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Tetrahedron Letters 44 (2003) 711–714

TETRAHEDRON LETTERS

The first enantioselective intramolecular aminocarbonylation of alkenes promoted by Pd(II)-spiro bis(isoxazoline) catalyst

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Received 29 October 2002; revised 15 November 2002; accepted 22 November 2002

Abstract—The highly ligand acceleration effect of spiro bis(isoxazoline) ligand (SPRIX) on the Pd(II)-catalyzed intramolecular aminocarbonylation of alkenyl amine derivatives was realized. Furthermore, the chiral Pd(II)–SPRIX catalyst accomplished the first enantioselective intramolecular aminocarbonylation. The reaction of *N*-(2,2-dimethyl-pent-4-enyl)-*p*-toluenesulfonamide in the presence of Pd(II)–SPRIX catalyst and *p*-benzoquinone in methanol under a carbon monoxide atmosphere afforded [4,4-dimethyl-1-(*p*-toluene-sulfonyl)-pyrrolidin-2-yl]-acetic acid methyl ester in good yield with moderate enantioselectivity.

The introduction of a new metal-coordinating moiety and/or new chiral backbone which have not been attempted so far as optically active ligands are very attractive for development of a new asymmetric reaction. We previously reported the novel spiro bis(isoxazoline) ligands (R-SPRIXs), which have a chiral spiro backbone and isoxazoline units (Fig. 1), and demonstrated the first example of an isoxazoline ligand used for a transition metal-catalyzed enantioselective reaction.[1a] In addition, the enantioselective Wacker-type cyclization of alkenyl alcohols was accomplished with Pd(II)–SPRIX catalysts for the first time.[1b] Encouraged by this finding, we envisioned an enantioselective aminopalladation system of alkenyl amine derivatives using chiral Pd(II)–SPRIX catalysts.

Although a variety of useful reactions has been realized using Pd(II) complexes under oxidative conditions, including the Wacker process,[2] development of a catalytic enantioselective reaction has begun to attract attention.[1b,3] The Pd(II)-catalyzed intramolecular aminocarbonylation of alkenyl amine derivatives has been proved to be one of the most efficient and straightforward methods for constructing biologically important β-amino acid derivatives, alkaloids, and related compounds (Scheme 1).[4,5] Tamaru et al. have developed an efficient Pd(II)-catalyzed aminocarbonylation by overcoming problems such as displacement of the coordinated alkene to Pd by amines and the oxidative destruction of amines.[5] Although substantial work has been done, to the best of our knowledge, a successful catalytic enantioselective reaction involving aminocarbonylation has not yet been reported. Herein, we report the first example of the enantioselective intramolecular aminocarbonylation of alkenyl amine derivatives promoted by Pd(II)–SPRIX catalyst.

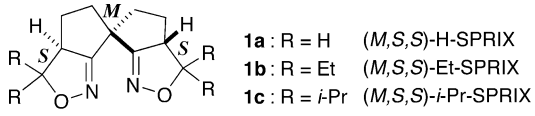
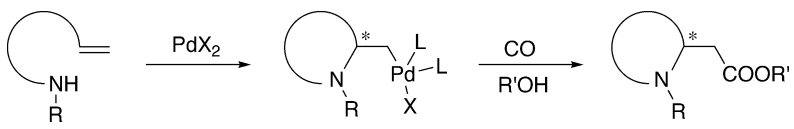


Figure 1. Spiro bis(isoxazoline) ligands (SPRIXs).

Initially, the reactivity of Pd(II)–SPRIX catalysts was examined in the intramolecular aminocarbonylation of *N*-(2,2-dimethyl-pent-4-enyl)-*p*-toluenesulfonamide (**2a**). In the presence of $Pd(OCOCF_3)_2$ (10 mol%), (±)-



Scheme 1. Pd(II)-catalyzed intramolecular aminocarbonylation of alkenyl amine derivatives.

