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Catalytic Diastereoselective Pauson–Khand Reaction: an Efficient Route to Enantiopure Cyclopenta[*c*]proline Derivatives

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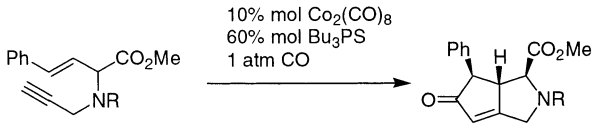
ABSTRACT



Cyclopenta[*c*]proline derivatives were synthesized in a stereocontrolled manner and in good yields via catalytic Pauson–Khand reactions. The starting materials, optically pure enyne amino acid derivatives, can be easily prepared by an alkenylboronic acid-mediated Mannich-type reaction.

Fused bicyclic amino acids are a very interesting class of heterocyclic amino acids and have received considerable attention with regard to the development of new drugs.[1] The structural features of a wide variety of natural products such as palauamine, which has a core structure of 3-azabicyclo-[3,3,0]-octane, have also attracted a great deal of interest.[2] Over the past few years, many efficient methods have been developed for the asymmetric construction of such a skeleton using a chiral cyclic template to obtain the key azabicyclic systems successfully.[3] The Pauson−Khand reaction has been considered a valuable and convergent method for the synthesis of cyclopentanone derivatives.[4] Our research goal is to establish a practical strategy for obtaining a chiral bicyclic core, which could provide access to a large number of natural products. The $Co_2(CO)_8$-catalyzed Pauson−Khand reaction may be a good route to chiral azabicycles. There have been many reports on the stereoselectivity of the intramolecular Pauson−Khand reaction by incorporating chirality in the cyclization precursor using stoichiometric dicobaltoctacarbonyl.[5] However, to the best of our knowledge, few reports have addressed the catalytic asymmetric synthesis of cyclopenta[*c*]proline using chiral enyne amino acids. In this communication, we report the first efficient catalytic approach using intramolecular Pauson−Khand reactions for the diastereoselective synthesis of cyclopenta-[*c*]proline derivatives.

Recently, a new practical approach to unsaturated amino acids, by reacting alkenyl boronic acid with glyoxylic acid and amines, was reported by Petasis.[6] This prompted us to investigate the stereocontrolled synthesis of enyne amino acid

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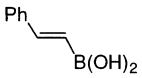
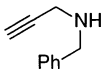
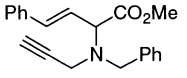
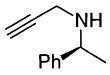
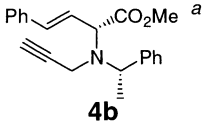
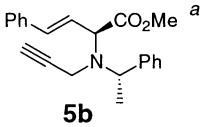
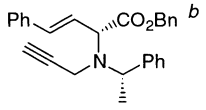
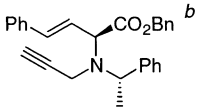
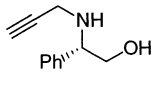
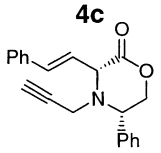
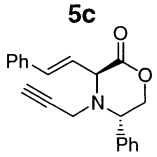
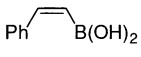
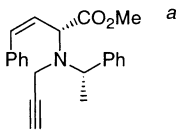
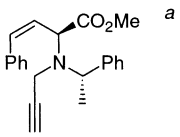
Table 1. Synthesis of 1,6-Enyne Amino Esters by the Reaction of Alkenylboronic Acids with *N*-Propargylamines and Glyoxylic Acid

entry	1	2	product		yield (%) [c,d] ratio of **4**:**5** [f]	yield (%) [c,e] ratio of **4**:**5** [f]
1	 **1a**	 **2a**	 **4a**		95 --	--
2	**1a**	 **2b**	 **4b** [a]	 **5b** [a]	90 1.5:1	90 7.5:2.5
3	**1a**	**2b**	 **4c** [b]	 **5c** [b]	87 1.5:1	88 7.5:2.5
4	**1a**	 **2c**	 **4d**	 **5d**	87 1.5:1	87 10:0
5	 **1b**	**2b**	 **4e** [a]	 **5e** [a]	92 1.5:1	92 7.5:2.5

[a] Resulting mixture was esterified with diazomethane. [b] Resulting mixture was esterified with benzyl alcohol. [c] Reaction was carried out by mixing the three starting materials in CH_2Cl_2 for 12 h at rt. [d] Isolated yields. [e] Reaction was carried out by mixing the three starting materials in CH_2Cl_2 for 24 h at rt in the presence of triethylamine. [f] Diastereomer ratio was determined by HPLC.

