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Authors: Tomoaki Inukai, Taichi Kano, and Keiji Maruoka

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Construction of a Quaternary Carbon Center by Catalytic Asymmetric Alkylation of 3-Arylpiperidin-2-ones under Phase-Transfer Conditions

Tomoaki Inukai,[a] Taichi Kano,*[a] and Keiji Maruoka*[a,b,c]

Abstract: A highly enantioselective synthesis of δ-lactams having a chiral quaternary carbon center at the α-position has been developed through an asymmetric alkylation of 3-arylpiperidin-2-ones under phase-transfer conditions. In this transformation, a 2,2-diarylvinyl group on the δ-lactam nitrogen plays a crucial role as a novel protecting group and an achiral auxiliary for improving both yield and enantioselectivity of the reaction.

Nitrogen heterocycles containing a chiral quaternary carbon center are frequently found in natural products and considered as an important and useful building block in organic synthesis. Among them, 3-alkyl-3-arylpiperidine is an attractive structural motif that constitutes the core structure of biologically active compounds as shown in Figure 1.[1–4] Asymmetric alkylation of 3-aryl-lactams is a simple and direct method to construct such chiral quaternary carbon centers;[5] however, only a few reports on the catalytic asymmetric synthesis of 3-alkyl-3-aryl-lactams have appeared to date with limited success (e.g., Pd-catalyzed allylation and conjugate addition under phase transfer-conditions)

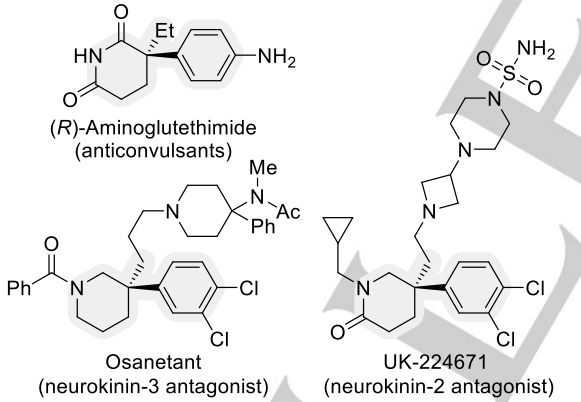
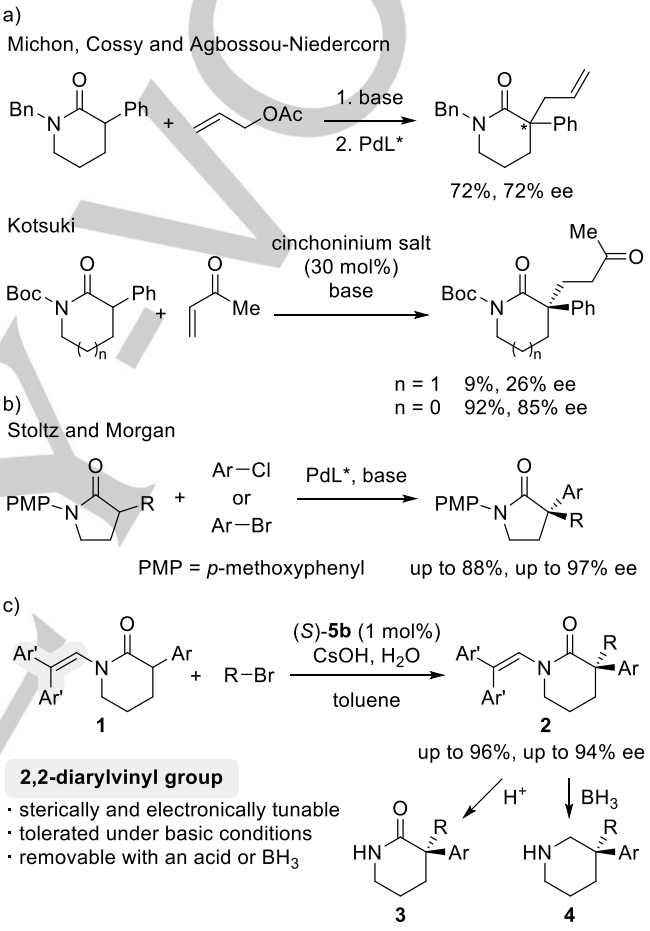


Figure 1. Bioactive molecules bearing a 3-alkyl-3-arylpiperidine scaffold.