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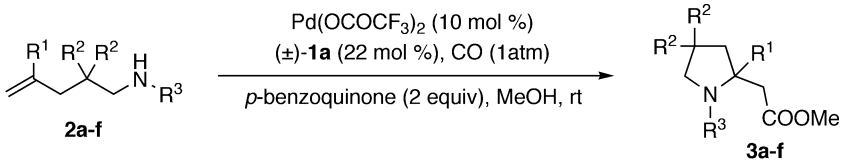
PII: S0040-4039(02)02650-3

Table 1. Intramolecular aminocarbonylation of alkenyl amine derivatives **2a–f** promoted by Pd(II)–**1a** catalyst[a]



2a-f **3a-f**

Entry	Substrate	R^1	R^2	R^3	Time (h)	Product	Yield (%)[b]
1	**2a**	H	Me	Ts	3	**3a**	88
2	**2b**	H	Me	SO_2Mes	1	**3b**	87
3	**2c**	H	Me	Bz	2.5	**3c**	60
4	**2d**	H	Me	Ns	7	**3d**	84
5	**2e**	H	Ph	Ts	1	**3e**	93
6	**2f**	Me	Me	Ts	6	**3f**	96

[a] Reactions were carried out using 10 mol% of $Pd(OCOCF_3)_2$, 22 mol% of **1a** (racemate), and 2 equiv. of *p*-benzoquinone under CO in MeOH.
[b] Isolated yield.

Table 2. Catalytic enantioselective intramolecular aminocarbonylation[a]

Entry	Substrate	Ligand	Temp. (°C)	Time (h)	Product	Yield (%)[b]	ee (%)[c]
1	**2a**	**1a**	rt	3.5	**3a**	80	31
2	**2a**	**1b**	rt	3	**3a**	76	10
3	**2a**	**1c**	rt	3	**3a**	47	24
4	**2a**	**1a**	0	72	**3a**	87	39
5[d]	**2a**	**1a**	−20	170	**3a**	53	52
6[e]	**2a**	**1a**	−20	170	**3a**	83	53
7[f]	**2a**	**1a**	−40	144	**3a**	46	65
8[e]	**2b**	**1a**	−20	170	**3b**	95	60

[a] Unless specified, reactions were carried out using 10 mol% of $Pd(OCOCF_3)_2$, 22 mol% of (*M*,*S*,*S*)-R-SPRIX and 2 equiv. of *p*-benzoquinone under CO in MeOH (0.2 M).
[b] Isolated yield.
[c] Optical purity was determined by HPLC analysis using a chiral stationary phase column (DAICEL CHIRALPAK AS) with hexane–*i*PrOH as eluent.
[d] Carried out using 4 equiv. of *p*-benzoquinone in MeOH (0.02 M).
[e] Carried out using 30 mol% of $Pd(OCOCF_3)_2$, 66 mol% of **1a** and 4 equiv. of *p*-benzoquinone in MeOH (0.02 M).
[f] Carried out using 100 mol% of $Pd(OCOCF_3)_2$, 220 mol% of **1a** and 4 equiv. of *p*-benzoquinone in MeOH (0.02 M).