derivatives using the reaction of propargylamines, phenylvinyl boronic acids, and glyoxylic acid. To test the reactivity of the propargylamine, the synthesis of racemic enyne amino acid esters was first studied. The reaction of *N*-propargylbenzylamine, glyoxylic acid, and (*E*)-phenylvinyl boronic acid **1a** in dichloromethane for 12 h and then esterification with diazomethane gave racemic 1,6-enyne amino ester **4a** in 95% yield (Table 1, entry 1). This result turned our attention to the asymmetric synthesis of enyne amino acid using a chiral propargylamine as a substrate. Thus, treatment of (*S*)-*N*-propargyl-α-methylbenzylamine **2b** with (*E*)- or (*Z*)-phenylethenyl boronic acid **1** and glyoxylic acid gave enyne amino acid with two isomers in a ratio of 1.5:1, which could be easily separated by standard chromatography (entries 2 and 5). To our delight, the reaction of (*S*)-*N*-propargyl-2-phenylglycinol **2c** gave enyne lactone in 91% yield with two isomers in a ratio of 1.5:1. We found that the minor diastereoisomer could be easily converted into the major one by treatment with triethylamine. Finally, the highly diastereoselective synthesis of enyne amino acid derivatives was carried out in one pot by mixing chiral *N*-propargylamines, glyoxylic acid, phenylethenyl boronic acid, and 2 molar equiv of triethylamine at room temperature for 12 h. All of the reactions diastereoselectively gave the enyne amino acid derivatives in excellent yields (Table 1). In particular, chiral *N*-propargyl-2-phenylglycinol only gave a single isomer. To determine the stereochemistry of the new chiral carbon, the enyne **4d** was recrystallized from hexane and dichloromethane. X-ray analysis of compound **4d** revealed that the absolute configuration at the α-carbon was *R* (Figure 1). Thus, the use of (*S*)-*N*-propargyl-2-phenyl glycinol as a chiral

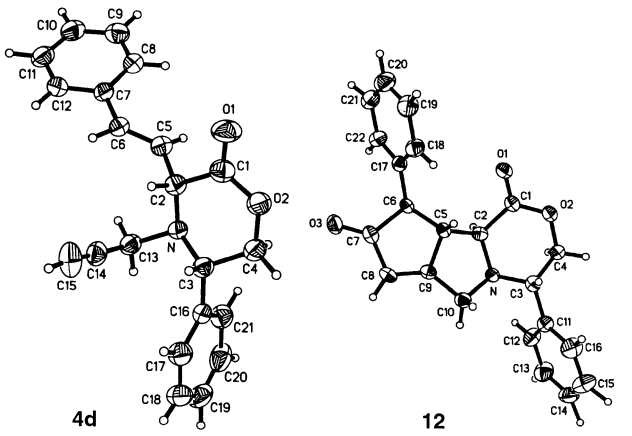


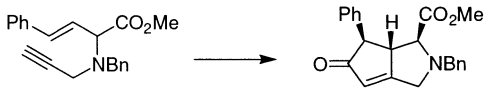
Figure 1. X-ray crystallography of compounds **4d** and **12**.

auxiliary gave an amino acid with an (*R*)-configuration, while (*R*)-*N*-propargyl-2-phenylglycinol gave the (*S*)-diastereoisomer, which was similar to our observation in the preparation of indoylglycines.[7]

The intramolecular Pauson−Khand reaction, a formal [2 + 2 + 1] cyclization of three components (alkynes, olefin moieties, and carbon monoxide), has been recognized as one of the most important methods for constructing cyclopentenone-fused bicyclic compounds.[8] The catalytic Pauson−Khand reaction shows high atom efficiency. Several catalytic versions have recently been developed, including the use of catalytic amounts of $Co_2(CO)_8$ in conjunction with either $P(OPh)_3$,[9] ultraviolet light,[10] or high-pressure carbon monoxide.[11]

To optimize the reaction conditions, the racemic 1,6-enyne amino ester **1a** was used in catalytic versions of the Pauson−Khand reaction. The results are summarized in Table 2.

Table 2. Examination of the Intramolecular Pauson−Khand Reaction with Various Catalytic Systems



4a **6**

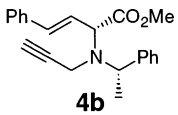
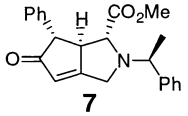
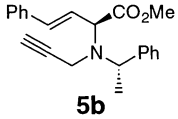
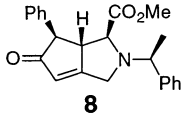
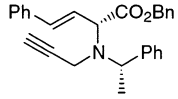
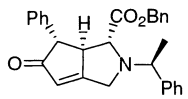
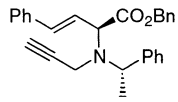
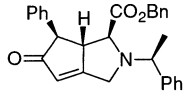
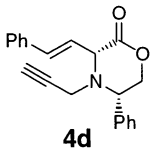
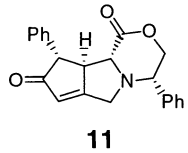
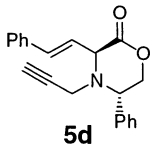
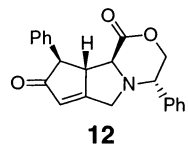
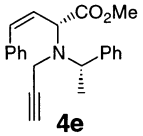
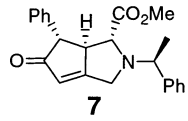
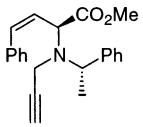
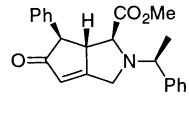
entry	$Co_2(CO)_8$ (mol %)	coligand, mol %	solvent	time (h)	temp (°C)	yield[a] (%)
1	10	$P(OPh)_3$, 30	DME	24	84	32
2	10	$CyNH_2$, 20	DME	24	70	40
3	10	Bu_3PS, 60	benzene	4	70	67
4	5	Bu_3PS, 30	benzene	24	70	50

[a] Isolated yield.

