for asymmetric Wacker-type cyclizations of *o*-allylphenols,[14] did not work in this aminocarbonylation

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(8) Shinohara, T.; Arai, M. A.; Wakita, K.; Arai, T.; Sasai, H. *Tetrahedron Lett.* **2003**, *44*, 711–714.

(9) For recent representative examples on the cyclization of alkenylurea, see: (a) Streuff, J.; Hövelmann, C. H.; Nieger, M.; Muñiz, K. *J. Am. Chem. Soc.* **2005**, *127*, 14586–14587. (b) Muñiz, K.; Hövelmann, C. H.; Streuff, J. *J. Am. Chem. Soc.* **2008**, *130*, 763–773. (c) Muñiz, K.; Hövelmann, C. H.; Campos-Gómez, E.; Barluenga, J.; González, J. M.; Streuff, J.; Nieger, M. *Chem. Asian J.* **2008**, *3*, 776–788. (d) Muñiz, K.; Streuff, J.; Chávez, P.; Hövelmann, C. H. *Chem. Asian J.* **2008**, *3*, 1248–1255. (e) Muñiz, K.; Hövelmann, C. H.; Streuff, J.; Campos-Gómez, E. *Pure Appl. Chem.* **2008**, *80*, 1089–1096. (f) Iglesias, A.; Muniz, K. *Chem.—Eur. J.* **2009**, *15*, 10563–10569. (g) Muniz, K.; Iglesias, A.; Fang, Y. *Chem. Commun.* **2009**, 5591–5593. (h) Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 5039–5042.

(10) The results using other solvents: toluene: trace, 31% ee; CH_2Cl_2: 24% yield, 12% ee; MeCN: 40% yield, 29% ee; THF: 34% yield, 47% ee; EtOH: 64% yield, 65% ee. See the Supporting Information.

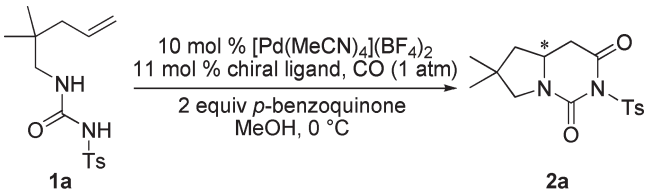
(11) When (*P*,*R*,*R*)-**3d** was employed, Pd black was gradually formed after replacement by CO. As a result of this deactivation of catalyst, the chemical yield of **2a** was diminished. In the reaction, a combination of 10 mol % of $Pd(OCOCF_3)_2$ and 22 mol % of (*M*,*S*,*S*)-**3d** showed better result. A 61% yield of **2a** was obtained with 54% ee when the reaction was conducted at −20 °C for 7.1 days as reported in ref 8.

(12) Shinohara, T.; Wakita, K.; Arai, M. A.; Arai, T.; Sasai, H. *Heterocycles* **2003**, *59*, 587–593.

(13) Abbreviations: (*R*)-BINAP = (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; (*S*,*S*)-*t*-Bu-BOX = 2,2-bis[(4*S*)-4-*tert*-butyl-2-oxazolin-2-yl]propane; (*S*,*S*)-*i*-Pr-BOXAX = (*S*)-2,2′-bis[(4*S*)-4-isopropyl-2-oxazolin-2-yl]-1,1′-binaphthyl.

(14) (a) Hosokawa, T.; Miyagi, S.; Murahashi, S.-I.; Sonoda, A. *J. Chem. Soc., Chem. Commun.* **1978**, 687–688. (b) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318–2323. (c) Hosokawa, T.; Okuda, C.; Murahashi, S.-I. *J. Org. Chem.* **1985**, *50*, 1282–1287.

