Asymmetric Catalysis

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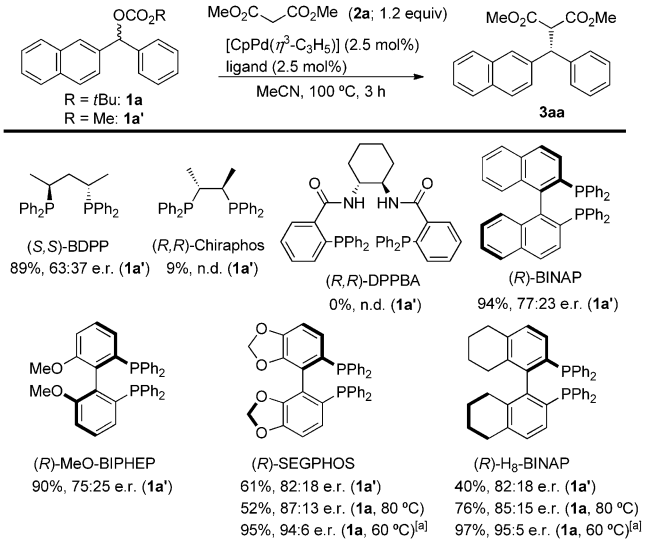
Palladium-Catalyzed Asymmetric Benzylic Alkylation of Active Methylene Compounds with α-Naphthylbenzyl Carbonates and Pivalates

Sho Tabuchi, Koji Hirano, and Masahiro Miura**

Abstract: *A Pd/(R)-H_8-BINAP-catalyzed asymmetric benzylic alkylation of active methylene compounds has been developed. The reaction proceeds without the use of an external base, and the starting racemic diarylmethyl carbonates are converted into the optically active coupling products which contain the benzylic chiral stereocenter by a dynamic kinetic asymmetric transformation (DYKAT). Additionally, with suitable carbonates bases, the same palladium catalysis allows the corresponding pivalates to be adopted in the same DYKAT process.*

Palladium-catalyzed cross-coupling reactions are one of the most powerful and reliable synthetic tools for the construction of versatile carbon frameworks in modern organic chemistry. Among them, the asymmetric allylic alkylation with allylic electrophiles via π-allylpalladium intermediates (Tsuji–Trost reaction) has been extensively studied and applied to the synthesis of various complex natural products and bioactive molecules.[1] In contrast, the asymmetric benzylic alkylation with benzylic electrophiles via π-benzylpalladium intermediates has been less developed despite its isoelectronic character to the π-allylpalladium.[2] Although related asymmetric palladium catalysis with prochiral nucleophiles and achiral primary benzylic carbonates or phosphates were recently reported by Trost and Czabaniuk,[3] a dynamic kinetic asymmetric transformation (DYKAT)[4] with racemic secondary benzyl electrophiles still remains largely elusive. Fiaud, Legros, and co-workers reported the seminal work on the palladium-catalyzed asymmetric nucleophilic substitution of racemic 1-(2-naphthyl)ethyl acetate with malonate anions. However, the yield and enantiomeric ratio were moderate, and a partial kinetic resolution was finally proposed.[5] The groups of Jarvo[6] and Watson[7] independently developed the nickel-catalyzed, condition-controlled enantiodivergent cross-coupling of secondary benzyl alcohol derivatives, but enantioenriched starting substrates are still required for the synthesis of optically active coupling products. Only limited successful examples include the nickel-catalyzed DYKAT of the secondary benzylic (pseudo)halides with organozinc reagents via radical intermediates, which is reported by Fu.[8] Thus, further development of DYKAT with racemic benzyl electrophiles is strongly desired. Herein, we report a Pd/(*R*)-H_8-BINAP catalyst system for the asymmetric benzylic alkylation of active methylene compounds: the DYKAT process proceeds and the starting racemic diarylmethyl carbonates are converted into the substitution products with high yields and high enantiomeric ratios. To the best of our knowledge, this reaction is the first successful example of a C–C bond-forming DYKAT with racemic benzyl electrophiles via a π-benzylpalladium intermediate.

