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Palladium/L-Proline-Catalyzed Enantioselective α-Arylative Desymmetrization of Cyclohexanones

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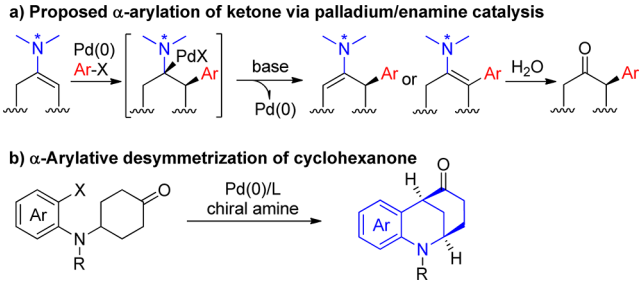
Supporting Information

ABSTRACT: A highly enantioselective palladium/L-proline-catalyzed α-arylative desymmetrization of cyclohexanones was developed. The new strategy for α-arylation reaction led to a series of optically active morphan derivatives bearing α-carbonyl tertiary stereocenters in good yields with excellent enantioselectivities (up to 99% ee).

Transition-metal-catalyzed enantioselective α-arylation of carbonyls represents one of the most important approaches to optically active α-aryl carbonyl compounds.[1] Since the seminal studies from the groups of Buchwald, Hartwig, and Miura,[2] a range of carbonyl compounds have been investigated in enantioselective cross-coupling with aryl halides, including ketones,[3] aldehydes,[4] esters,[5] and amides.[6] However, the aforementioned approaches are very limited to the construction of quaternary carbon stereocenters because the benzylic α-H atom of the tertiary carbon stereocenter is more acidic and prone to racemization under basic conditions. In addition, the demand of commercially unavailable chiral ligands still remains an issue for these transformations. It is noteworthy that a few other catalytic enantioselective arylation protocols to generate α-carbonyl benzylic tertiary stereocenters have been developed, including (1) cross-coupling of α-halo carbonyls with arylmetal reagents,[7] (2) electrophilic coupling of diaryliodonium salts with silyl ketenimides, silyl enolates, or aldehydes,[8] and (3) cross-coupling of aryl triflates with silyl ketene acetals or tin enolates.[9] In comparison, the direct coupling of readily available aryl halides with α-C−H bonds of carbonyl moieties to form the tertiary carbon stereocenters is highly attractive from the viewpoint of atom economy and step efficiency.

In recent years, cooperative catalysis by merging transition-metal and organic catalysis has enabled a series of new enantioselective transformations.[10] Among these, the combined use of palladium/enamine catalysis has been widely investigated for asymmetric allylic alkylation reactions.[11] Consequently, we envisaged that an enantioselective α-arylation of ketones might be realized by this strategy through the formation of enamine intermediates and subsequent Heck arylation (Scheme 1a).[12] Herein we report a palladium/L-proline-catalyzed intramolecular α-arylative desymmetrization of cyclohexanones to deliver a series of chiral compounds containing the hexahydro-2,6-methano-1-benzazocine structural motif with excellent enantioselectivities (Scheme 1b).[13,14] It is worth noting that the racemic variant of this reaction has been established by Solé's group.[15] The resulting unique bridged ring system is analogous

Scheme 1. Palladium/Enamine Catalysis for α-Arylation of Ketones



to the important morphan scaffold (2-azabicyclo[3.3.1]nonane)[16] and frequently occurs in many natural products, such as sespenine, aspernomine, and strychnochromine (Figure 1).[17]

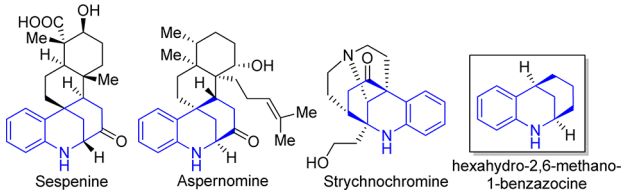


Figure 1. Selected natural products containing the hexahydro-2,6-methano-1-benzazocine framework.

