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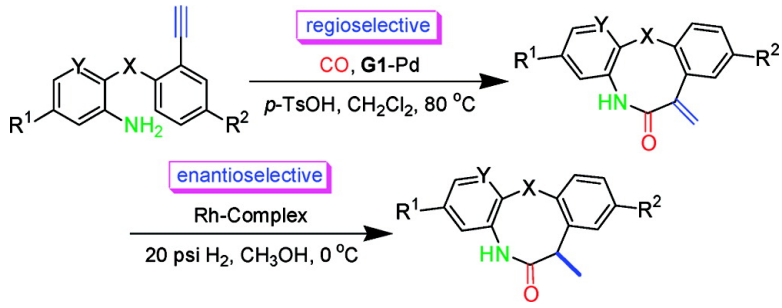

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Sequence of Intramolecular Carbonylation and Asymmetric Hydrogenation Reactions: Highly Regio- and Enantioselective Synthesis of Medium Ring Tricyclic Lactams

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Abstract: The intramolecular cyclocarbonylation reaction with palladium-complexed dendrimers on silica is a very effective method for the regioselective synthesis of methylene 8-, 9-, and 10-membered rings. The heterogeneous dendritic catalysts are easily recovered by simple filtration and reused for up to 10 cycles with only a slight loss of activity. Asymmetric hydrogenation of the resulting unsaturated heterocycles affords optically active tricyclic lactams in excellent yields and in high enantiomeric excess. This process can tolerate a wide array of functional groups, including halide, ether, nitrile, ketone, and ester. Moreover, the variation of heteroatom on the rings does not have any influence on the efficiency and enantioselectivity of the reaction.

Introduction

Heterocyclic compounds are often encountered in many biologically active natural products as well as drug candidates.[1] For example, dibenzoxazocinone derivatives are non-nucleoside inhibitors of HIV-1 RT, psychotropic, and hypotensive agents.[2] Success has been achieved over the past decades in the construction of cyclic templates by means of transition metal catalysis.[3] Among them, carbonylation reactions represent a convenient and efficient one-step method to prepare a wide variety of ring systems.[4] On the other hand, dendrimers have drawn increasing attention due to their valuable applications in medicine, nanoscience, and catalysis.[5] As an interface between homogeneous and heterogeneous catalysts,[6] the introduction of metallodendrimers into the carbonylation reactions is particularly attractive from a sustainability point of view. Recently, we found that dendrimer complexes are very effective catalysts for the cyclocarbonylation reactions to give medium and large ring fused heterocycles.[7]

Typically for chiral drugs, only one of the two enantiomers is responsible for pharmacological activity, while the other is either inactive or may cause side effects. In this context, an innovative strategy leading to the enantioselective synthesis of dibenzoxazocinone derivatives is of considerable merit. Asymmetric hydrogenation reactions provide a powerful approach to the preparation of optically active organic molecules.[8] Therefore, it is envisioned that the intramolecular aminocarbonylation of

(1) (a) Katritzky, A. R.; Pozharskii, A. F. *Handbook of Heterocyclic Chemistry*, 2nd ed.; Pergamon Press: New York, 2000. (b) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 4th ed.; Blackwell: Oxford, 2000. (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238. (d) Wang, Y.; Tennyson, R. L.; Romo, D. *Heterocycles* **2004**, *64*, 605–658. (e) Krakowiak, K. E.; Izatt, R. M.; Bradshaw, J. S. *J. Heterocycl. Chem.* **2001**, *38*, 1239–1248. (f) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131–9166.

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(3) (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: New York, 2000. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873–2920. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2309. (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (f) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079–3160.

(4) (a) Church, T. L.; Byrne, C. M.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2007**, *129*, 8156–8162. (b) Church, T. L.; Getzler, Y. D. Y. L.; Byrne, C. M.; Coates, G. W. *Chem. Commun.* **2007**, 657–674. (c) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vol. 2. (d) El Ali, B.; Alper, H. *Synlett* **2000**, 161–171. (e) Khumtaveeporn, K.; Alper, H. *Acc. Chem. Res.* **1995**, *28*, 414–422. (f) Colquhoun, H. M.; Thompson, D. J.; Twigg, M. V. *Carbonylation: Direct Synthesis of Carbonyl Compounds*; Plenum Press: New York, 1991.