(*M**,*S**,*S**)-H-SPRIX (**1a**) (22 mol%), and *p*-benzoquinone (2 equiv.) under carbon monoxide, the reaction of **2a** proceeded very smoothly to completion in only 3 h at room temperature, affording [4,4-dimethyl-1-(*p*-toluenesulfonyl)-pyrrolidin-2-yl]-acetic acid methyl ester (**3a**) in 88% yield (Table 1, entry 1).[6] Meanwhile, using only $Pd(OCOCF_3)_2$ (10 mol%) in the absence of SPRIXs, the reaction proceeded extremely slowly at room temperature (22% yield after 24 h). This result clearly indicates that **1a** has an accelerating effect on this aminocarbonylation, and that the $Pd(OCOCF_3)_2$–**1a** catalyst system has higher catalytic activity than Tamaru's conditions[5c] (24 h, 97% yield) on the aminocarbonylation of **2a**. The reactions of the alkenyl mesitylenesulfonylamide **2b**, the alkenyl benzoylamide **2c**, and the alkenyl 2-nitrobenzenesulfonylamide **2d** also proceeded smoothly to produce the *N*-protected β-amino acid derivatives **3b**, **3c** and **3d**, respectively (entries 2, 3 and 4). The Pd(II)–**1a** catalyst similarly promoted aminocarbonylation of the diphenyl substituted alkenyl tosylamide **2e** and the 4-methyl substituted alkenyl tosylamide **2f** to give the corresponding products **3e** and **3f** in high yield (entries 4 and 5).

Based on these results, we next examined the catalytic enantioselective intramolecular aminocarbonylation using chiral SPRIXs (Table 2). The reaction of **2a** using 10 mol% of $Pd(OCOCF_3)_2$ and 22 mol% of chiral **1a** gave the β-amino acid derivative **3a** in 31% ee (entry 1).[7] Other SPRIX ligands such as (*M*,*S*,*S*)-Et-SPRIX (**1b**) or (*M*,*S*,*S*)-*i*Pr-SPRIX (**1c**) which have ethyl or isopropyl substituent groups on the isoxazoline rings, respectively, were less effective in terms of the reactivity and enantioselectivity than those obtained with **1a** (entries 2 and 3).

When the reaction was carried out at 0°C, the optical purity of **3a** was improved to 39% ee (entry 4). At lower temperature (−20°C) the target product was obtained in 53% yield with a higher enantiomeric excess, 52% ee (entry 5). In the presence of 30 mol% Pd(II)–**1a** catalyst and 4 equiv. of *p*-benzoquinone at −20°C, the reaction was improved to give the product in 83% yield with the same enantioselectivity (entry 6). Furthermore, using a stoichiometric amount of Pd(II)–**1a** complex at −40°C, the β-amino acid derivative **3a** was obtained in 65% ee (entry 7). In the case of **2b**, Pd(II)–**1a** catalyst (30

mol%) gave the cyclized product **3b** in 95% yield with 60% ee at −20°C (entry 8).

It is notable that the aminocarbonylation of **2a** was not promoted using hitherto known asymmetric catalysts or known ligands such as [(3,2,10-η^3-pinene)-PdOAc]$_2$ (**4**),[3a–c] Pd(OCOCF$_3$)$_2$–BINAP (**5**), Pd(OCOCF$_3$)$_2$–(*S*,*S*)-ip-boxax (**6**),[3d–f] Pd(OCOCF$_3$)$_2$–bis(oxazolinyl)-propane **7a**[8] or **7b**,[9] or Pd(OCOCF$_3$)$_2$–monodentate oxazoline ligand **8**[10] (Fig. 2).

A plausible mechanism of the catalytic enantioselective aminocarbonylation of alkenyl tosylamide **2a** is shown in Scheme 2. Intramolecular nucleophilic attack of the amino group at the activated C–C double bond of complex **I** would afford alkyl Pd(II) intermediate **II**. CO insertion in **II** would give the acylpalladium intermediate **III** and following alcoholysis would yield the β-amino acid derivative **3a** with generating Pd(0). The Pd(0) would be oxidized to Pd(II) by *p*-benzoquinone[11] to complete the catalytic cycle. According to our previous research of Wacker-type cyclization, the active catalytic species was believed to be a 1:1 complex of Pd(OCOCF$_3$)$_2$ and SPRIX.[12] However, when aminocarbonylation of **2a** was carried out using 10 mol% of Pd(OCOCF$_3$)$_2$ and 12 mol% of **1a** (Pd:**1a** = 1:1.2), the