Scheme 1. Approaches for catalytic asymmetric synthesis of 3-alkyl-3-aryl-lactams. a) Examples of catalytic asymmetric alkylation. b) Example of catalytic asymmetric arylation. c) This work.

[a] T. Inukai, Prof. Dr. T. Kano
Department of Chemistry, Graduate School of Science
Kyoto University, Sakyo, Kyoto 606-8502 (Japan)
E-mail: kano@kuchem.kyoto-u.ac.jp
[b] Prof. Dr. K. Maruoka
Department of Organocatalytic Chemistry, Graduate School of Pharmaceutical Sciences
Kyoto University, Sakyo, Kyoto 606-8501, Japan
Guangdong University of Technology, Guangzhou 510006 (China)
E-mail: maruoka@kuchem.kyoto-u.ac.jp
[c] School of Chemical Engineering and Light Industry
Guangdong University of Technology, Guangzhou 510006 (China)

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(Scheme 1a).[6,7] Asymmetric arylation of 3-alkyl-lactams is an alternative approach toward the construction of the chiral quaternary carbon center (Scheme 1b). To the best of our knowledge, however, the catalytic asymmetric reaction has only been reported for the arylation of 3-alkyl-γ-lactams.[8] In contrast to the previous attempts, phase-transfer-catalyzed asymmetric alkylation using alkyl halides is undoubtedly one of the most reliable methods to introduce alkyl substituents in an enantioselective fashion,[9] though such an approach has not been developed to a useful level, regardless of the lactam ring size.[10] Accordingly, we have developed an asymmetric alkylation of 3-aryl-δ-lactams bearing an *N*-2,2-diarylvinyl group as a protecting

10.1002/anie.201913518

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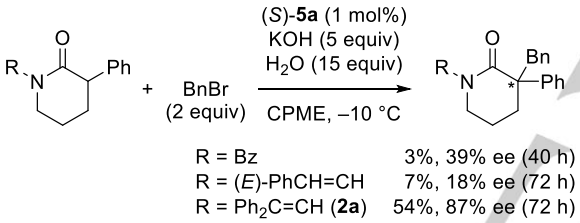
group as well as a tunable achiral auxiliary (Scheme 1c). This novel protecting group for the amide nitrogen of lactams is found to be well tolerated under strong basic conditions and be removed by treatment with an acid or BH_3. In the latter case, the corresponding cyclic amine is obtained directly by reduction of the amide moiety with BH_3·THF. Here, we wish to disclose our initial results on this study.

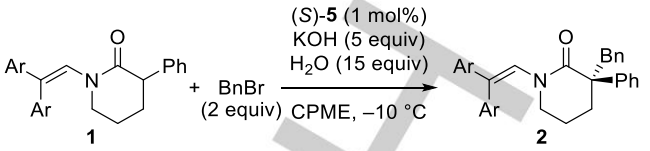
In the presence of a chiral quaternary ammonium salt (*S*)-**5a**,[9j] the reaction between *N*-benzoyl-3-phenylpiperidin-2-one and benzyl bromide in cyclopentyl methyl ether (CPME) under phase-transfer conditions gave the benzylated product in low yield and enantioselectivity (Scheme 2). In contrast to the smooth conjugate addition under phase transfer conditions,[7] the alkylation of a trace amount of the in-situ generated enolate with alkyl halides is much slower. We then hypothesized that the electronical and structural modification in the lactam would result in the facile formation of the ammonium enolate as well as an efficient enantioface discrimination, which are attributable to tight interaction between the catalyst and the enolate, leading to higher yield and enantioselectivity. Hence, (*E*)-styryl or 2,2-diphenylvinyl group was installed as a tunable achiral auxiliary at the amide nitrogen of 3-phenylpiperidin-2-one. Indeed, a significant improvement of both yield and enantioselectivity was observed in the reaction of the modified 3-phenylpiperidin-2-one **2a**.



Scheme 2. Asymmetric alkylation of 3-phenylpiperidin-2-ones.