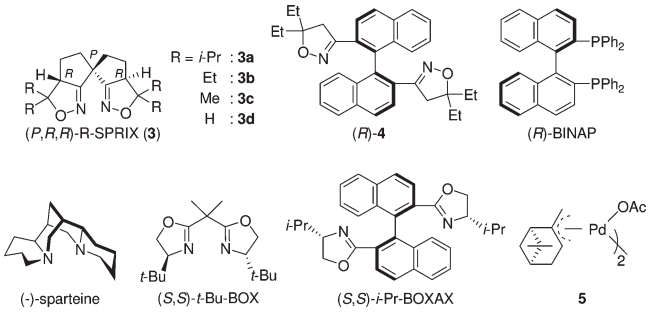
TABLE 1. Screening of Catalyst Systems in the Reaction of Alkenylurea 1a[a]



entry	chiral ligand	time (h)	yield (%)	ee (%)[b]
1	(*P*,*R*,*R*)-**3a**	3	94	66
2	(*P*,*R*,*R*)-**3b**	1.5	quant.	25
3	(*P*,*R*,*R*)-**3c**	1.5	quant.	15
4	(*P*,*R*,*R*)-**3d**	48	41	8
5	(*R*)-**4**	48	trace	ND[c]
6[e]	(*R*)-BINAP	24	NR[d]	ND[c]
7[e]	(−)-sparteine	24	NR[d]	ND[c]
8[e]	(*S*,*S*)-*t*-Bu-BOX	24	NR[d]	ND[c]
9[e]	(*S*,*S*)-*i*-Pr-BOXAX	24	NR[d]	ND[c]
10	none	24	trace	
11[e]	**5**[f]	24	NR[d]	ND[c]

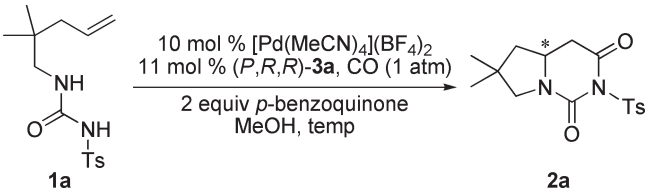
[a]All reactions were carried out in the presence of 10 mol % of $[Pd(MeCN)_4](BF_4)_2$, 11 mol % of ligand, and 2 equiv of *p*-benzoquinone at 0 °C in MeOH (0.1 M for **1a**) under a carbon monoxide atmosphere unless otherwise noted. [b]Determined by HPLC analysis (Chiralpak AD-H). [c]Not determined. [d]No reaction. [e]At 25 °C. [f]10 mol % of chiral complex **5** was used instead of $[Pd(MeCN)_4](BF_4)_2$.

(entry 11). Pd black and/or insoluble materials were immediately formed after replacement by CO in entries 5−11, whereas no such precipitation was observed in the reactions with SPRIX (entries 1−3). These results clearly demonstrate the high suitability of SPRIXs **3** for the enantioselective intramolecular oxidative aminocarbonylation of **1a**.



Being encouraged by the results in Table 1, we performed further optimization of the reaction conditions in regards to the ligand/metal ratio and reaction temperature (Table 2). As the ligand/metal ratio was increased, reaction time was longer, although **2a** was obtained in comparable yields with the same enantioselectivities. Thus, complete consumption of **1a** was detected at 0 °C after 3 h in the case of 11 mol % of (*P*,*R*,*R*)-**3a**, while reactions with 22 and 33 mol % of (*P*,*R*,*R*)-**3a** under otherwise identical conditions were complete in 4.5 and 9 h, respectively (entries 1−3). These results indicate that an excess amount of (*P*,*R*,*R*)-**3a** retards the reaction. The enantiopurity of **2a** was successfully improved by lowering the reaction temperature, although a prolonged reaction time and a dilute concentration of **1a**

TABLE 2. Effects of Ligand/Pd Ratio and Reaction Temperature[a]



entry	L/Pd ratio	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	1.1	0	3	94	66
2[c]	2.2	0	4.5	85	66
3[d]	3.3	0	9	83	66
4[e]	1.1	−20	36	98	75
5[f]	1.1	−40	165	89	88
6[f]	1.1	−50	210	10	91

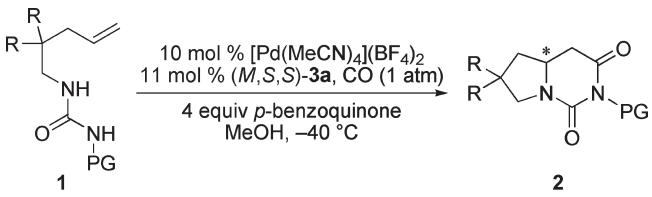
[a]All reactions were carried out in the presence of 10 mol % of $[Pd(MeCN)_4](BF_4)_2$, 11 mol % of (*P*,*R*,*R*)-**3a**, and 2 equiv of *p*-benzoquinone in MeOH (0.1 M for **1a**) under a carbon monoxide atmosphere unless otherwise noted. [b]Determined by HPLC analysis (Chiralpak AD-H). [c]22 mol % of (*P*,*R*,*R*)-**3a** was used. [d]33 mol % of (*P*,*R*,*R*)-**3a** was used. [e]In MeOH (0.05 M for **1a**). [f]4 equiv of *p*-benzoquinone was used in MeOH (0.02 M for **1a**).