(5) (a) Martin, H.; Kinns, H.; Mitchell, N.; Astier, Y.; Madathil, R.; Howorka, S. *J. Am. Chem. Soc.* **2007**, *129*, 9640–9649. (b) Veprek, P.; Hajduch, M.; Dzubak, P.; Kuklik, R.; Polakova, J.; Bezouska, K. *J. Med. Chem.* **2006**, *49*, 6400–6407. (c) Campidelli, S.; Sooambar, C.; Lozano Diz, E.; Ehli, C.; Guldi, D. M.; Prato, M. *J. Am. Chem. Soc.* **2006**, *128*, 12544–12552. (d) Ouali, A.; Laurent, R.; Caminade, A.-M.; Majoral, J.-P.; Taillefer, M. *J. Am. Chem. Soc.* **2006**, *128*, 15990–15991. (e) Nlate, S.; Astruc, D.; Neumann, R. *Adv. Synth. Catal.* **2004**, *346*, 1445–1448. (f) Plault, L.; Hauseler, A.; Nlate, S.; Astruc, D.; Ruiz, J.; Gatard, S.; Neumann, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 2924–2928. (g) Lu, S.-M.; Alper, H. *J. Org. Chem.* **2004**, *69*, 3558–3561. (h) Arya, P.; Rao, N. V.; Singkhonrat, J.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Org. Chem.* **2000**, *65*, 1881–1886.

(6) (a) Andres, R.; De Jesus, E.; Flores, J. C. *New J. Chem.* **2007**, *31*, 1161–1191. (b) Mery, D.; Astruc, D. *Coord. Chem. Rev.* **2006**, *250*, 1965–1979. (c) Helms, B.; Frechet, J. M. J. *Adv. Synth. Catal.* **2006**, *348*, 1125–1148. (d) Liang, C.; Frechet, J. M. J. *Prog. Polym. Sci.* **2005**, *30*, 385–402. (e) Astruc, D.; Heuze, K.; Gatard, S.; Mery, D.; Nlate, S.; Plault, L. *Adv. Synth. Catal.* **2005**, *347*, 329–338. (f) Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991–3023. (g) Lu, S.-M.; Alper, H. *J. Am. Chem. Soc.* **2003**, *125*, 13126–13131. (h) Arya, P.; Panda, G.; Rao, N. V.; Alper, H.; Bourque, S. C.; Manzer, L. E. *J. Am. Soc. Chem.* **2001**, *123*, 2889–2890.

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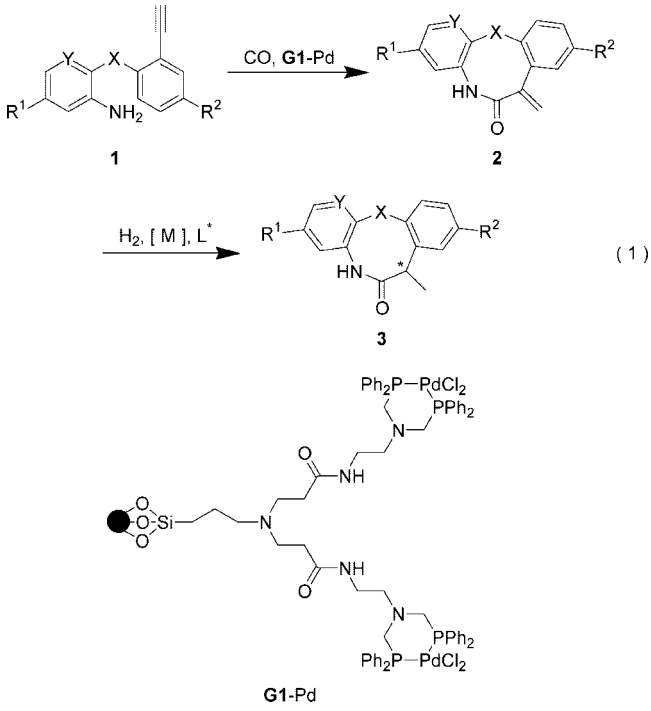
alkynes **1** with **G1**-Pd[7,9] as the catalyst, followed by asymmetric hydrogenation of the resulting prochiral heterocyles **2**, could give enantiomerically pure tricyclic lactams **3** (eq 1). We now report the interesting results obtained from this investigation.



