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Palladium-catalyzed asymmetric synthesis of 2-pyrrolidinones with a quaternary carbon stereocenter†

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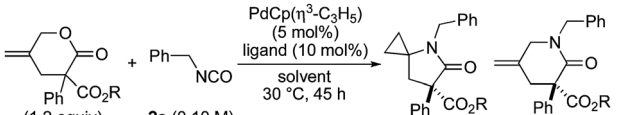
A palladium-catalyzed asymmetric synthesis of 2-pyrrolidinones with a quaternary stereocenter at the 3-position has been achieved by the reaction of γ-methylidene-δ-valerolactones with alkyl isocyanates. High enantioselectivity has been realized by employing a newly synthesized chiral phosphoramidite ligand.

Enantioenriched 3-substituted 2-pyrrolidinones constitute a useful and biologically relevant class of compounds,[1] many of which are synthesized using stoichiometric amounts of chiral reagents,[1,2] and only a few catalytic enantioselective methods have been known to date for the synthesis of these compounds.[3] In this context, herein we describe a palladium-catalyzed enantioselective synthesis of 2-pyrrolidinones with a quaternary stereocenter at the 3-position from γ-methylidene-δ-valerolactones and alkyl isocyanates through the nucleophilic ring-closure at the central carbon of a π-allylpalladium intermediate,[4,5] whose modes of stoichiometric and catalytic reactions have been both explored in the past few decades since the first report by Hegedus and coworkers.[5a]

With regard to catalytic asymmetric preparation of lactams, we previously developed a palladium-catalyzed asymmetric synthesis of 3,3-disubstituted 2-piperidinones by decarboxylative cyclization of γ-methylidene-δ-valerolactones with aryl isocyanates with high enantioselectivity.[4a] We also described that the use of alkyl isocyanates instead of aryl isocyanates changed the course of the reaction presumably due to the more electron-rich nature of the nitrogen atom,[4b] leading to the formation of 3,3-disubstituted 2-pyrrolidinones with a spirocyclopropyl moiety.[4,6] On the basis of these findings, we decided to focus on the development of enantioselective synthesis of 2-pyrrolidinones and began our study by conducting a reaction of γ-methylidene-δ-valerolactone **1a** with benzyl isocyanate (**2a**) in THF at 30 °C in the presence of a palladium catalyst coordinated with chiral phosphoramidite (*S*,*S*,*S*)-**L1**,[7] a highly effective ligand for the related asymmetric synthesis of 2-piperidinones.[4a] Under these conditions, 2-pyrrolidinone **3aa** was obtained as the major product over 2-piperidinone **4aa** as expected, but the yield and ee were only moderate (42% ee; Table 1, entry 1). By changing the ligand to (*S*,*S*,*S*)-**L2**,[8] significantly higher yield and ee of **3aa** were realized (entry 2),[9] and further improvement of enantioselectivity was achieved by conducting the reaction in toluene instead of in THF (67% ee; entry 3). We subsequently found that 2,5-diphenylpyrrolidine-based phosphoramidite ligand (*S*,*S*,*S*)-**L3**[10] gave **3aa** with 81% ee (entry 4). In the hope of further enhancement of enantioselectivity, we newly synthesized ligand (*S*,*S*,*S*)-**L4** having 3,5-dimethylphenyl groups on the pyrrolidine ring and it turned out that **3aa** could be obtained with as high as 92% ee (entry 5).[11] In comparison, substituting *tert*-butyl ester of lactone **1a** with methyl ester (**1b**) somewhat decreased the enantioselectivity (78% ee; entry 6).

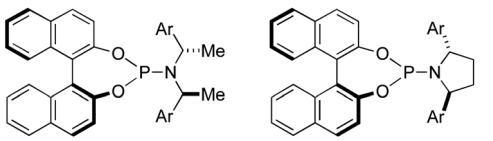
Table 1 Palladium-catalyzed asymmetric decarboxylative cyclization of γ-methylidene-δ-valerolactones **1** with benzyl isocyanate **2a**: optimization



(1.2 equiv) **1a**: R = *t*-Bu, **1b**: R = Me; **2a** (0.10 M); **3**; **4**

Entry	**1**	Ligand	Solvent	Yield[a] (%)	**3**/**4**[b]	ee of **3**[c] (%)
1	**1a**	(*S*,*S*,*S*)-**L1**	THF	35	91/9	42
2	**1a**	(*S*,*S*,*S*)-**L2**	THF	81	95/5	63
3	**1a**	(*S*,*S*,*S*)-**L2**	Toluene	74	93/7	67
4[d]	**1a**	(*S*,*S*,*S*)-**L3**	Toluene	75	90/10	81
5[d]	**1a**	(*S*,*S*,*S*)-**L4**	Toluene	89	90/10	92
6[d]	**1b**	(*S*,*S*,*S*)-**L4**	Toluene	89	92/8	78

[a] Combined isolated yield of **3** and **4**. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC with hexane/2-propanol. [d] The reaction was conducted for 12 h.