were necessary due to the low reactivity of **1a** and the poor solubility of *p*-benzoquinone (entries 4−6). In the reactions at −20 and −40 °C, **2a** was obtained in excellent yields (98% and 89%) with high enantioselectivities (75% ee and 88% ee), respectively (entries 4 and 5). The selectivity was further improved to 91% ee at −50 °C, but the chemical yield of **2a** disappointingly dropped to 10% even after 210 h (entry 6).

Scope and Limitations. Having successfully optimized the reaction conditions, we explored the scope of this transformation with a variety of alkenylurea substrates **1** (Table 3). The reaction of **1b** proceeded sluggishly to give a 48% yield of **2b** with 89% ee after 260 h, presumably due to the steric bulkiness of the 2-tolyl group (entry 2). X-ray crystallographic analysis of enantiopure **2b** unambiguously established its *S* absolute configuration as well as the desired tetrahydropyrrolo[1,2-*c*]pyrimidine-1,3-dione skeleton (see the Supporting Information). Similar to the tosyl group of **1a**, benzenesulfonyl and 4-chlorobenzenesulfonyl groups were tolerated as protecting groups, leading to the formation of the corresponding products **2c** and **2d** in 89% and 76% yields with 87% ee and 86% ee, respectively (entries 3 and 4). The chemical yield was considerably influenced by the substituents R on the homoallylic position. Excellent to good yields (97% and 76%) were observed for **2e** and **2f** based on a cyclohexane and a cyclopentane backbone (entries 5 and 6). Despite low chemical yield, the enantioselectivity of **2f** was improved to 72% ee at −40 °C (entry 7). Phenyl-substituted substrate **1g** was also tolerated yielding the corresponding product **2g** in 80% yield with 30% ee (entry 8). However, the products **2h** (R = CO_2Et) and **2i** (R = H) were produced in moderate to low yields (entries 9 and 10).

(15) For recent representative examples on the cyclization of alkenyl sulfamide, see: (a) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250–11251. (b) Zabawa, T. P.; Chemler, S. R. *Org. Lett.* **2007**, *9*, 2035–2038. (c) Muñiz, K.; Streuff, J.; Hövelmann, C. H.; Núñez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7125–7127. (d) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153–1160. (e) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009−3019 and references cited therein.

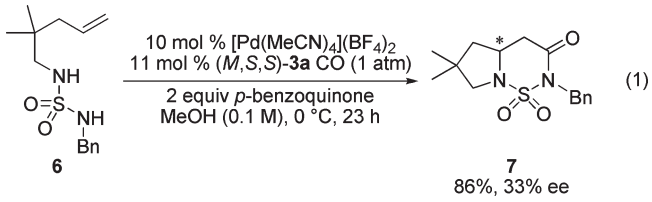
TABLE 3. Scope and Limitations[a]



entry	1	R	PG	2	time (d)	yield (%)	ee (%)[b]
1	**1a**	Me	Ts	**2a**	6.9	89	88
2	**1b**	Me	2-$MeC_6H_4SO_2$	**2b**	10.8	48	89 (*S*)[c]
3	**1c**	Me	$C_6H_5SO_2$	**2c**	6.9	89	87
4	**1d**	Me	4-$ClC_6H_4SO_2$	**2d**	6.9	76	86
5[d]	**1e**	$-CH_2(CH_2)_3CH_2-$	Ts	**2e**	1.9	97	52
6[d]	**1f**	$-CH_2(CH_2)_2CH_2-$	Ts	**2f**	2.0	76	61
7	**1f**	$-CH_2(CH_2)_2CH_2-$	Ts	**2f**	7.0	36	72
8[d]	**1g**	Ph	Ts	**2g**	2.0	80	30
9[d]	**1h**	CO_2Et	Ts	**2h**	7.0	50	51
10[d]	**1i**	H	Ts	**2i**	7.0	28	61