Results and Discussion

Intramolecular Cyclocarbonylation Reactions: Regioselective Synthesis of Methylene Eight-Membered Ring Tricyclic Heterocycles. The intramolecular cyclocarbonylation of various aminoalkynes was used for the synthesis of methylene eight-membered ring tricyclic heterocycles. Treatment of substituted 2-(2-ethynylphenoxy)anilines **1**[9] in anhydrous dichloromethane with 100 psi of carbon monoxide in the presence of **G1**-Pd and *p*-toluenesulfonic acid at 80 °C for 22 h afforded the corresponding dibenzoxazocinones **2** in 89−99% isolated yields, and the results are presented in Table 1. The heterogeneous dendritic catalyst facilitated excellent substrate reactivity, irrespective of the position and the nature of substituents on the aromatic rings. *Furthermore, this process was highly regioselective and gave exclusively the exo-methylene products. In all cases, no endo isomers were detected.* For example, aminoalkyne **1a** was converted smoothly to the desired eight-membered ring **2a** in 99% yield (Table 1, entry 1). The structure of the product was unambiguously confirmed by X-ray diffraction (Figure 1). The cyclocarbonylation of substrates **1b**−**1e** bearing electron-donating substituents such as methyl and methoxy groups worked very well, affording the corresponding methylene tricyclic heterocycles **2b**−**2e** in excellent yields (Table 1, entries 2−5). Electron-withdrawing substituents including chloro, trifluoromethyl, cyano, acetyl, and methoxycarbonyl groups **1f**−**1j** were also tolerated in this reaction (Table 1, entries 6−10), although a slightly lower yield was observed in the case of **1h**

Table 1. Synthesis of Methylene Eight-Membered Ring Tricyclic Heterocycles by **G1**-Pd Catalyzed Intramolecular Cyclocarbonylation of Substituted 2-(2-Ethynylphenoxy)anilines[a]

Entry	Substrate	Product	Yield[b]
1	**1a**	**2a**	99%
2	**1b**	**2b**	97%
3	**1c**	**2c**	98%
4	**1d**	**2d**	97%
5	**1e**	**2e**	96%
6	**1f**	**2f**	95%
7	**1g**	**2g**	96%
8	**1h**	**2h**	89%
9	**1i**	**2i**	93%
10	**1j**	**2j**	94%
11	**1k**	**2k**	97%
12	**1l**	**2l**	99%

[a] 1 mmol of **1**, 15 mg of **G1**-Pd, 0.03 mmol of *p*-TsOH, 10 mL of CH_2Cl_2, 100 psi of CO, 80 °C and 22 h. [b] Isolated yield.

(8) (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I. , Ed.; Wiley-VCH: New York, 2000. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobson, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999. (c) Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711–720. (d) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151. (e) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. (f) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998–2007.

(9) See Supporting Information for details.

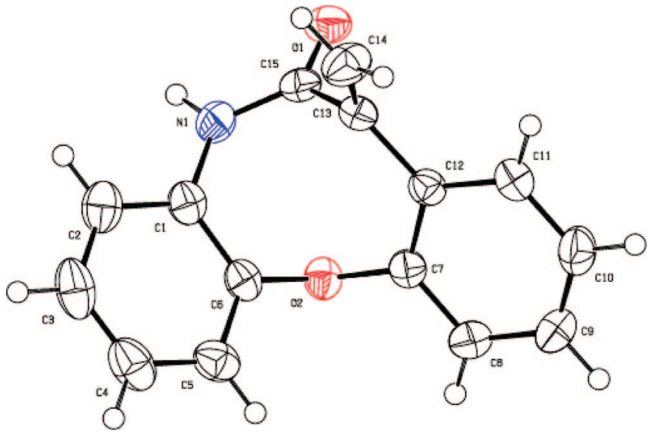
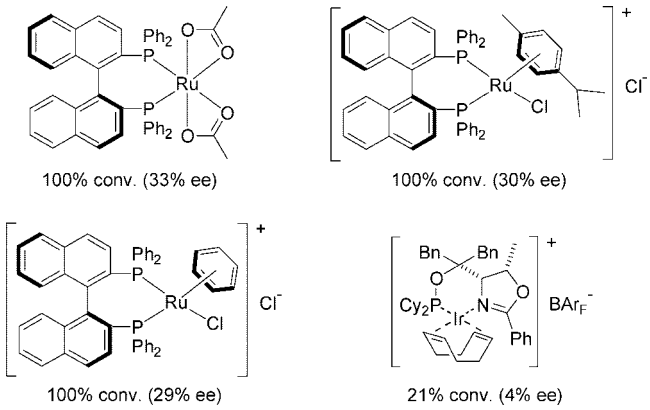