More importantly, an α-carbonyl tertiary stereogenic center is generated in this bridged ring system, and its racemization is prevented by the rigid structural property.

At the outset, 4-(benzyl(2-bromophenyl)amino)cyclohexanone (**1a**) was prepared, and its intramolecular arylation reaction was studied (Table 1). The first test began with the reaction of **1a** under the catalysis of 5 mol % $Pd(OAc)_2$/12 mol % achiral PPh_3 ligand combined with 10 mol % L-proline in tetrahydrofuran (THF) with Cs_2CO_3 (1.5 equiv) as a base. As expected, the desired arylation product **2a** was isolated in 60% yield with 23% ee after reaction at 85 °C (oil bath) for 48 h (entry 1). When the stronger base NaO^{t}Bu was used, the ee was even poorer in spite of an increased yield (entry 2). In contrast, the enantioselectivity was enhanced to 60% when the weaker base K_3PO_4 was used, while no reaction occurred in the presence of K_2CO_3 (entries 3 and 4). Subsequent experiments revealed that the addition of 1.5 equiv of acid was beneficial for the enantioselectivity. A range of carboxylic acid additives afforded

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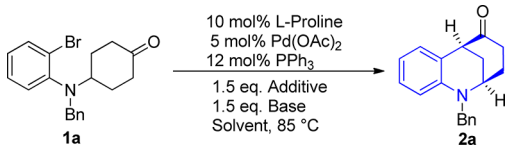
Table 1. Optimization of the Reaction Conditions[a]



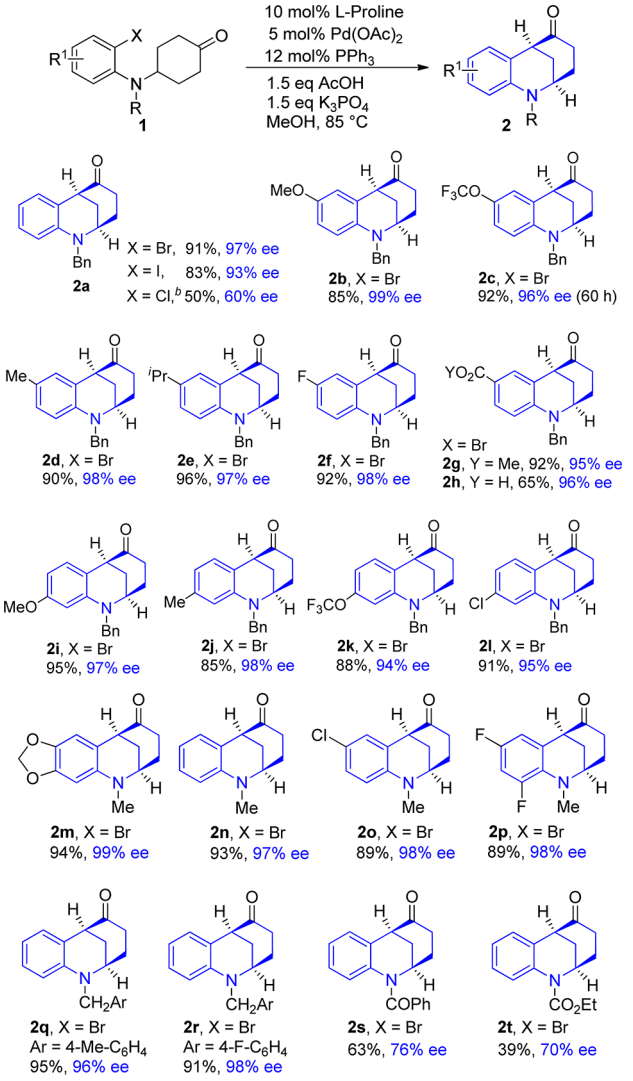
entry	base	solvent	additive	yield (%)[b]	ee (%)[c]
1	Cs_2CO_3	THF	–	60	23
2	NaO^{t}Bu	THF	–	71	<10
3	K_3PO_4	THF	–	60	60
4	K_2CO_3	THF	–	nr	–
5	K_3PO_4	THF	4-$NO_2C_6H_4CO_2H$	60	73
6	K_3PO_4	THF	2-$NO_2C_6H_4CO_2H$	20	70
7	K_3PO_4	THF	4-$MeOC_6H_4CO_2H$	40	72
8	K_3PO_4	THF	3-$ClC_6H_4CO_2H$	87	73
9	K_3PO_4	THF	CF_3CO_2H	79	81
10	K_3PO_4	THF	CH_3CO_2H	95	76
11	K_3PO_4	THF	$TsOH·H_2O$	10	nd
12	K_3PO_4	DMSO	CH_3CO_2H	10	nd
13	K_3PO_4	toluene	CH_3CO_2H	70	20
14	K_3PO_4	MeOH	CH_3CO_2H	91	97
15	K_3PO_4	MeOH	CF_3COOH	90	95
16[d]	K_3PO_4	MeOH	CH_3CO_2H	70	63
17[e]	K_3PO_4	MeOH	CH_3CO_2H	50	76
18[f]	K_3PO_4	MeOH	CH_3CO_2H	31	nd