During our recent studies on the base-free, palladium-catalyzed enantiospecific C–C cross-coupling reaction of terminal alkynes with diarylmethyl carbonates, we found that a Pd/(*S*,*S*)-BDPP (for structure, see Scheme 1) catalyst induced small but significant stereoinduction with a racemic secondary benzyl carbonate in a DYKAT manner.[9] While preliminary, this intriguing result prompted us to investigate the asymmetric benzylic alkylation of dimethyl malonate (**2a**), the representative soft carbon nucleophile in the Tsuji–Trost allylic alkylation, with racemic methyl (2-naphthyl)-(phenyl)methyl carbonate (**1a′**) in the presence of various chiral bisphosphine ligands combined with [CpPd(η^3-C_3H_5)] (Scheme 1). Similar to the original work by Fiaud, Legros, and co-workers,[5] as well as our previous finding,[9a] (*S*,*S*)-BDPP showed high performance (89% of **3aa**) but relatively low enantioselectivity (63:37 e.r.). In the presence of well-known



Scheme 1. Optimization studies for the palladium-catalyzed asymmetric benzylic alkylation of dimethyl malonate (**2a**) with diarylmethyl carbonates **1**. [a] With 5 mol% of [CpPd(η^3-C_3H_5)]/ligand in DMSO. Cp = cyclopentadiene, DMSO = dimethylsulfoxide.

[*] S. Tabuchi, Prof. Dr. K. Hirano, Prof. Dr. M. Miura
Department of Applied Chemistry, Graduate School of Engineering, Osaka University
Suita, Osaka 565-0871 (Japan)
E-mail: k_hirano@chem.eng.osaka-u.ac.jp
miura@chem.eng.osaka-u.ac.jp

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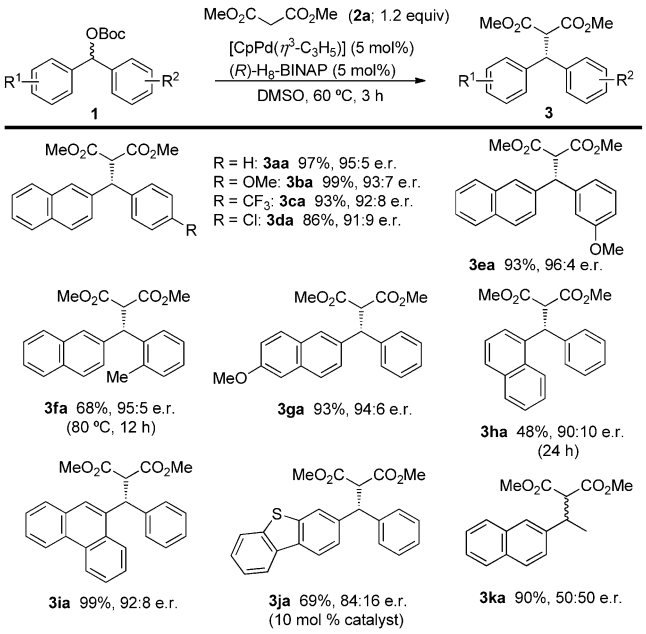
(*R*,*R*)-Chiraphos and (*R*,*R*)-DPPBA, which is a promising class of chiral ligands in related asymmetric allylic[1b] and benzylic[3] alkylations, the reaction was sluggish. In contrast, common chiral biaryl bis(phosphine) ligands promoted the reaction with better efficiency and enantioselectivity. Particularly, (*R*)-SEGPHOS and (*R*)-H_8-BINAP were good candidates, and the desired **3aa** was obtained with 82:18 e.r. The replacement of **1a′** with the Boc carbonate **1a** allowed the reaction to proceed at lower temperature (80 °C), and the enantiomeric ratio slightly increased to 87:13 (with (*R*)-SEGPHOS) and 85:15 e.r. (with (*R*)-H_8-BINAP). Subsequent solvent screening revealed that a combination of 5 mol % of [CpPd(η^3-C_3H_5)] and (*R*)-H_8-BINAP in DMSO at 60 °C was optimal, and **3aa** was formed in 97 % yield with 95:5 e.r. Notably, substituents bulkier than Ph on phosphorous gave negative impact on the enantioselectivity.[10]