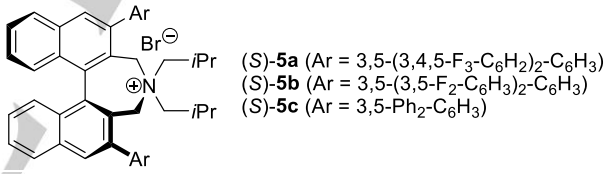
We then tuned the structure of a 2,2-diarylvinyl group (Table 1). Introduction of electron withdrawing groups such as *p*-fluoro groups improved the yield, while the enantioselectivity decreased (entry 2). On the other hand, introducing *p*-CF_3 group was found to be effective for achieving high yield and enantioselectivity, although the reaction was performed at lower concentration for shorter reaction time (entry 4). Fine-tuning of the catalyst led to a slight increase in yield and enantioselectivity (entry 5). The reaction in toluene gave **2d** with increased enantioselectivity, albeit in moderate yield (entry 7). Use of CsOH as base at lower temperature resulted in higher enantioselectivity, while a longer reaction time was required (entry 8, see also the Supporting information for details).

Table 1. Effects of *N*-protecting group in the asymmetric alkylation of 3-arylpiperidin-2-ones.[a]



Entry	(*S*)-**5**	Ar	*t* [h]	Yield [%][b]	*ee* [%][c]
1[d]	(*S*)-**5a**	Ph	72	**2a** 54	87
2[d]	(*S*)-**5a**	4-F-C_6H_4	72	**2b** 76	79
3	(*S*)-**5a**	3,5-F_2-C_6H_3	24	**2c** 76	63
4	(*S*)-**5a**	4-CF_3-C_6H_4	24	**2d** 79	87
5	(*S*)-**5b**	4-CF_3-C_6H_4	24	**2d** 82	88
6	(*S*)-**5c**	4-CF_3-C_6H_4	24	**2d** 85	64
7[e]	(*S*)-**5b**	4-CF_3-C_6H_4	24	**2d** 47	90
8[f]	(*S*)-**5b**	4-CF_3-C_6H_4	72	**2d** 73	93

[a] Reactions were performed on a 0.1 mmol scale in 1 mL of CPME. [b] Isolated yield. [c] Determined by HPLC using a chiral column. [d] CPME (0.2 mL) was used. [e] Toluene was used as solvent. [f] Performed at –35 °C in toluene (0.4 mL) using 5 equiv of BnBr, 10 equiv of CsOH·H_2O and 20 equiv of H_2O.



With the optimized conditions in hand, we examined the substrate scope and the results are shown in Table 2. In the presence of 1 mol% of (*S*)-**5b**, the reactions of 3-phenylpiperidin-2-one **1d** with various alkyl bromides gave the corresponding products in moderate to good yields and high enantioselectivities (**2d**–**2i**). Use of a propargyl bromide, 1-bromo-2-butyne resulted in a decrease in both yield and enantioselectivity (**2j**). We then tested the scope of the reaction by varying the substituents on the phenyl ring of the modified 3-arylpiperidin-2-one (**2k–2s**).[11] Introduction of a *para*-methoxy group significantly decreased the yield (**2k**, 21%); however, the reaction at higher temperature (–15 °C) gave **2k** in high yield and enantioselectivity. In general, *para* and/or *meta*-substituents did not significantly affect the enantioselectivity (**2k**–**2p**), whereas *ortho*-substitution resulted in no conversion (**2q**). While the electronic nature of the aryl group has only a small effect on the stereoselectivity, an electron-deficient heteroaryl substituent such as 3-pyridyl lowered both yield and enantioselectivity (**2r**). On the other hand, 3-thiophenyl group was tolerated, giving **2s** in good yield and enantioselectivity. The reaction with a less reactive alkylating agent, ethyl iodide gave **2u** in low yield. When a 3-aryl-γ-lactam, 3-phenylpyrrolidin-2-one having an *N*-2,2-diarylvinyl group was used instead of **1**,