(*S*,*S*,*S*)-**L1**: Ar = 2-MeOC$_6$H$_4$
(*S*,*S*,*S*)-**L2**: Ar = Ph

(*S*,*S*,*S*)-**L3**: Ar = Ph
(*S*,*S*,*S*)-**L4**: Ar = 3,5-Me$_2$C$_6$H$_3$

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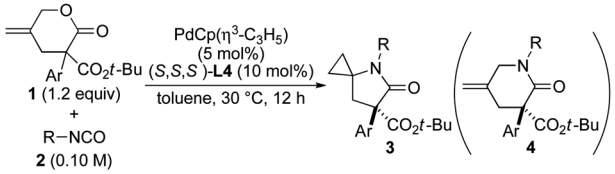
Table 2 Palladium-catalyzed asymmetric decarboxylative cyclization of γ-methylidene-δ-valerolactones **1** with alkyl isocyanates **2**: scope



Entry	**1** (Ar)	**2** (R)	Yield[a] (%)	**3**/**4**[b]	ee of **3**[c] (%)
1	**1a** (Ph)	**2b** (4-MeOC$_6$H$_4$CH$_2$)	86	88/12	93
2	**1a**	**2c** (4-MeC$_6$H$_4$CH$_2$)	92	89/11	92
3	**1a**	**2d** (4-BrC$_6$H$_4$CH$_2$)	76	93/7	92
4[d]	**1a**	**2e** (2-furylmethyl)	82	90/10	93
5[e]	**1a**	**2f** (ClCH$_2$CH$_2$)	77	91/9	90
6[d]	**1a**	**2g** (EtO$_2$CCH$_2$CH$_2$)	72	>99/1	92
7	**1c** (4-MeOC$_6$H$_4$)	**2a** (PhCH$_2$)	81	89/11	93
8	**1d** (4-MeC$_6$H$_4$)	**2a**	83	89/11	93
9	**1e** (4-PhC$_6$H$_4$)	**2a**	93	92/8	93
10	**1f** (4-FC$_6$H$_4$)	**2a**	94	90/10	93
11	**1g** (3,4-(OCH$_2$O)C$_6$H$_3$)	**2a**	85	91/9	92
12	**1h** (3-MeC$_6$H$_4$)	**2a**	83	90/10	92
13[f]	**1i** (2-MeOC$_6$H$_4$)	**2a**	53	97/3	83

[a] Combined isolated yield of **3** and **4**. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC with hexane/2-propanol. [d] The reaction was conducted with 1.6 equiv. of **1a**. [e] The reaction was conducted for 45 h. [f] The reaction was conducted with 2.0 equiv. of **1i**.

Under the conditions of using ligand (*S*,*S*,*S*)-**L4**, several substituted benzyl isocyanates undergo the reaction with lactone **1a** to give 2-pyrrolidinones **3** selectively over 2-piperidinones **4** with high enantioselectivity (92–93% ee; Table 2, entries 1–3). Other functionalized alkyl isocyanates such as **2e–2g** also provide products **3** with high efficiency (90–93% ee; entries 4–6). With respect to the α-substituent of γ-methylidene-δ-valerolactones **1**, various *para*- or *meta*-substituted aryl groups are well tolerated, selectively giving 2-pyrrolidinones **2** in the reaction with benzyl isocyanate with uniformly high ee (92–93% ee; entries 7–12). The use of lactones **1** having *ortho*-substituted aryl groups results in somewhat lower yield and ee, but the selectivity toward 2-pyrrolidinones **2** stays high (entry 13). Unfortunately, however, lactones with α-alkyl substituents are not suitable substrates under the present conditions. The absolute configuration of product **3af** (entry 5) was determined to be *S* by X-ray crystallographic analysis after recrystallization from Et$_2$O (Fig. 1).[12]