With the optimized reaction conditions in hand, we conducted the asymmetric benzylic alkylation of **2a** with various secondary benzyl carbonates **1** (Scheme 2). The

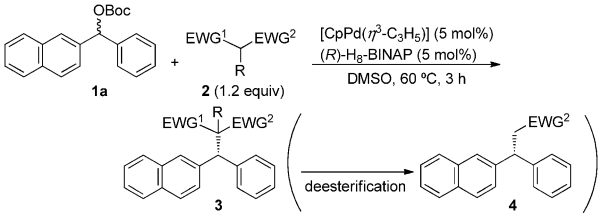


Scheme 2. Palladium-catalyzed asymmetric benzylic alkylation of dimethyl malonate (**2a**) with various secondary benzyl carbonates (**1**). Boc = *tert*-butoxycarbonyl.

enantioselective palladium catalysis was compatible with electron-donating methoxy as well as electron-withdrawing trifluoromethyl and chloro groups at the *para*-position of the benzene ring of **1**, and the corresponding **3ba**, **3ca**, and **3da** were formed in good yields (86–99 %) with high enantioselectivity (91:9–93:7 e.r.). The *meta*- and *ortho*-substituted carbonates also underwent the DYKAT smoothly to deliver **3ea** (96:4 e.r.) and **3fa** (95:5 e.r.), respectively. The replacement of the 2-naphthyl group with 6-methoxy-2-naphthyl, 1-naphthyl, and higher fused phenanthryl substituents was possible, and the optically active **3ga**, **3ha**, and **3ia** were obtained in 90:10–94:6 e.r. Additionally, the heterocyclic dibenzothiophene substrate could also be employed under slightly modified reaction conditions (**3ja**; 69 %, 84:16 e.r.). In contrast, the (2-naphthyl)ethyl carbonate gave the racemate of **3ka** (50:50 e.r.).[11,12]

In addition to **2a**, some representative symmetrical active methylene compounds coupled with **1a** to furnish the corresponding benzylic alkylation products enantioselectively: diethyl malonate (**2b**), acetylacetone (**2c**), and malononitrile (**2d**) gave **3ab**, **3ac**, and **3ad**, respectively, with 93:7–95:5 e.r. (Table 1, entries 1–3). The unsymmetrical β-

Table 1: Palladium-catalyzed asymmetric benzylic alkylation of various active methylene and methine compounds (**2**) with **1a**.[a]

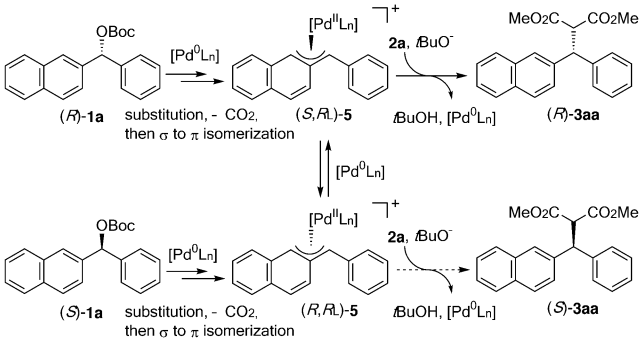


Entry	2	3, Yield [%][b], e.r.[c]
1	EtO2C CO2Et **2b**	**3ab**, 87, 95:5
2[d]	O O **2c**	**3ac**, 71, 93:7
3[e,f]	NC CN **2d**	**3ad**, 79, 94:6
4	EtO2C O **2e**	**3ae**, 76, 91:9[g]
5[e]	MeO2C CN **2f**	**3af**, 88, 94:6[g]
6[d,h,i]	MeO2C SO2Ph **2g**	**3ag**, 61, 94:6[g]
7[j]	EtO2C CO2Et **2h**	**3ah**, 70, 89:11
8[d,i]	EtO2C CO2Et NHAc **2i**	**3ai**, 83, 93:7