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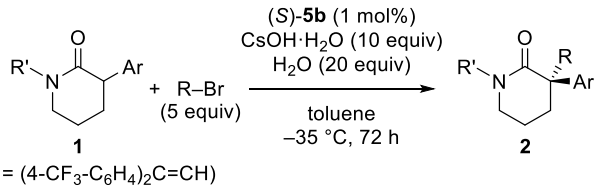
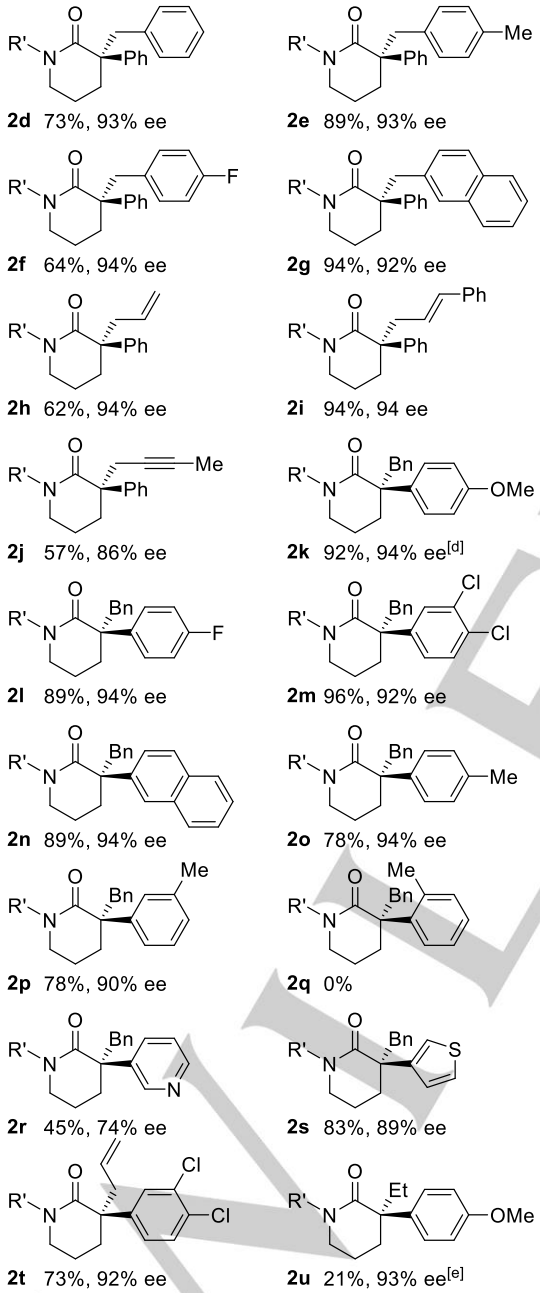
the benzylated product was obtained in 17% ee (see the Supporting Information for details).

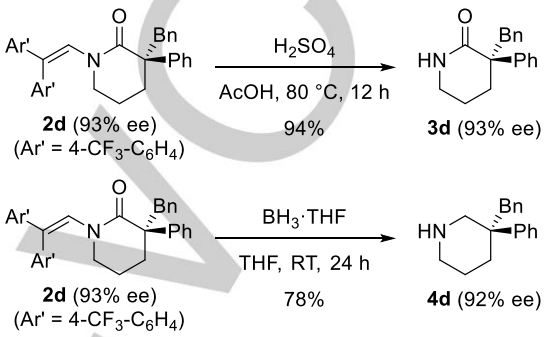
Table 2. Substrate Scope.[a-c]





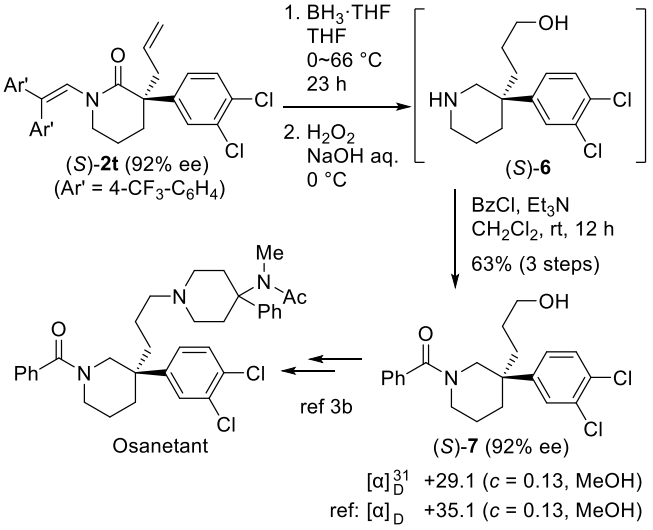
[a] Reactions were performed on a 0.1 mmol scale in 0.4 mL of toluene. [b] Isolated yield. [c] Ee was determined by HPLC using a chiral column. [d] Performed at –15 °C. [e] Performed with Et-I (10 equiv) at –15 °C for 168 h.