Figure 1. X-ray crystal structure of 7-methylene-5*H*,7*H*-12-oxa-5-aza-dibenzo[*a*,*d*]cycloocten-6-one (**2a**).

Chart 1. Asymmetric Hydrogenation of **2a** Catalyzed by Ruthenium Complexes[a] or Iridium Complex[b]



100% conv. (33% ee) 100% conv. (30% ee)

100% conv. (29% ee) 21% conv. (4% ee)

[a] 1 mmol of **2a**, 0.01 mmol of ruthenium complex, 5 mL of CH_3OH, 1000 psi of H_2, 50 °C and 24 h. [b] 1 mmol of **2a**, 0.02 mmol of iridium complex, 5 mL of CH_2Cl_2, 1000 psi of H_2, rt and 24 h.

Table 2. Asymmetric Hydrogenation of **2a** Catalyzed by $Rh(COD)_2BF_4$ and (*S*,*S*)-BDPP under Different Reaction Conditions[a]

entry	solvent	pressure (psi)	temp (°C)	time (h)	conv (%)[b]	ee (%)[c]
1	MeOH	1000	22	16	100	88
2	EtOH	1000	22	16	100	87
3	THF	1000	22	16	100	85
4	*i*-PrOH	1000	22	16	100	79
5	CH_2Cl_2	1000	22	16	100	79
6	EtOAc	1000	22	16	100	79
7	$CHCl_3$	1000	22	16	100	78
8	Acetone	1000	22	16	100	75
9	Toluene	1000	22	16	0	0
10	Benzene	1000	22	16	0	0
11	MeOH	600	22	16	100	89
12	MeOH	300	22	16	100	90
13	MeOH	100	22	16	100	91
14	MeOH	20	22	16	100	92
15	MeOH	20	50	2	100	72
16	**MeOH**	**20**	**0**	**48**	**100**	**96**

[a] 1 mmol of **2a**, 0.01 mmol of $Rh(COD)_2BF_4$, 0.01 mmol of (*S*,*S*)-BDPP, 5 mL of solvent. [b] Determined by GC and/or ^1H NMR. [c] Determined by chiral HPLC with a Chiralcel OJ-H column.

(Table 1, entry 8). An aminoalkyne **1k** containing a heterocyclic component was subjected to the standard conditions, and a 97% yield of the desired product **2k** was obtained (Table 1, entry 11). By changing the atom connecting the two aromatic rings from oxygen to nitrogen, one can isolate the methylene eight-membered ring **2l** in 99% yield (Table 1, entry 12). It is worth noting that the dendritic catalyst **G1**-Pd could be recovered by simple filtration in air and reused up to the tenth cycle with only a slight loss of activity.[9]

