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Palladium-Catalyzed Asymmetric Decarboxylative Lactamization of γ-Methylidene-δ-valerolactones with Isocyanates: Conversion of Racemic Lactones to Enantioenriched Lactams

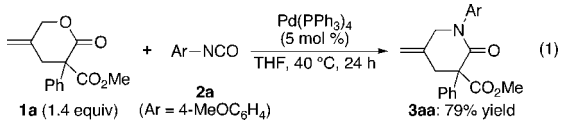
Ryo Shintani,* Soyoung Park, Fumitaka Shirozu, Masataka Murakami, and Tamio Hayashi*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

Received September 30, 2008; E-mail: shintani@kuchem.kyoto-u.ac.jp; thayashi@kuchem.kyoto-u.ac.jp

2-Piperidones having a stereocenter at the 3-position constitute a useful class of compounds,[1] and asymmetric construction of these compounds is therefore an important objective. Although various methods are available to this end, most of them rely on the use of a stoichiometric amount of enantiopure chiral reagents.[2] In contrast, only a few catalytic enantioselective routes to these compounds are known to date, many of which are for the synthesis of 3-monosubstituted 2-piperidones.[3] In fact, successful examples of the catalytic asymmetric construction of 3,3-disubstituted 2-piperidones are very limited.[4] In this Communication, we describe the development of a palladium-catalyzed asymmetric decarboxylative reaction of γ-methylidene-δ-valerolactones[5] with isocyanates,[6] effectively converting racemic lactones to 3,3-disubstituted 2-piperidones with high enantioselectivity.

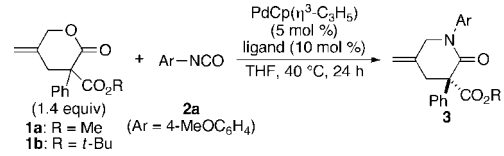
Initially, we conducted a reaction of γ-methylidene-δ-valerolactone **1a** (1.4 equiv) with 4-methoxyphenyl isocyanate (**2a**) in the presence of 5 mol % of $Pd(PPh_3)_4$ as a catalyst in THF at 40 °C (eq 1). The reaction proceeded smoothly to give the expected 3,3-disubstituted 2-piperidone **3aa** in 79% yield. Having established the catalytic formation of **3aa**, we turned our attention to asymmetric catalysis. Unfortunately, the reaction was shut down with (*S*)-MeO-mop,[7] a chiral monophosphine ligand (Table 1, entry 1). By changing the ligand to (*S*)-binap,[8] a chiral bisphosphine ligand, moderate yield of **3aa** was achieved with low enantioselectivity (49% yield, 29% ee; entry 2). In contrast, the use of chiral phosphoramidite ligand (*S*,*R*,*R*)-**4a**[9,10] or its diastereomer (*S*,*S*,*S*)-**4a**[9] gave the desired product in high yield (84−95% yield) with somewhat higher enantioselectivity (51% ee and 57% ee, respectively; entries 3 and 4). The change of methyl ester of lactone **1a** to *tert*-butyl ester (**1b**) improved the enantioselectivity to 68% ee with ligand (*S*,*R*,*R*)-**4a** (entry 5) and to 76% ee with ligand (*S*,*S*,*S*)-**4a** (entry 6). We subsequently identified that higher enantioselectivity for **3ba** can be achieved by employing Alexakis phosphoramidite (*S*,*S*,*S*)-**4b**[11] as the ligand (88% ee; entry 7).