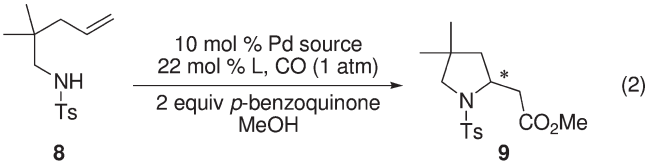
[a]All reactions were carried out in the presence of 10 mol % of $[Pd(MeCN)_4](BF_4)_2$, 11 mol % of (*M*,*S*,*S*)-**3a**, and 4 equiv of *p*-benzoquinone at −40 °C in MeOH (0.02 M for **1**) under a carbon monoxide atmosphere unless otherwise noted. [b]Determined by HPLC analysis (Chiralpak AD-H). [c]Determined by X-ray analysis. [d]2 equiv of *p*-benzoquinone was used in MeOH (0.05 M for **1**) at −20 °C.

Alkenyl sulfamide **6**[15] also participated in this cyclization to afford bicyclic sulfamide **7** in 86% yield with 33% ee (eq 1).



(1)

It was also feasible to construct a homoproline skeleton in this cyclization. Thus, a mixture of alkenyl tosylamide **8**[16] and *p*-benzoquinone in MeOH was stirred at 25 °C for 8 h in the presence of 10 mol % of $[Pd(MeCN)_4](BF_4)_2$ and 22 mol % of (*M*,*S*,*S*)-**3a** to afford methyl 2-(4,4-dimethyl-1-tosylpyrrolidin-2-yl)acetate (**9**) in 27% yield with 45% ee (eq 2). In this reaction, a combination of $Pd(OCOCF_3)_2$ and (*M*,*S*,*S*)-**3d** displayed higher catalytic activity.[8] Accordingly, the chemical yield of **9** was improved to 87% when the reaction was conducted at 0 °C.

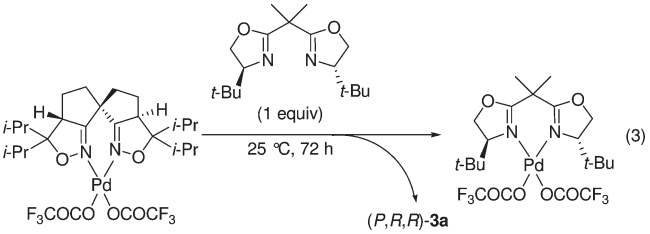


(2)

$[Pd(MeCN)_4](BF_4)_2$-(*M*,*S*,*S*)-**3a**, 25 °C, 8 h; 27%, 45% ee
$Pd(OCOCF_3)_2$-(*M*,*S*,*S*)-**3d**, 0 °C, 72 h; 87%, 39% ee

We have accomplished the Pd-catalyzed enantioselective intramolecular oxidative aminocarbonylation of alkenylurea derivatives **1**, alkenyl sulfamide **6**, and alkenyl tosylamide **8**, in which SPRIXs serve as efficient chiral ligands. The desired cyclic β-amino acid derivatives **2**, **7**, and **9** were obtained in high yields with moderate to good enantioselectivities.

Unique Feature of Spiro Bis(isoxazoline) Ligands. The results of ligand screening shown in Table 1 clearly indicate that an isoxazoline coordination site plays an essential role for this intramolecular oxidative aminocarbonylation. It is speculated that a low σ-donor ability of isoxazolines keeps the strong Lewis acidity of the "naked" Pd^{II} metal intact, allowing high activity of the Pd-SPRIX catalysts. To evaluate the σ-donor ability of isoxazolines, we monitored the ligand exchange process between SPRIX and BOX by ^1H NMR spectroscopy (eq 3). To a solution of $Pd(OCOCF_3)_2$[(*P*,*R*,*R*)-**3a**] complex in CD_2Cl_2 was added an equimolar amount of (*S*,*S*)-*t*-Bu-BOX ligand. After 72 h, peaks corresponding to the original complex completely disappeared and new signals assignable to $Pd(OCOCF_3)_2$[(*S*,*S*)-*t*-Bu-BOX] and free (*P*,*R*,*R*)-**3a** were observed. This result suggests that the coordination of (*P*,*R*,*R*)-**3a** to Pd^{II} is weaker than that of (*S*,*S*)-*t*-Bu-BOX, implying the small σ-donor ability of isoxazolines. Axially chiral ligand (*R*)-**4**, however, does not promote the aminocarbonylation in spite of its isoxazoline coordination sites (vide supra). The more flexible 1,1′-binaphthyl skeleton of (*R*)-**4** would be insufficient to fix the conformation of the weakly coordinating isoxazolines in a chelating fashion, compared to the spiro[4.4]nonane scaffold. Therefore, a rapid formation of Pd black was observed in the reaction with (*R*)-**4** (Table 1, entry 5).

