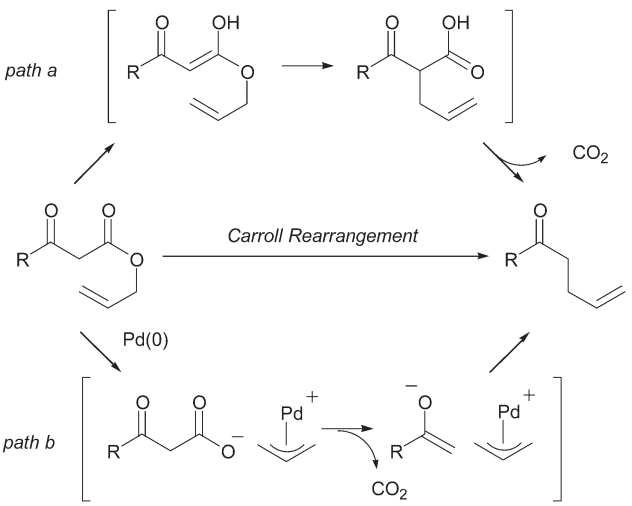
Asymmetric Carroll rearrangement of allyl α-acetamido-β-ketocarboxylates catalysed by a chiral palladium complex

Ryoichi Kuwano,† Naoki Ishida and Masahiro Murakami*

Received (in Cambridge, UK) 3rd March 2005, Accepted 14th June 2005
First published as an Advance Article on the web 7th July 2005
DOI: 10.1039/b505105c

Asymmetric decarboxylative rearrangement (Carroll rearrangement) of allyl α-acetamido-β-ketocarboxylates was catalysed by a palladium complex modified with a chiral phosphine ligand, giving optically active γ,δ-unsaturated α-aminoketones with up to 90% ee.

Carroll rearrangement, a variant of ester Claisen rearrangement, is an efficient C–C bond-forming method to produce γ,δ-unsaturated carbonyl compounds from allylic esters of β-ketocarboxylic acids.[1] Two mechanisms can operate for the decarboxylative rearrangement (Scheme 1). The reaction, occurring at a high temperature or under strongly basic conditions, proceeds by an electrocyclic pathway (*path a*), and has often been used in natural product syntheses.[2] Alternatively, the rearrangement is catalysed by palladium(0)/phosphine complexes under milder conditions (*path b*).[3] Oxidative addition, decarboxylation, and recombination constitute the catalytic cycle. This catalytic pathway inspired us to explore asymmetric Carroll rearrangement by means of chiral phosphine–palladium complexes. This paper describes catalytic asymmetric Carroll rearrangement,[4,5] which affords optically active γ,δ-unsaturated ketones bearing an N-substituted quaternary chiral α-carbon with up to 90% ee.



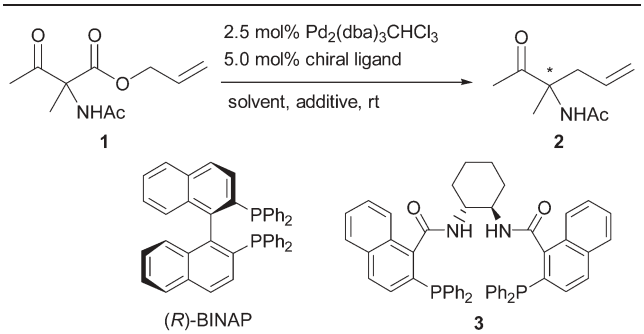
Scheme 1 Carroll rearrangement

Department of Synthetic Chemistry and Biological Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Kyoto 615-8510, Japan. E-mail: murakami@sbchem.kyoto-u.ac.jp; Fax: +81 75 383 2748; Tel: +81 75 383 2747
† Present address: Department of Chemistry, Graduate School of Sciences, Kyushu University, 6-10-1 Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan.