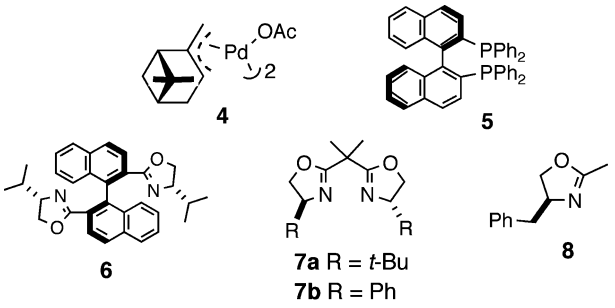
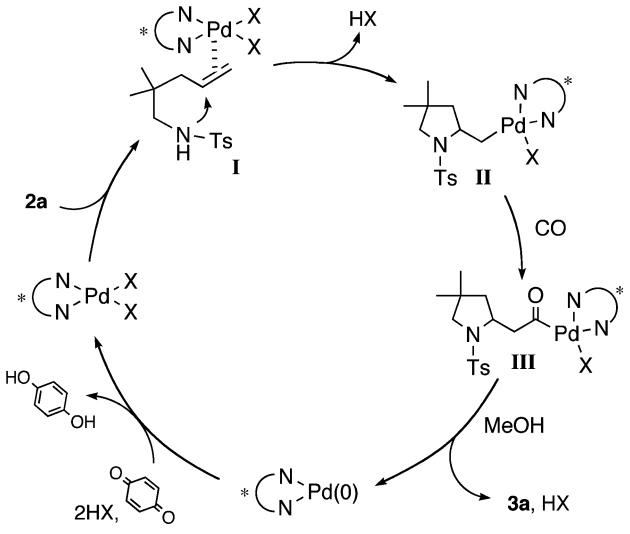
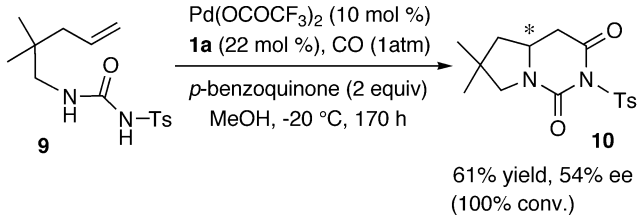


Figure 2.



Scheme 2. Plausible mechanism of intramolecular amino-carbonylation of alkenyl tosylamide **2a**.



Scheme 3. Intramolecular aminocarbonylation of alkenyl urea **9**.

reaction was completed in only 30 min to give **3a** in 70% yield, and with lower enantioselectivity (20% ee) along with the appearance of Pd black, which might indicate dissociation of the ligand from Pd under a carbon monoxide atmosphere. In the use of 10 mol% of Pd(OCOCF$_3$)$_2$ with 22 mol% of **1a** (Pd:**1a** = 1:2.2), the stability of Pd was apparently increased and product **3a** was obtained with a higher enantioselectivity (31% ee), although the reaction rate became slower (Table 2, entry 1). From these results, the 1:2 complex of Pd(OCOCF$_3$)$_2$ and **1a** might exist as a pre-catalyst and/or the excess of **1a** might prevent the formation of an undesired species that gives products with low enantioselectivity.

To examine the generality of the present reaction as well as to develop synthetic methods for other enantioenriched nitrogen containing heterocyclic compounds, we are interested in the use of alkenyl urea **9** as a substrate.[5c] In this type of reaction, interesting optically active bicyclic compounds, including two nitrogen atoms, are prepared in one step. Pd(II)–**1a** catalyst gave the bicyclic 5,6-dihydrouracil derivative **10** as a single product in 54% ee (Scheme 3).[13] Product **10** would be derived by intramolecular nucleophilic attack of the tosylamide group instead of methanol toward acylpalladium intermediate.