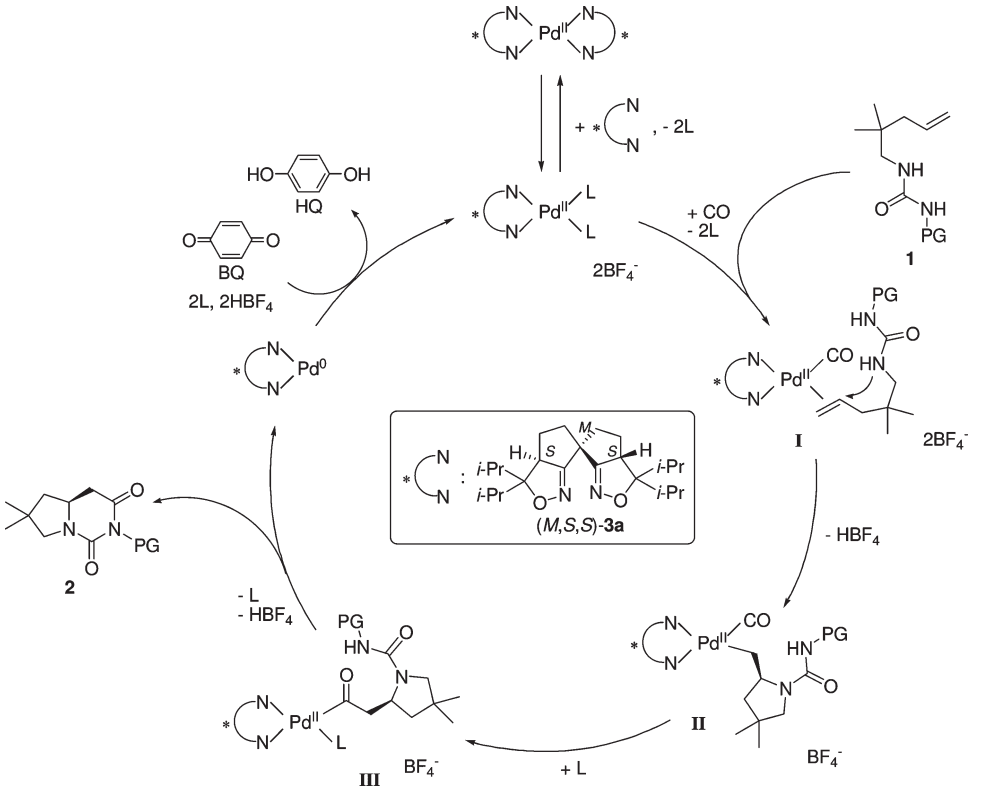


(3)

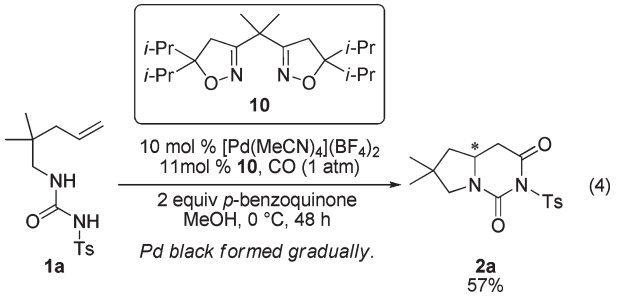
To gain insight into the effects of the spiro framework, achiral bis(isoxazoline) ligand **10** bearing an isopropylidene skeleton was prepared and applied to the intramolecular oxidative aminocarbonylation. The reaction of **1a** proceeded at 0 °C to furnish a 57% yield of racemic **2a**, accompanied by the gradual formation of Pd black (eq 4). Since (*P*,*R*,*R*)-**3a** promoted the reaction efficiently without Pd black formation (Table 1, entry 1), it was demonstrated