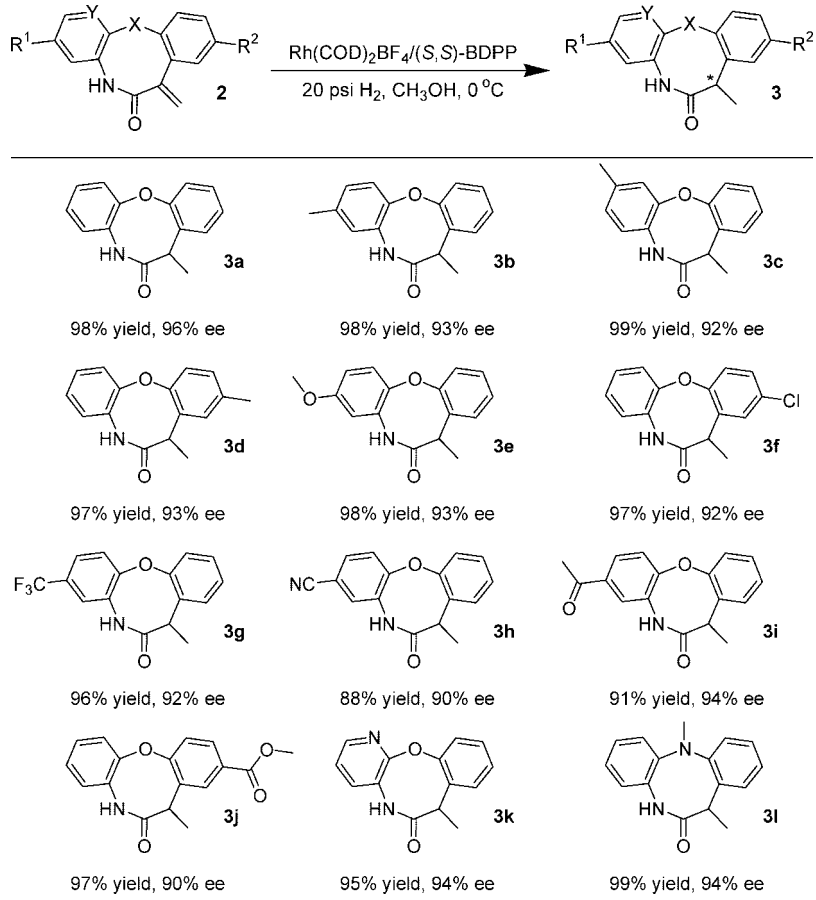
Asymmetric Hydrogenation Reactions: Enantioselective Synthesis of Eight-Membered Ring Tricyclic Lactams. After accomplishing the synthesis of the *exo*-methylene eight-membered rings, we were interested in exploring the asymmetric hydrogenation of the resulting unsaturated heterocycles **2** to hopefully attain the corresponding tricyclic lactams **3** in high enantiomeric excess. Although the enantioselective hydrogenation of acyclic and cyclic enamides has been well documented,[8a,e] there are no examples involving the asymmetric hydrogenation of α,β-unsaturated lactams of this type. A potential problem is the nature of the exocyclic double bond; the inability of this bond to rotate toward the carbonyl oxygen is expected to diminish the efficiency of chelation of such a substrate to the metal atom of a catalyst. Substrate chelation has long been recognized to be an important element in achieving highly enantioselective hydrogenation.[10] Therefore, development of a superior catalytic system for this transformation is a significant challenge. Initial studies focused on screening different transition metals and chiral ligands.[9] It is known that ruthenium complexes (Chart 1) have been applied successfully to the asymmetric hydrogenation of various olefins.[11] Unfortunately, all of them (three ruthenium complexes in Chart 1) exhibited low enantioselectivity for the hydrogenation of **2a** to **3a**. The use of an iridium complex as the catalyst also afforded poor results with 21% yield and 4% ee (Chart 1).

We then turned our attention to rhodium complexes. The combination of $Rh(COD)_2BF_4$ with a wide array of chiral ligands was examined for the asymmetric hydrogenation of **2a** (Supporting Information Table 8).[9] Although BINAP, MonoPhos, DIOP, NorPhos, DuPhos, JosiPhos, and other chiral bidentate and monodentate phosphorus ligands gave unsatisfactory results in terms of the enantiomeric excess of **3a**, we were pleased to observe that (*S*,*S*)-BDPP afforded complete conversion of **2a** to **3a** in 89% ee. Encouraged by these promising results, (*S*,*S*)-BDPP was next used as the ligand for further optimization of the reaction conditions. As can be seen from Table 2, the solvent plays a role in this process. Methanol proved to be the solvent of choice (Table 2, entry 1), but the reaction of **2a** also gave good enantiomeric excesses in ethanol and tetrahydrofuran (Table 2, entries 2 and 3). The employment of other solvents such as *iso*-propanol, dichloromethane, ethyl acetate, chloroform, and acetone afforded **3a** in 79−75% ee (Table 2 entries 4−8). No hydrogenation occurred in toluene and benzene (Table 2, entries 9 and 10). The pressure has a limited impact on this transformation. 89, 90, and 91% ee were obtained under 600, 300, and 100 psi of hydrogen, respectively (Table 2, entries 11−13), while decreasing the pressure to 20 psi resulted in 92% ee (Table 2, entry 14). Temperature is another factor for the successful hydrogenation. When the reaction was run at 50 °C, 2 h were sufficient to achieve full conversion of **2a** but in low enantiomeric excess (Table 2, entry

(10) (a) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106–112. (b) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952–5954.