In summary, we have developed an enantioselective intramolecular aminocarbonylation of alkenyl amine derivatives catalyzed by Pd(II) with chiral SPRIXs. This is the first report of an enantioselective aminocarbonylation. We are currently attempting to improve asymmetric catalysts for this reaction and clarify active catalytic species.

Acknowledgements

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.S. and M.A.A. appreciate Research Fellowships from the Japan Society for the Promotion of Science (JSPS) for Young Scientists. We also thank the technical staff at the Materials Analysis Center of ISIR.

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6. We tested the effects of several palladium salts in the reaction of **2a**. Combinations of **1a** and palladium salts other than $Pd(OCOCF_3)_2$ (e.g. $PdCl_2$, $Pd(CH_3CN)_2Cl_2$, $Pd(OAc)_2$, $[Pd(CH_3CN)_4](BF_4)_2$, and $Pd(acac)_2$) resulted in low reactivity. Among the solvents examined, MeOH gave the best result. The other solvents (DMSO, DMF, CH_3CN, and CH_2Cl_2) with 6 equiv. of MeOH to substrate were less effective.
7. Typical procedure: A solution of **1a** (22 μmol) and $Pd(OCOCF_3)_2$ (10 μmol) in 0.5 mL of methanol was stirred at rt for 2 h. To the solution, *p*-benzoquinone (0.2 mmol) was added, and the apparatus was purged with carbon monoxide by pumping–filling via a three-way stopcock. The substrate **2a** (0.1 mmol) was added to the stirred mixture at the same temperature and the entire mixture was stirred for 3.5 h. After the usual treatments, the crude mixture was purified by column chromatography on silica-gel to give an 80% yield of the β-amino acid derivative **3a**. Optical purity was determined by HPLC analysis using a chiral stationary phase column (DAICEL CHIRALPAK AS) with hexane-*i*PrOH as eluent.
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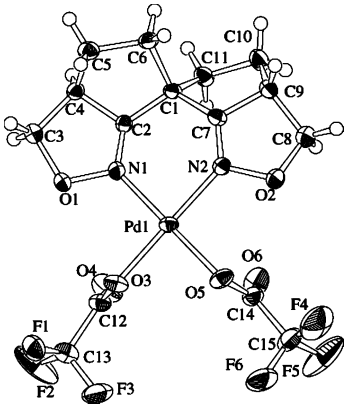
11. The use of 4 equiv. of *p*-benzoquinone smoothly promoted the reaction at low temperature.
12. $Pd(OCOCF_3)_2$ and **1a** formed single crystals, which were shown to be the 1:1 complex. Crystal data: monoclinic; space group $P2_1/c$; $a=9.418(3)$, $b=15.452(7)$, $c=12.826(6)$ Å; $V=1829(1)$ Å^3, $Z=4$; MoKα radiation (−75°C); $R=0.046$, $Rw=0.075$.



13. Compound **10**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.16 (s, 6H), 1.42 (dd, $J=9.7$ and 12.7 Hz, 1H), 2.01 (dd, $J=6.2$ and 12.7 Hz, 1H), 2.35 (dd, $J=12.3$ and 17.6 Hz, 1H), 2.43 (s, 3H), 2.92 (dd, $J=3.5$ and 17.6 Hz, 1H), 3.18 (d, $J=11.2$ Hz, 1H), 3.41 (d, $J=11.2$ Hz, 1H), 4.03–4.14 (m, 1H), 7.33 (d, $J=8.6$ Hz, 2H), 8.18 (d, $J=8.6$ Hz, 2H). ^{13}C NMR (67.7 MHz, $CDCl_3$): δ 21.8, 26.5, 26.6, 37.6, 41.2, 46.2, 51.1, 58.1, 129.1, 129.2, 135.2, 145.3, 147.6, 167.6. Conversion yield was determined by ^{1}H NMR. Optical purity was determined by HPLC analysis using a chiral stationary phase column (DAICEL CHIRALPAK AS) with hexane–*i*PrOH as eluent.