[a] Reaction conditions: [CpPd(η^3-C_3H_5)] (0.013 mmol), (*R*)-H_8-BINAP (0.013 mmol), **1a** (0.25 mmol), **2** (0.30 mmol), DMSO (3.0 mL), 60 °C, 3 h, N_2. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At 80 °C. [e] At 100 °C. [f] For 6 h. [g] Obtained as nearly 1:1 mixture of diastereomers. The enantiomeric ratio (e.r.) was determined after derivatization into the corresponding **4**. See the Supporting Information for details. [h] With [CpPd(η^3-C_3H_5)] (0.025 mmol) and (*R*)-H_8-BINAP (0.025 mmol). [i] In MeCN (3.0 mL). [j] For 9 h. EWG = electron-withdrawing group.

ketoester **2e**, cyanoacetate **2f**, and β-sulfonylester **2g** were also suitable coupling partners (entries 4–6). In these cases, the products **3ae**–**ag** were obtained as nearly a 1:1 mixture of diastereomers, but the stereochemistry of their benzylic positions was well controlled (91:9–94:6 e.r.), which are confirmed after derivatization into **4** by deesterification under appropriate reaction conditions.[13] Moreover, the Pd/(*R*)-H_8-BINAP catalyst system was tolerated with relatively sterically hindered active methine compounds **2h** and **2i**, and we obtained **3ah** (70 %, 89:11 e.r.) and **3ai** (83 %, 93:7 e.r.), respectively (entries 7 and 8).

Our proposed mechanism for the formation of (*R*)-**3aa** could involve the racemization process analogous to that of π-allylpalladium intermediates[14] (Scheme 3). Initial S_N2-type substitution[15] of the secondary benzyl carbonates (*R*)-**1a** and (*S*)-**1a** with [Pd^0L_n] [L = (*R*)-H_8-BINAP] is followed by decarboxylation and σ-to-π isomerization to form the corre-