Treatment of **4a** with 10 mol % $Co_2(CO)_8$ and 30 mol % $P(OPh)_3$ in DME under 1 atm of carbon monoxide gave cyclopenta[*c*]proline derivatives **6** in 32% yield (entry 1). The reactant never disappeared, even when the reaction was prolonged to 24 h. Switching to cyclohexylamine as a coligand[12] in DME also gave a lower yield (entry 2). Fortunately, with 10 mol % $Co_2(CO)_8$ in the presence of 60 mol % Bu_3PS,[13] we were pleased to find a significant improvement in yield, and the cyclic amino ester **6** was isolated as a single isomer in 67% yield (entry 3). The use of only 5 mol % $Co_2(CO)_8$ gave a poor yield (entry 4).

Consequently, the best result was obtained with 10 mol % $Co_2(CO)_8$ and 1,6-enyne amino ester in the presence of 60 mol % Bu_3PS as a coligand in benzene at 70 °C under 1 atm of carbon monoxide. The configuration of cycloaddition product **6** was established by NMR studies and chemical correlations. The NOESY spectrum of **6** showed correlation between H_2 and H_4, indicating a cis relationship between the phenyl ring and the carboxyl group. The large value of

Table 3. Catalytic Diastereoselective Pauson−Khand Reaction with a Series of 1,6-Enyne Amino Esters[a]

entry	substrate	product	yield (%)[b]
1	 **4b**	 **7**	65
2	 **5b**	 **8**	66
3	 **4c**	 **9**	61
4	 **5c**	 **10**	63
5	 **4d**	 **11**	82
6	 **5d**	 **12**	75
7	 **4e**	 **7**	33
8	 **5e**	 **8**	35

[a] Reaction was carried out in the presence of 10 mol % $Co_2(CO)_8$ catalyst and 60 mol % Bu_3PS as a co-ligand in benzene at 70 °C under 1 atm of CO. [b] Isolated yields.

(6) (a) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463. (b) Petasis, N. A.; Goodman, A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.

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(10) Pagenkopf, B. C.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285.

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$J_{3,4}$ (9.8 Hz) also confirmed that the product had an exo configuration.[14]

The extension of this catalytic system to the asymmetric synthesis of chiral bicyclic amino acids is summarized in Table 3. The reaction of 2(*R*)-enyne **4b** or **4c** gave (2*R*,3*S*,4*R*)-bicyclic amino acid derivatives in good yields and as single isomers, while the reaction of (2*S*)-**5b** or **5c** gave (2*S*,3*R*,4*S*)-adduct (entries 1−4). Remarkably, the reaction of 1,6-enyne lactone **4d** or **5d** (entries 5 and 6) gave rigid tricyclic compounds **11** and **12**, respectively, in high yields. Interestingly, the configurations of Pauson−Khand reaction adducts were only controlled by the direction of the carbonyl group and were not affected by the configuration of the vinyl part. The reaction of (*R*,*S*)-(*Z*)-enyne **4e** gave the same product **7** as **4b** in low yield (33%), while the reaction of (*S*,*S*)-(*Z*)-enyne **5e** gave the same product (**8**) as **5b** (entries 7 and 8). Comparing the NMR and NOSEY data of **6** with those of **7** shows that the chiral cyclopenta[*c*]proline derivatives also had an exo configuration. The absolute configuration of the exo product was further confirmed by X-ray crystal analysis of compound **12** (Figure 1). It was particularly interesting that the Pauson−Khand reaction of enyne amino ester occurred with excellent stereocontrol to give a single isomer and predominantly exo adducts and allowed the Pauson−Khand procedure to generate two new chiral centers in one step without epimerization of the amino chiral carbon.

In summary, this strategy, which involves an alkenylboronic acid-mediated Mannich-type reaction followed by a $Co_2(CO)_8$-catalyzed Pauson−Khand reaction, opens a new route to enantiopure-fused cyclic chiral amino acids. This strategy is remarkable for its conciseness and convergence. Furthermore, the entire process is atom efficient. Due to the diversity of the starting materials and excellent stereocontrol, this strategy provides an expeditious route to chiral cyclic amino acids.

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Supporting Information Available: Characterization data and spectra for compounds **4a**, **4d**, **4e**, **5d**, and **6**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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