Communication

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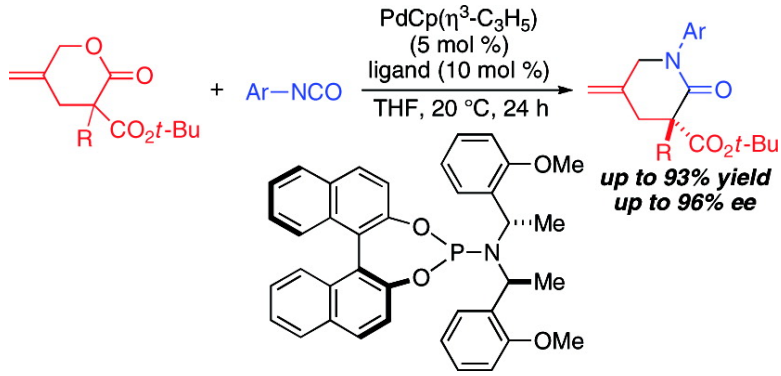
J. Am. Chem. Soc., **2008**, 130 (48), 16174-16175 • DOI: 10.1021/ja807662b • Publication Date (Web): 11 November 2008



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

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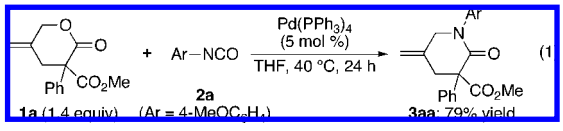
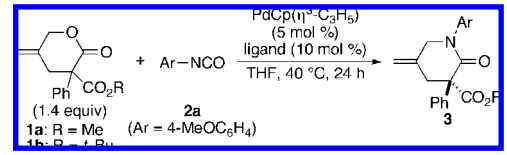
2-Piperidones having a stereocenter at the 3-position constitute a useful class of compounds,[1] and asymmetric construction of these compounds is therefore an important objective. Although various methods are available to this end, most of them rely on the use of a stoichiometric amount of enantiopure 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).



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

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.

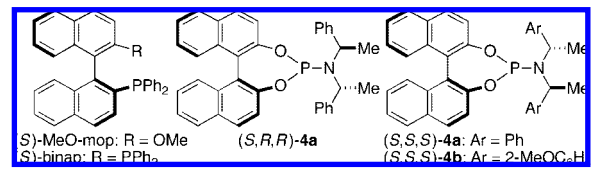
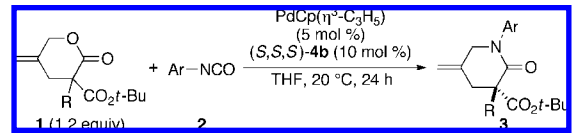


Table 2. Palladium-Catalyzed Asymmetric Reaction of **1** with **2**: Scope



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

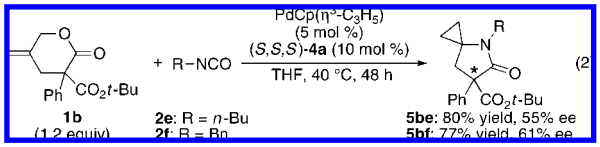
[a] Isolated yield. [b] Determined by chiral HPLC with hexane/2-propanol. [c] The reaction was conducted at 40 °C. [d] Run using 2.0 equiv of **1**. [e] Run using 4.0 equiv of **1**. [f] Ligand (*S*,*S*,*S*)-**4a** was used.

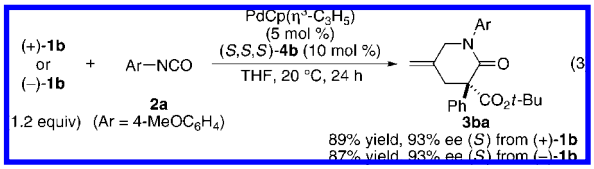
products **3** with high enantioselectivity (87−96% ee; entries 5−10). In addition, alkyl-substituted lactone **1i** also undergoes the decar-

10.1021/ja807662b CCC: $40.75

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]

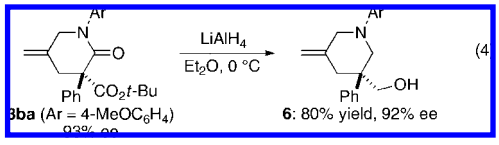
It is worth noting that, during the course of the reaction of **1b** with **2a**, the ee of remaining **1b** is less than 15% ee and the ee of product **3ba** stays constant (93% ee (*S*)). In addition, when enantiopure (+)-**1b** or (−)-**1b** is employed, high yield of **3ba** with 93% ee (*S*) was 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.

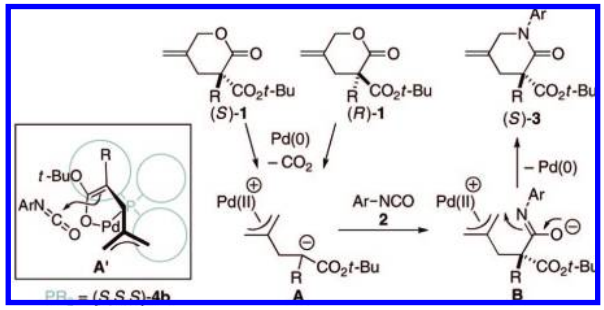


Figure 1. Proposed reaction pathway for the palladium-catalyzed asymmetric decarboxylative lactamization of (±)-**1** with **2**.

Acknowledgment. Support has been provided in part by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science and Technology, Japan (the Global COE Program "Integrated Materials Science" on Kyoto University), and in part by the Sumitomo Foundation.

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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