(16) For recent representative examples on the cyclization of alkenyl tosylamide, see: (a) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164–166. (b) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573–1575. (c) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618–5621. (d) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691. (e) Rogers, M. M.; Wendlandt, J. E.; Guzei, I. A.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 2257–2260. (f) Scarborough, C. C.; Stahl, S. S. *Org. Lett.* **2006**, *8*, 3251–3254. (g) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910–1923. (h) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335. (i) Sherman, E. S.; Fuller, P. H.; Kasi, D.; Chemler, S. R. *J. Org. Chem.* **2007**, *72*, 3896–3905. (j) Muñiz, K. *J. Am. Chem. Soc.* **2007**, *129*, 14542–14543. (k) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948–12949. (l) Zeng, W.; Chemler, S. R. *J. Org. Chem.* **2008**, *73*, 6045–6047. (m) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638–17639. (n) Paderes, M. C.; Chemler, S. R. *Org. Lett.* **2009**, *11*, 1915–1918. (o) Scarborough, C. C.; Bergant, A.; Sazama, G. T.; Guzei, I. A.; Spencer, L. C.; Stahl, S. S. *Tetrahedron* **2009**, *65*, 5084–5092.

SCHEME 2. Plausible Catalytic Cycle



that the spiro skeleton contributed to the catalyst stability. Most likely, the highly rigid structure directs the lone pairs on the isoxazoline nitrogens into the stable bidentate mode.



Reaction Mechanism and Stereochemistry. A plausible catalytic cycle of the enantioselective intramolecular oxidative aminocarbonylation of alkenylurea derivatives **1** is illustrated in Scheme 2. On the basis of the results in Table 2, the catalytically active species is thought to be a 1:1 complex of Pd and (*M*,*S*,*S*)-**3a**, which is in equilibrium with an inert 1:2 [Pd{(*M*,S,S)-**3a**}$_2$](BF$_4$)$_2$[4c] complex in the presence of an excess amount of the ligand. The structure of this 1:2 complex was confirmed by X-ray crystallography (see the Supporting Information). The production of bicyclic β-amino acid derivatives **2** seems to be initiated by the coordination of the olefinic moiety in substrates **1** to the catalytically active species, leading to intermediate **I**. The activated alkene is subjected to the nucleophilic attack of the intramolecular urea group to afford alkylpalladium intermediate **II**. The subsequent CO insertion gives acylpalladium intermediate **III**. Finally, ring closure via nucleophilic trapping of the acylpalladium by the tethered tosylamide group proceeds to yield **2** and Pd^0, of which the latter is oxidized by the action of *p*-benzoquinone to regenerate the Pd^{II} catalyst.

Enantioselectivity is determined in the aminopalladation, viz. the formation of intermediate **II** by way of **I**. Figure 1 depicts the asymmetric environment around Pd based on the X-ray structure of [Pd{(*M**,*S**,*S**)-**3a**}$_2$](BF$_4$)$_2$ and the schematic transition state assembly in the intermediate **I**. It is evident that the chiral ligand (*M*,*S*,*S*)-**3a** creates a C_2-symmetric environment with isopropyl substituents located in the second and fourth quadrants (Figure 1a). In the intermediate **I**, the carbon−carbon double bond of **1** coordinates to Pd to avoid steric repulsion between the substrate and isopropyl substituents of (*M*,S,S)-**3a** (Figure 1b). Consequently, the activated olefin undergoes intramolecular nucleophilic attack of the nitrogen from its *re*-face to give the bicyclic β-amino acid products **2** of the observed *S* configuration.