The newly developed phosphoramidite ligand (*S*,*S*,*S*)-**L4** was found to be highly effective as well for the synthesis of 3,3-disubstituted 2-piperidinones **4** by using aryl isocyanates as the reaction partner. For example, reaction of lactone **1a** with 4-methoxyphenyl isocyanate (**2h**) selectively provides 2-piperidinone **4ah** in high yield with 94% ee (Table 3, entry 1). Several other combinations of lactones **1** and aryl isocyanates **2** also led to compounds **4** with high selectivity as summarized in entries 2–5. It is worth noting that these results using ligand (*S*,*S*,*S*)-**L4** compare favorably with our previous results with ligand (*S*,*S*,*S*)-**L1**.[4a]

Enantioenriched 2-pyrrolidinones **3** obtained in the present catalysis can be used for further derivatizations. For example, compound **3aa** (92% ee) is converted to pyrrolidine-based aminoalcohol **5** in 87% yield with 91% ee by reducing it with LiAlH$_4$ (eqn (1)). In addition, retro-Michael addition takes

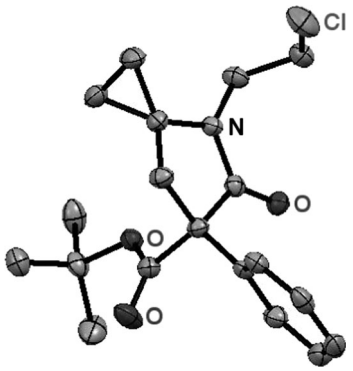
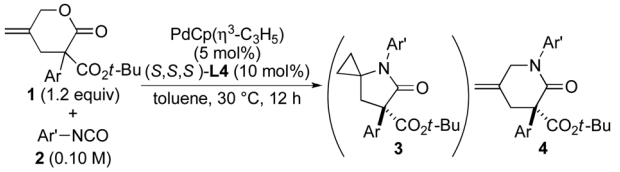


Fig. 1 X-ray crystal structure of (*S*)-**3af** with thermal ellipsoids drawn at the 50% probability level (Flack parameter = 0.040(15); hydrogen atoms are omitted for clarity).

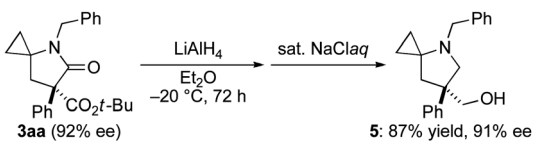
Table 3 Palladium-catalyzed asymmetric decarboxylative cyclization of γ-methylidene-δ-valerolactones **1** with aryl isocyanates **2**: examples



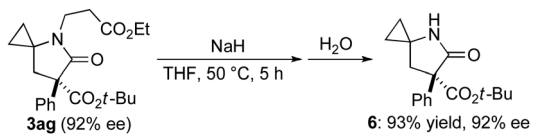
Entry	**1** (Ar)	**2** (Ar′)	Yield[a] (%)	**3**/**4**[b]	ee of **4**[c] (%)
1	**1a** (Ph)	**2h** (4-MeOC$_6$H$_4$)	89	6/94	94
2	**1a**	**2i** (Ph)	89	1/99	94
3	**1a**	**2j** (4-ClC$_6$H$_4$)	95	<1/99	94
4	**1e** (4-PhC$_6$H$_4$)	**2i**	91	1/99	94
5	**1h** (3-MeC$_6$H$_4$)	**2i**	91	1/99	93

[a] Combined isolated yield of **3** and **4**. [b] Determined by ^{1}H NMR. [c] Determined by chiral HPLC with hexane/2-propanol.

place for compound **3ag** (92% ee) in the presence of NaH to give *N*-deprotected product **6** with high efficiency (93% yield, 92% ee; eqn (2)).



(1)



(2)

In summary, we have developed a palladium-catalyzed asymmetric synthesis of 2-pyrrolidinones with a quaternary stereocenter at the 3-position from γ-methylidene-δ-valerolactones and alkyl isocyanates. High enantioselectivity has been achieved by employing a newly synthesized chiral phosphoramidite ligand ((*S*,*S*,*S*)-**L4**), and this ligand has also turned out to be highly effective for the enantioselective synthesis of 3,3-disubstituted 2-piperidinones by employing aryl isocyanates as the reaction partner.

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12 CCDC 892796. See also ESI†.