The 2,2-diarylvinyl group is well tolerated under reaction conditions. Treatment of **2d** with aqueous KOH even under reflux conditions led to an essentially quantitative recovery of the starting material. On the other hand, enamides are known to be hydrolyzed under acidic conditions,[12] and treatment of **2d** with H_2SO_4 afforded 3-benzyl-3-phenylpiperidin-2-one (**3d**) in high yield without loss of enantiopurity (Scheme 3). Treatment of **2d** with BH_3 in THF gave 3-benzyl-3-phenylpiperidine (**4d**) directly as a result of deprotection and the subsequent reduction of the in-situ generated **3d**.[13]



Scheme 3. Deprotection of 3-benzyl-3-phenylpiperidin-2-one.

Further synthetic utility of the present asymmetric alkylation was successfully demonstrated in the formal synthesis of a neurokinin-3 antagonist, osanetant,[3] as shown in Scheme 4. Optically enriched 3-allyl-3-aryl-piperidin-2-one **2t**, which is prepared by the asymmetric alkylation of the corresponding 3-arylpiperidin-2-one with allyl bromide (Table 2), was converted to the amino alcohol **6** in one-pot through BH_3–mediated deprotection, reduction and hydroboration followed by oxidation with H_2O_2 and NaOH. The obtained amino alcohol **6** with high polarity was converted to **7** by treatment with benzoyl chloride and triethylamine without purification. Since **7** was an intermediate in previous total synthesis of osanetant,[3b] this work contributes to its formal synthesis. The absolute configuration of the allylation



Scheme 4. Formal asymmetric synthesis of osanetant.

product **2t** was determined to be *S* by comparison of the optical rotation of **7** to the literature value (Scheme 4):[3c] the alkylating agent (allyl bromide) should approach from the *Si* face of the enolate anion generated from the 3-arylpiperidin-2-one derivative under the influence of chiral phase-transfer catalyst (*S*)-**5b**.

In summary, we have realized a highly enantioselective alkylation of 3-arylpiperidin-2-ones by installing an achiral auxiliary, 2,2-diarylvinyl group on the lactam nitrogen. The auxiliary was readily removed from the alkylation product by treatment with an acid or BH_3. This methodology certainly expands the synthetic utility of chiral phase-transfer-catalyzed alkylation and provides a practical entry to the construction of chiral quaternary carbon centers in organic synthesis.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation • asymmetric synthesis • lactams • organocatalysis • phase-transfer catalysis

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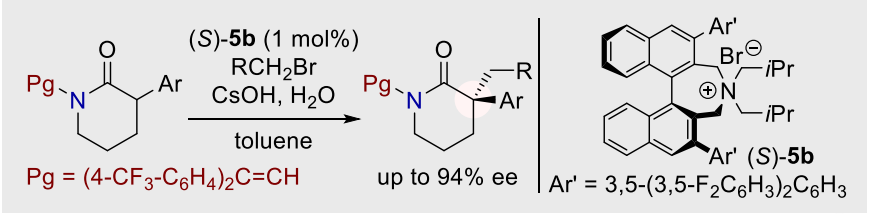

Tomoaki Inukai, Taichi Kano, Keiji Maruoka**

Page No. – Page No.

Construction of a Quaternary Carbon Center by Catalytic Asymmetric Alkylation of 3-Arylpiperidin-2-ones under Phase-Transfer Conditions

δ-Lactams having a chiral quaternary carbon center were synthesized through an asymmetric alkylation of 3-arylpiperidin-2-ones under phase-transfer conditions. A 2,2-diarylvinyl group on the δ-lactam nitrogen plays a crucial role as a novel protecting group and an achiral auxiliary for improving both yield and enantioselectivity of the reaction.