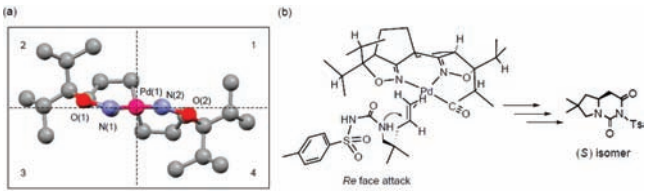


FIGURE 1. (a) Quadrant representation for the asymmetric environment of Pd-(*M*,*S*,*S*)-**3a** complex stemming from the X-ray structure of [Pd{(*M**,*S**,*S**)-**3a**}$_2$](BF$_4$)$_2$ and (b) a plausible stereochemical pathway for the oxidative enantioselective aminocarbonylation of alkenylureas **1** catalyzed by Pd-(*M*,*S*,*S*)-**3a**.

Conclusion

We have developed a catalytic enantioselective intramolecular oxidative aminocarbonylation of alkenylureas **1**. Chiral spiro bis(isoxazoline) ligands, SPRIXs **3**, have proven to be useful for this reaction, affording bicyclic β-amino acid derivatives **2** with up to 89% ee. Alkenyl sulfamide **6** and tosylamide **8** are also applicable to the asymmetric catalysis to give the corresponding products in good yields with moderate enantioselectivities. The unique acceleration effect of **3** in these reactions is rationalized by two structural features. One is the isoxazoline coordination site whose σ-donor ability is low since the intrinsic Lewis acidity of the Pd metal is not altered. The other is the rigid spiro skeleton that provides not only an effective asymmetric environment but a suitable chelate. Further investigations into the extension of substrate scope, reaction mechanism including asymmetric induction, and transformation of products **2** to biologically active molecules are now in progress.

Experimental Section

General Procedure for Pd^{II}−SPRIX-Catalyzed Enantioselective Intramolecular Oxidative Aminocarbonylation of Alkenylureas 1. Under an argon atmosphere, a solution of (*M*,*S*,*S*)-**3a** (11 mol %) and $[Pd(MeCN)_4](BF_4)_2$ (10 mol %) in MeOH (5.0 mL) was stirred at 25 °C for 2 h. After addition of *p*-benzoquinone (4 equiv), the apparatus was purged with carbon monoxide by pumping-filling via a three-way stopcock. Alkenylurea **1** (0.10 mmol) was then added to the solution at −40 °C and the entire mixture was stirred at that temperature for the time indicated in Table 3. After quenching by the addition of 1 M aq HCl, the reaction mixture was diluted with ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/acetone = 3/1) to afford bicyclic β-amino acid derivative **2**.

6,6-Dimethyl-2-tosyltetrahydropyrrolo[1,2-*c*]pyrimidine-1,3-(2*H*,4*H*)-dione (2a): 89% yield; white solid; mp 143.8−145.4 °C (hexane/EtOAc); HRMS (ESI) calcd for $C_{16}H_{20}N_2NaO_4S$ *m*/*z* 359.1041 ($[M + Na]^+$), found *m*/*z* 359.1042; $[\alpha]^{25}_D$ +61.4 (*c* 0.56, 62% ee, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.16 (s, 3H), 1.42 (dd, *J* = 12.5 Hz, *J* = 9.9 Hz, 1H), 2.01 (dd, *J* = 12.5 Hz, *J* = 6.4 Hz, 1H), 2.35 (dd, *J* = 17.6 Hz, *J* = 12.6 Hz, 1H), 2.43 (s, 3H), 2.92 (dd, *J* = 17.6 Hz, *J* = 3.5 Hz, 1H), 3.18 (d, *J* = 11.1 Hz, 1H), 3.41 (d, *J* = 11.1 Hz, 1H), 4.05−4.11 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 8.17 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.7, 26.4, 26.5, 37.5, 41.1, 46.1, 51.1, 58.0, 129.3, 129.3, 135.3, 145.4, 147.8, 167.7; IR (neat) ν (C═O) 1746, 1711, (O═S═O) 1362, 1173 cm^{-1}. The enantiomeric excess was determined to be 88% ee by HPLC analysis using a chiral stationary phase column [Chiralpak AD-H, hexane/*i*-PrOH = 3/1, flow rate = 0.5 mL/min, λ = 227 nm: 21.6 min (major) and 29.1 min (minor)].

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Supporting Information Available: Experimental details including screening of the reaction conditions, preparation of substrates, characterization of products, and X-ray crystallographic data for **2b**, (*M*,*S*,*S*)-**3a**, and $[Pd\{(M^*,S^*,S^*)\text{-}\mathbf{3a}\}_2](BF_4)_2$ in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.