We reported previously a highly enantioselective allylation of α-acetamido-β-ketoesters, whose acetamido group was crucial for the control of stereochemistry.[6] Thus, we used an allylic esters of α-acetamido-β-ketocarboxylic acids as the substrate for asymmetric Carroll rearrangement. A variety of chiral phosphine ligands were examined in the palladium-catalysed decarboxylative rearrangement of 2-propenyl 2-(*N*-acetylamino)-2-methyl-3-oxobutanoate (**1**), with the selected results listed in Table 1. Only 25% ee was observed with BINAP, which was the chiral ligand of choice in the asymmetric allylation reaction previously reported (entry 1).[6] So-called Trost ligand (naphthyl) **3** showed a better enantioselectivity (entry 2).[7,8] Dichloroethane (DCE) was preferred to THF as the solvent (entry 3). Finally, it was found that addition of phenol derivatives brought about a dramatic enhancement of the enantioselectivity (entries 4–6). A satisfactory result in terms of both chemical yield and selectivity was obtained when the reaction was carried out in the presence of 0.5 equiv 1-naphthol.[9]

The results of the asymmetric Carroll rearrangement of allyl α-acetamido-β-ketocarboxylates catalysed by palladium/**3** are summarised in Table 2. A higher enantioselectivity (90% ee) was observed with the substrate having a propanoyl group (entry 1, R^1 = Et). Substrates bearing ethyl and benzyl groups at the α-position gave the corresponding products with 80% ee and 71%

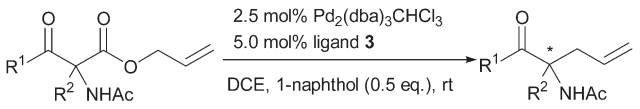
Table 1 Asymmetric Carroll rearrangement of **1**[a]

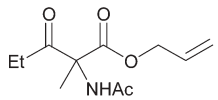
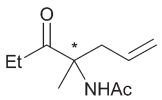
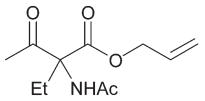
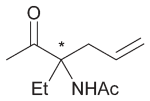
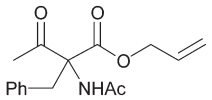
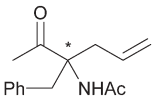


Entry	Chiral ligand	Solvent	Additive	Yield (%)[b]	ee (%)[c]
1	(*R*)-BINAP	THF	—	81	25 (−)
2	**3**	THF	—	99	36 (+)
3	**3**	DCE	—	89	51 (+)
4	**3**	DCE	phenol (1 eq.)	72	81 (+)
5	**3**	DCE	1-naphthol (1 eq.)	70	88 (+)
6	**3**	DCE	1-naphthol (0.5 eq.)	79	87 (+)[d]

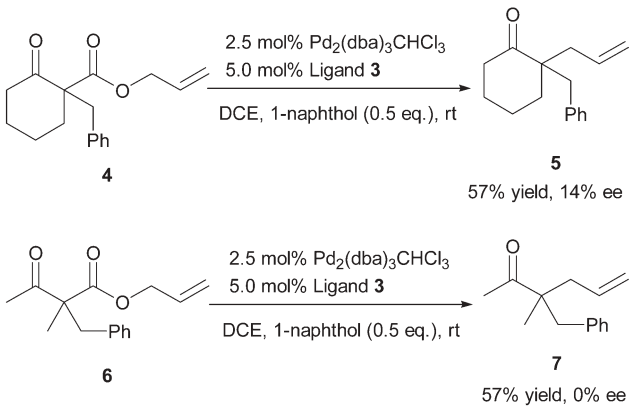
[a] Reactions were conducted on 0.2 mmol scale at room temperature. [b] Isolated yield. [c] By GC analysis with Chiraldex G-BP. Signs of optical rotation are given in parentheses. [d] $[\alpha]^{20}_{D}$ = +7.0 (*c* 0.50, $CHCl_3$).

Table 2 Asymmetric Carroll rearrangement of allyl α-acetamido-β-ketocarboxylates



Entry	Substrate	Product	Yield (%)[b]	ee (%)
1			81	90[c]
2			55	80[d]
3			82	71[e]

[a] Reactions were conducted on 0.2 mmol scale at room temperature. [b] Isolated yield. [c] By GC analysis with Chiraldex G-BP. [d] By HPLC analysis with Chiralcel OJ-H. [e] By HPLC analysis with Chiralcel OD-H.



Scheme 2 Carroll rearrangement of allyl β-ketocarboxylates.

ee, respectively (entries 2, 3). Lower reactivities were observed with allylic ester groups other than a 2-propenyl group, like methallyl (low yield), cinnamyl (low yield), crotyl ((*E*)-α-, (*Z*)-α- and diastereomeric mixture of γ-coupling products), and prenyl (no prenylated product) groups.