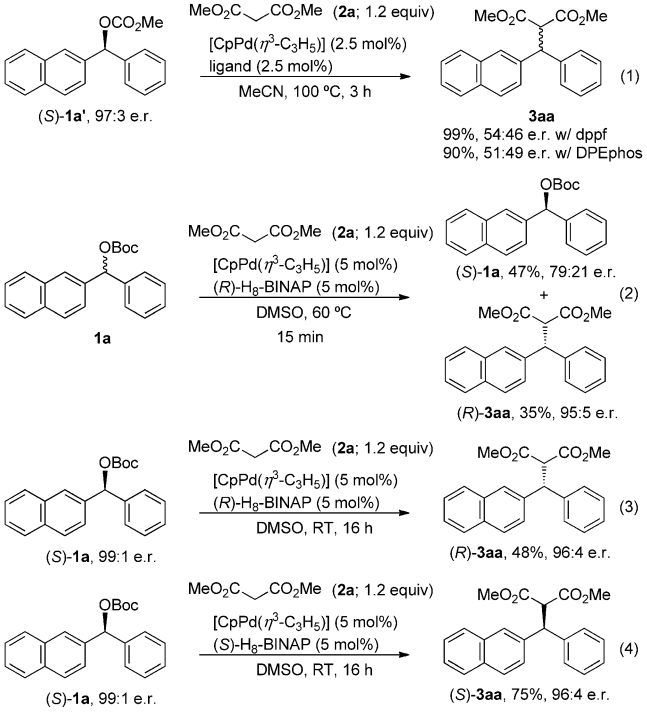


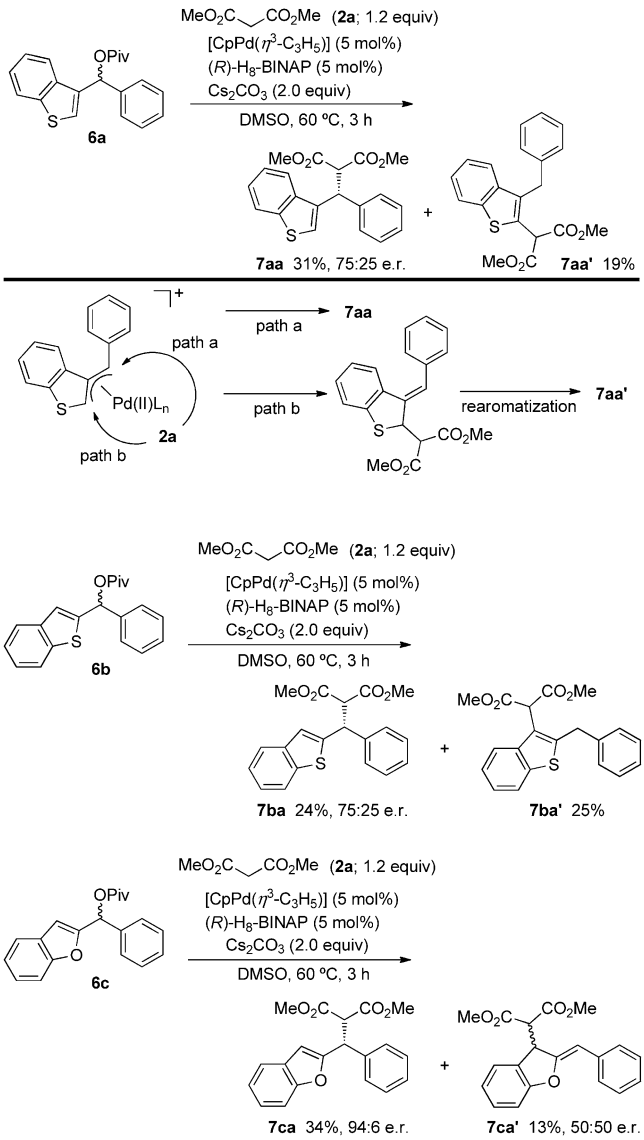
Scheme 3. Plausible mechanism. L = (*R*)-H_8-BINAP. The descriptor R_L means the absolute configuration of the ligand L.

sponding diastereomeric cationic π-benzyl intermediates (S,R_L)-**5** and (R,R_L)-**5**, respectively (R_L means the absolute configuration of the ligand L). They then undergo the rapid interconversion, which is racemization at the benzylic chiral center, probably by the attack of additional [Pd^0L_n] species.[5b,6f,14] The asymmetric induction arises from a selective backside attack of the active methylene compound **2a**, which can be deprotonated by *t*BuO^-, with one (S,R_L)-**5** isomer to produce the observed major enantiomer (*R*)-**3aa**.

To get more insight into the reaction mechanism, we performed the following control experiments. When the enantioenriched substrate (*S*)-**1a′** was subjected to reaction conditions with an achiral dppf or DPEphos ligand, the expected **3aa** was obtained in good yield essentially as a racemate [Eq. (1)]. Thus, the racemization proceeds smoothly, and no enantiospecific reaction occurs. In contrast, at an early stage of the enantioselective reaction (15 min), the starting carbonate **1a** was recovered in 47% yield with moderate 79:21 e.r., but the enantioselectivity of the coupling product **3aa** was identical to that of the optimized reaction conditions [Eq. (2)]. This result indicates that the substrate-dependent partial kinetic resolution occurs in the substitution step, but the subsequent racemization of π-benzyl palladium intermediates proceeds much more readily and overall stereochemistry is thus controlled by the catalyst in the final C–C forming event. Actually, the room-temperature reactions of (*S*)-**1a** under (*R*)- and (*S*)-H_8-BINAP-ligated palladium catalysis gave different product yields, but (*R*)-**3aa** and (*S*)-**3aa**, respectively, were obtained with the same e.r. value (96:4) [Eqs. (3) and (4)].