[a]Reaction conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (12 mol %), L-proline (10 mol %), base (0.3 mmol), and the solvent (2.0 mL) in a sealed Schlenk tube at 85 °C (oil bath) for 48 h, unless otherwise indicated. nr = no reaction; nd = not detected. [b]Isolated yields. [c]Determined by chiral HPLC. [d]With 5 mol % $Pd(dba)_2$ instead of $Pd(OAc)_2$. [e]With 5 mol % $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ and PPh_3. [f]At 70 °C (oil bath) for 60 h.

products with over 70% ee but showed different reactivities (entries 5–11). Acetic acid led to an excellent yield with moderate enantioselectivity (entry 10). As a comparison, a higher enantioselectivity but a relatively lower yield were observed for trifluoroacetic acid (TFA) (entry 9). TsOH was proved to be an inferior additive (entry 11). Subsequent investigation revealed a significant solvent effect. A poor yield was observed when the reaction was performed in DMSO, and a poor ee value was detected in toluene (entries 12 and 13). To our delight, however, excellent yield and enantioselectivity were achieved in MeOH, and in this case TFA additive led to results comparable to those for acetic acid (entries 14 and 15). Moreover, the reaction was also dramatically affected by the nature of the catalyst, and other palladium precursors ($Pd(dba)_2$ and $Pd(PPh_3)_4$) delivered inferior results (entries 16 and 17). Finally, lowering the temperature to 70 °C resulted in a significantly lower yield (entry 18). Therefore, the optimal reaction conditions were determined to be the following: $Pd(OAc)_2$ (5 mol %), PPh_3 (12 mol %), L-proline (10 mol %), 1.5 equiv of K_3PO_4, and 1.5 equiv of CH_3CO_2H in MeOH (2.0 mL) at 85 °C for 48 h.

Under the optimal conditions, we examined the scope of this reaction, and the results are shown in Scheme 2. The effect of halogen was first examined. In comparison with the bromo substrate, the yield and ee were both slightly decreased for the reaction of the iodo substrate. However, almost no reaction took place for the chloro substrate under the standard conditions. In this case, modification of PPh_3 to PCy_3 led to product **2a** in 50% yield with 60% ee. Next, the influence of substitution at C4–C6

Scheme 2. Substituent Effect of Substrate 1[a]



[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (12 mol %), L-proline (10 mol %), K_3PO_4 (0.3 mmol), CH_3CO_2H (0.3 mmol), and MeOH (2.0 mL) in a sealed Schlenk tube at 85 °C (oil bath) for 48 h, unless otherwise noted. [b]With 12 mol % $Cy_3P·HBF_4$ instead of PPh_3.