For comparison, the Carroll rearrangement of allyl β-ketocarboxylates lacking an α-acetamido group was examined (Scheme 2). The reaction of cyclohexanone **4** gave γ,δ-unsaturated ketone **5** with only 14% ee. No asymmetric induction was observed in the reaction of acyclic β-ketoester **6**. These results indicated that the α-acetamido group played a crucial role in enantioface-selection of the enolate generated from β-ketocarboxylate *via* decarboxylation.[10]

In conclusion, the chiral palladium catalyst generated *in situ* from $Pd_2(dba)_3{\cdot}CHCl_3$ and the optically active bisphosphine ligand **3** accomplished a high degree of asymmetric induction on a N-substituted quaternary chiral carbon center (up to 90% ee) in the Carroll rearrangement of allyl α-acetamido-β-ketocarboxylates.‡

Notes and references

‡ **A general procedure of the catalytic asymmetric Carroll rearrangement**: A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (5.2 mg, 5.0 μmol), chiral ligand **3** (8.0 mg, 10 μmol) and 1-naphthol (14.4 mg, 0.1 mmol) in DCE (1.0 ml) was stirred for 30 min at room temperature. Allyl β-ketocarboxylate (0.2 mmol) was added to the reaction mixture, which was stirred until the starting material was completely consumed (0.5–3 h). The solvent was evaporated, and the residue was purified by flash column chromatography on silica gel (EtOAc/hexane) to give the corresponding γ,δ-unsaturated ketone. Spectroscopic data for **1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 3H), 2.03 (s, 3H), 2.21 (s, 3H), 4.65–4.69 (m, 2H), 5.25–5.36 (m, 2H), 5.87 (ddt, J = 17.1, 10.2, 5.7 Hz, 1H), 7.01 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.16, 22.97, 24.05, 66.93, 68.40, 119.43, 131.02, 168.80, 169.10. 200.23; HRMS (CI) Calcd. for $C_{10}H_{16}NO_4$ [M$^+$] 214.1079, Found 214.1078. Spectroscopic data for **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H), 1.99 (s, 3H), 2.19 (s, 3H), 2.49 (dd, J = 14.4, 7.8 Hz, 1H), 3.05 (q, J = 14.4, 7.2 Hz, 1H), 5.08–5.13 (m, 2H), 5.58 (ddt, J = 17.3, 9.9, 7.5 Hz, 1H), 6.44 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.64, 23.58, 23.73, 39.26, 64.25, 119.24, 132.18, 169.44, 207.98; HRMS (CI) Calcd. for $C_9H_{16}NO_2$ [M$^+$] 170.1181, Found 170.1179.

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4 For asymmetric Carroll rearrangement by using stoichiometric SAMP or RAMP, see: D. Enders and M. Knopp, *Tetrahedron*, 1996, **52**, 5805.

5 Very recently, two groups reported enantioselective decarboxylative intramolecular allylation of cycloalkanones: (*a*) D. C. Behenna and B. M. Stoltz, *J. Am. Chem. Soc.*, 2004, **126**, 15044; (*b*) B. M. Trost and J. Xu, *J. Am. Chem. Soc.*, 2005, **127**, 2846.

6 (*a*) R. Kuwano and Y. Ito, *J. Am. Chem. Soc.*, 1999, **121**, 3236; (*b*) R. Kuwano, R. Nishio and Y. Ito, *Org. Lett.*, 1999, **1**, 837.

7 B. M. Trost and R. C. Bunt, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 99.

8 The chiral ligand **3** is commercially available from Strem Chemicals, Inc.

9 It might be that hydrogen bonding between the protic hydrogens with the amido groups of **3** favors a desired conformation or disfavors undesired amido coordination to palladium. For a similar effect of alcohol addition to improve an enantioselectivity, see:B. M. Trost, C. P. Soldermann, I. Chen and G. M. Schroeder, *J. Am. Chem. Soc.*, 2004, **126**, 4480.

10 We assumed that the acetamido group serves to fix the transition state conformation, probably through interaction with the cationic palladium center.