(11) (a) Noyori, R.; Kitamura, M.; Ohkuma, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356–5362. (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008–2022. (c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350.

Table 3. Enantioselective Synthesis of Eight-Membered Ring Tricyclic Lactams by Rhodium Complex Catalyzed Asymmetric Hydrogenation of **2**[a]



[a] 1 mmol of **2**, 0.01 mmol of $Rh(COD)_2BF_4$, 0.01 mmol of (*S*,*S*)-BDPP, 5 mL of CH_3OH, 20 psi of H_2, 0 °C and 48 h.

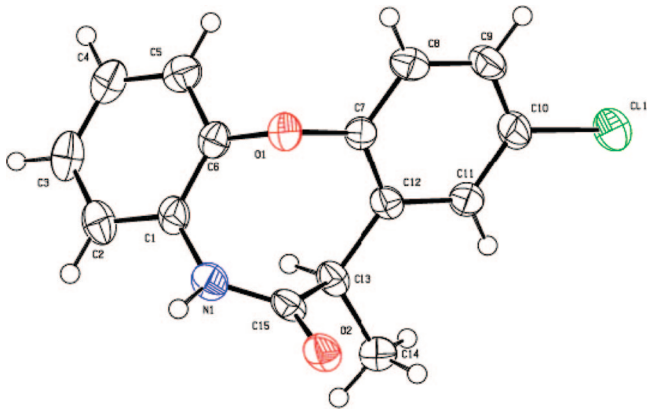


Figure 2. X-ray crystal structure of (*R*)-9-chloro-7-methyl-5*H*,7*H*-12-oxa-5-azadibenzo[*a*,*d*]cycloocten-6-one (**3f**).

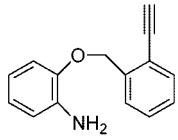
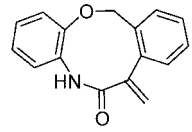
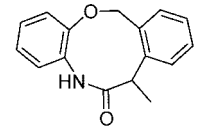
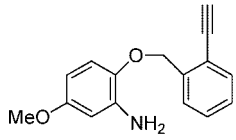
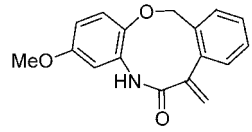
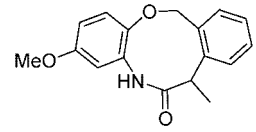
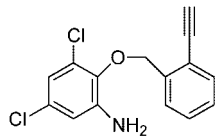
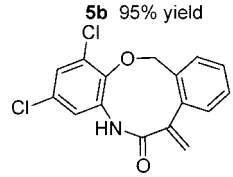
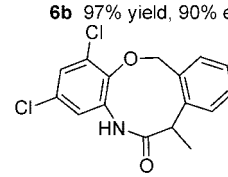
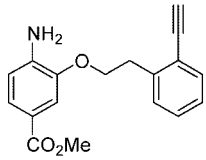
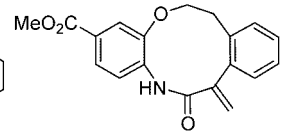
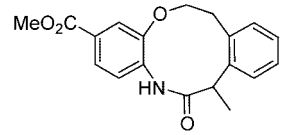
15). Lower temperature had a beneficial effect on the enantioselectivity; performing the hydrogenation of **2a** at 0 °C gave **3a** in 96% ee (Table 2, entry 16). Therefore, the best reaction conditions are 1 mmol of substrate, 0.01 mmol of $Rh(COD)_2BF_4$, and 0.01 mmol of (*S*,*S*)-BDPP in 5 mL of methanol under 20 psi of hydrogen at 0 °C for 48 h.