(1)

In the presence of ligand (*S*,*S*,*S*)-**4b**, the amount of lactone **1b** can be reduced to 1.2 equiv and higher enantioselectivity can be realized by conducting the reaction at 20 °C, giving **3ba** in 88% yield with 93% ee (Table 2, entry 1). Several other aryl isocyanates, such as **2b**−**2d**, can also be used for the synthesis of lactams **3** with **1b** in high yield with similarly high stereoselectivity (83−93% ee; entries 2−4). Interestingly, the use of alkyl isocyanates, on the other hand, selectively leads to the formation of azaspiro[2.4]heptanones **5** (eq 2).[5b,12] With respect to the substituent on lactones **1**, various aryl and heteroaryl groups can be tolerated to give the corresponding products **3** with high enantioselectivity (87−96% ee; entries 5−10). In addition, alkyl-substituted lactone **1i** also undergoes the decar-

Table 1. Palladium-Catalyzed Asymmetric Reaction of **1** with **2a**: Effect of Ligands and Ester Groups on **1**



entry	1	product	ligand	yield (%)[a]	ee (%)[b]
1	**1a**	**3aa**	(*S*)-MeO-mop	<2	−
2[c]	**1a**	**3aa**	(*S*)-binap	49	29
3	**1a**	**3aa**	(*S*,*R*,*R*)-**4a**	84	51
4	**1a**	**3aa**	(*S*,*S*,*S*)-**4a**	95	57
5	**1b**	**3ba**	(*S*,*R*,*R*)-**4a**	70	68
6	**1b**	**3ba**	(*S*,*S*,*S*)-**4a**	88	76
7	**1b**	**3ba**	(*S*,*S*,*S*)-**4b**	87	88

[a] Determined by ^{1}H NMR against an internal standard (3,5-dimethylphenol). [b] Determined by chiral HPLC on a Chiralpak AD-H with hexane/2-propanol = 90/10. [c] 5 mol % of ligand was used.

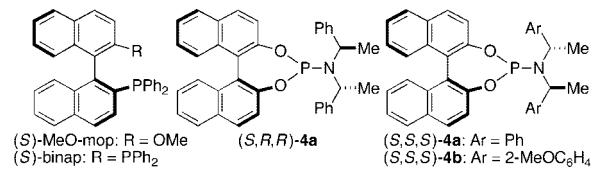
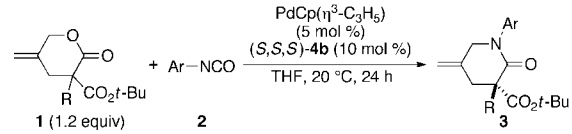


Table 2. Palladium-Catalyzed Asymmetric Reaction of **1** with **2**: Scope



entry	1 (R)	2 (Ar)	product	yield (%)[a]	ee (%)[b]
1	**1b** (Ph)	**2a** (4-$MeOC_6H_4$)	**3ba**	88	93
2	**1b**	**2b** (4-PhC_6H_4)	**3bb**	80	91
3[c]	**1b**	**2c** (4-ClC_6H_4)	**3bc**	79	83
4	**1b**	**2d** (3,5-$(MeO)_2C_6H_3$)	**3bd**	73	93
5	**1c** (4-$MeOC_6H_4$)	**2a**	**3ca**	85	90
6	**1d** (4-MeC_6H_4)	**2a**	**3da**	82	91
7	**1e** (3-MeC_6H_4)	**2a**	**3ea**	79	87
8	**1f** (2-naphthyl)	**2a**	**3fa**	93	87
9[d]	**1g** (3-thienyl)	**2a**	**3ga**	86	96
10[e]	**1h** (3-furyl)	**2a**	**3ha**	75	94
11[c,d,f]	**1i** (Bn)	**2a**	**3ia**	51	74

[a] Isolated yield. [b] Determined by chiral HPLC with hexane/2-propanol. [c] The reaction was conducted at 40 °C. [d] Run using 2.0 equiv of **1**. [e] Run using 4.0 equiv of **1**. [f] Ligand (*S*,*S*,*S*)-**4a** was used.