Some (heteroaryl)methyl *tert*-butyl carbonates are relatively unstable and often difficult to prepare in a pure form. We thus tested the more stable (heteroaryl)methyl pivalates (Scheme 4). With Cs_2CO_3 as an external base, (3-benzothiophenyl)(phenyl)methyl pivalate (**6a**) reacted with





Scheme 4. Palladium-catalyzed asymmetric benzylic alkylation of dimethyl malonate (**2a**) with secondary (heteroaryl)methyl pivalates (**6**).

2a under otherwise identical reaction conditions to form the expected product **7aa** in 31% with moderate 75:25 e.r. Notably, the constitutional isomer **7aa′** was also isolated, and strongly supports the intermediacy of the π-benzylic palladium species: the outer-sphere attack of **2a** at the C2-position of the benzothiophene ring in the π-benzylpalladium (path b) is followed by rearomatization to furnish **7aa′**, while the reaction course as shown in Scheme 3 (path a) leads to the usual product **7aa**. The 2-benzothienylmethyl and 2-benzofuranylmethyl pivalates (**6b** and **6c**) also gave a mixture of isomers with 75:25 e.r. for **7ba** and 94:6 e.r. for **7ca**, respectively, but in the latter case the dearomatized **7ca′** was detected as the byproduct, probably because of the weaker aromaticity of the furan than that of the thiophene.[16,17]

In conclusion, we have developed a Pd/(*R*)-H_8-BINAP-catalyzed asymmetric benzylic alkylation of active methylene compounds with racemic diarylmethyl carbonates and pivalates. To the best of our knowledge, this is the first successful example of the dynamic kinetic asymmetric transformation (DYKAT) of secondary benzylic electrophiles via π-benzylpalladium intermediates. The present results provide an enantioconvergent approach to optically active benzylic alkylation products from racemic benzyl alcohol derivatives and prompt further development of related asymmetric catalysis based on the DYKAT process of secondary benzyl electrophiles. Expansion of the scope of nucleophiles and overcoming the "naphthalene limitation"[12] are currently underway in our laboratory.

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[10] See the Supporting Information for more detailed optimization studies.

[11] The exact reason in not clear yet, but the diarylmethyl system can be essential for the rapid interconversion of two diastereomeric π-benzylpalladium intermediates or their sufficient kinetic difference in the backside attack reaction with the malonate anion (see Scheme 3).

[12] As far as we tested, the present catalyst system did not address the "naphthalene problem": (phenyl)(2-thienyl)methyl, (4-methoxyphenyl)(phenyl)methyl, and (4-biphenylyl)-(phenyl)methyl carbonates gave no desired products. Homocoupling byproducts of carbonates were detected even under more forcing conditions. This homocoupling is probably because of easy accessibility of naphthalene and related fused aromatics to the π-benzyl intermediates, which is associated with their weaker aromaticity. Similar trends are often observed in metal-catalyzed cross-coupling reactions with C–O electrophiles. See: a) M. Tobisu, N. Chatani, *Acc. Chem. Res.* **2015**, *48*, 1717; b) A. Correa, T. Léon, R. Martin, *J. Am. Chem. Soc.* **2014**, *136*, 1062; c) K. Muto, J. Yamaguchi, K. Itami, *J. Am. Chem. Soc.* **2012**, *134*, 169; d) S. N. Mendis, J. A. Tunge, *Org. Lett.* **2015**, *17*, 5164. And Refs. [2], [6], and [7].

[13] The absolute configuration at the benzylic position of **3af** was determined to be *R* after derivatization into the known compound **4af**, and others are tentatively assigned by analogy. See the Supporting Information for details.

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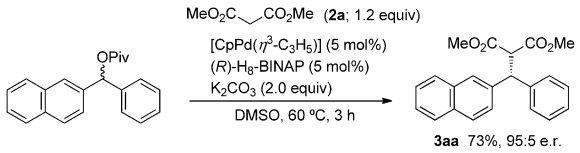
[17] The corresponding naphthalene-derived pivalate gave the usual benzylic substitution product with the comparable enantiose-

lectivity (see the scheme below). Thus, the observed unique reactivity of **6a–c** can be associated with the weaker aromaticity of the benzothiophene and benzofuran but not with the nature of the leaving group.



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