A variety of methylene tricyclic heterocycles **2a**−**2l** were reacted under the conditions optimized for **2a** to **3a**, and the results are listed in Table 3. The asymmetric hydrogenation of **2**, regardless of whether the substituents on the aromatic rings were electron-donating or electron-withdrawing, afforded the corresponding optically active lactams **3** in 88−99% yields and 90−96% ee. The wide functional group compatibility is a significant advantage for these transformations, as the asymmetric hydrogenation reactions can encompass methyl, chloro, methoxy, trifluoromethyl, cyano, acetyl, and methoxycarbonyl groups. Furthermore, with **2k** as a pyridine-based substrate, the pyridinyl-fused lactam **3k** was obtained in excellent yield and enantiomeric excess. In the case of **2l**, the methylene tricylic heterocyle was reduced to the nitrogen-containing product **3l** in 99% yield and 94% ee. This reaction indicates that variation of the atom connecting the two aromatic rings does not have any influence on the enantioselectivity. The absolute configuration of compound **3f** was determined to be *R* by X-ray crystallographic analysis, as shown in Figure 2.[12]

Intramolecular Cyclocarbonylation and Asymmetric Hydrogenation Reactions: Regio- and Enantioselective Synthesis of Nine- and Ten-Membered Ring Tricyclic Lactams. The sequence of intramolecular cyclocarbonylation and asymmetric hydrogenation reactions were extended to the regio- and enantioselective synthesis of larger ring (9 and 10) tricyclic lactams, and the results are illustrated in Table 4. For instance, aminoalkynes **4a**−**4c**, on reaction with carbon monoxide in the

(12) For the X-ray crystal structure of **3a**, see Supporting Information.

Table 4. Regio- and Enantioselective Synthesis of Nine- and Ten-Membered Ring Tricyclic Lactams by Sequence of Intramolecular Cyclocarbonylation[a] and Asymmetric Hydrogenation[b] Reactions

Substrate	Intermediate	Product
 **4a**	 **5a** 97% yield	 **6a** 88% yield, 92% ee
 **4b**	 **5b** 95% yield	 **6b** 97% yield, 90% ee
 **4c**	 **5c** 96% yield	 **6c** 98% yield, 89% ee
 **4d**	 **5d** 92% yield	 **6d** 96% yield, 85% ee

[a] 1 mmol of **4**, 15 mg of **G1**-Pd, 0.03 mmol of *p*-TsOH, 10 mL of CH_2Cl_2, 100 psi of CO, 80 °C and 22 h. [b] 1 mmol of **5**, 0.01 mmol of $Rh(COD)_2BF_4$, 0.01 mmol of (*S*,*S*)-BDPP, 5 mL of CH_3OH, 20 psi of H_2, 0 °C and 48 h.

presence of **G1**-Pd, regioselectively gave the methylene nine-membered rings **5a**−**5c** in excellent yields. Asymmetric hydrogenation of the resulting unsaturated heterocycles afforded the corresponding products **6a**−**6c** in 88−98% yields and 89−92% ee. Similarly, the ten-membered ring tricyclic lactam **6d** was obtained in excellent yield and high enantiomeric excess from **4d** under the same conditions. These examples further demonstrate the efficiency and versatility of this approach for the construction of optically active medium ring fused heterocycles.

Summary

In conclusion, we have developed an effective method for the highly regio- and enantioselective synthesis of 8-, 9-, and 10-membered ring tricyclic lactams under mild conditions. This protocol is based on a sequential use of carbonylation and hydrogenation chemistry: the intramolecular carbonylation reactions with dendrimer palladium complexes as catalysts for regioselective cyclization, and then the rhodium-catalyzed asymmetric hydrogenation reactions for the formation of optically active fused heterocycles.

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Supporting Information Available: Experimental details, characterization data for all new compounds; Table 5 of recycling and reuse of the dendritic catalyst **G0**-Pd–**G3**-Pd and **G3**(C6)-Pd for the intramolecular cyclocarbonylation of **1a**; Tables 6−9 of optimization of asymmetric hydrogenation reaction conditions for **2a** to **3a**; copies of ^{1}H NMR and ^{13}C NMR spectra for products **2**, **3**, **5**, and **6**; and X-ray crystallographic analyses for **2a**, **3a**, and **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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