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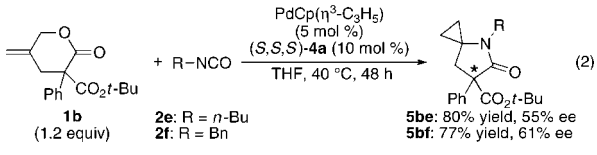
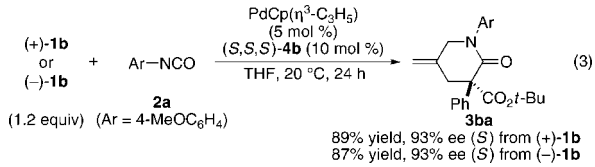
boxylative reaction, albeit with somewhat lower efficiency (51% yield, 74% ee; entry 11). The absolute configuration of compound **3bc** (entry 3) was determined to be (*S*) by X-ray crystallographic analysis after recrystallization from Et_2O.[13]

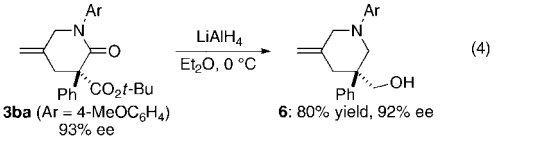
It is worth noting that, during the course of the reaction of **1b** with **2a**, the ee of remaining **1b** is less than 15% ee and the ee of product **3ba** stays constant (93% ee (*S*)). In addition, when enantiopure (+)-**1b** or (−)-**1b** is employed, high yield of **3ba** with 93% ee (*S*) was obtained in each case (eq 3). These results indicate that no effective kinetic resolution of (±)-**1** occurs during catalysis and the stereochemical outcome of **3** is solely controlled by the chirality of Pd/(*S*,*S*,*S*)-**4b** catalyst.





A reaction pathway of the present catalysis with aryl isocyanates can therefore be proposed as shown in Figure 1. Thus, both enantiomers of **1** undergo oxidative addition to palladium(0) almost nonselectively, and the successive decarboxylation[14,15] destroys their original stereochemical information, giving identical 1,4-zwitterionic species **A**. Considering the observed high stereoselectivity, the structure of this intermediate is presumably highly organized, and structure **A′** with its *si* face effectively blocked by the phosphoramidite ligand seems plausible.[16] Stereoselective carbon−carbon bond formation with **2** at the *re* face then gives intermediate **B**, ring-closure of which takes place through a nucleophilic attack of the nitrogen atom to the π-allylpalladium moiety,[17] leading to enantioenriched lactam **3** with regeneration of palladium(0).

We have also begun to explore further derivatizations of enantioenriched lactams **3** obtained in these reactions. For example, compound **3ba** is smoothly converted to piperidine-based aminoalcohol **6** by reducing it with $LiAlH_4$ at 0 °C (eq 4).



In summary, we have developed a palladium-catalyzed asymmetric decarboxylative lactamization of racemic γ-methylidene-δ-valerolactones with isocyanates to give enantioenriched 3,3-disubstituted 2-piperidones. By tuning the ester group on **1** and the substituents of phosphoramidite ligand, high enantioselectivity has been achieved for various substrate combinations.

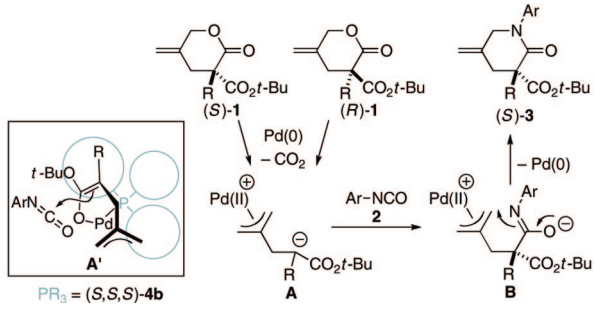


Figure 1. Proposed reaction pathway for the palladium-catalyzed asymmetric decarboxylative lactamization of (±)-**1** with **2**.

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Supporting Information Available: Experimental procedures and compound characterization data and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Formation of **5** occurs through the central carbon attack by nitrogen in intermediate **B** when alkyl isocyanates are used. The origin of this selectivity is not clear at this stage and will be investigated in the future.

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