on the benzene ring of the aniline was examined. Electron-withdrawing and electron-donating substituents were generally well-tolerated, affording the desired products **2b–m** bearing alkyl, halide, alkoxyl, and ester functionalities in good yields with excellent enantioselectivities. Remarkably, a free carboxylic acid was compatible in the reaction, and product **2h** was obtained with 96% ee. Moreover, the N-protecting group has a remarkable effect on the reaction outcome. The reactions of substrates bearing methyl or substituted benzyl protecting groups proceeded smoothly to afford products **2n–r** in good yields with excellent enantioselectivities. However, the reaction was influenced unfavorably by *N*-benzoyl and *N*-ethoxycarbonyl groups, which afforded products **2s** and **2t** in remarkably lower yields and enantioselectivities.

To further extend the reaction scope, substrate **3a** bearing a tetrasubstituted carbon center was prepared and tested under the above optimal conditions. As shown in Scheme 3, to our disappointment, the desired arylation product **4a** was isolated with poor enantioselectivity. Optimization of the phosphine

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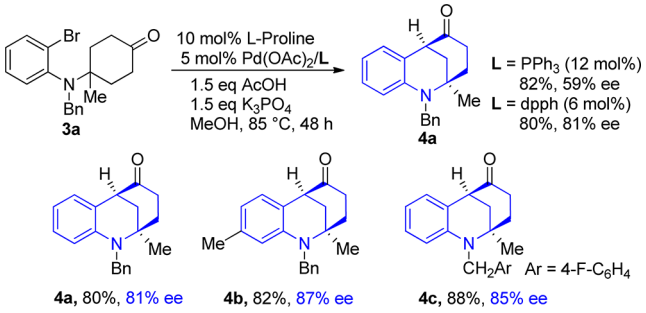
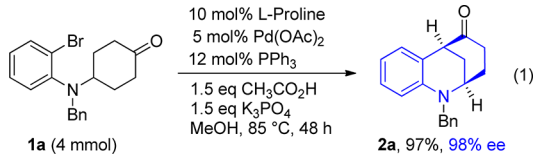
Scheme 3. Asymmetric Arylation of Cyclohexanones Bearing Tetrasubstituted Carbon Centers



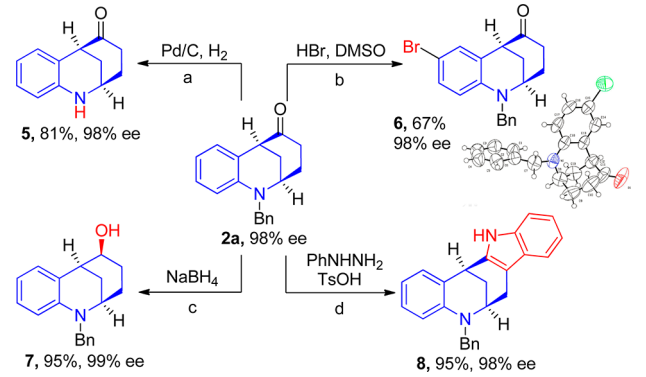
ligand was then conducted, and the enantioselectivity was improved to 81% ee when 1,6-bis(diphenylphosphino)hexane (dpph) was used as the ligand instead of PPh_3 (see Table S1 in the Supporting Information for ligand examination). In the presence of dpph as the ligand, two other bridged ring products **4b** and **4c** bearing tetrasubstituted stereocenters were also formed in good yields and enantioselectivities.

To confirm the scalability of the present method, a scaled-up reaction of **1a** was carried out, and product **2a** was readily isolated in 97% yield with 98% ee (eq 1).



Subsequently, synthetic transformations of the product were conducted. As shown in Scheme 4, Pd/C-catalyzed hydrogenation

Scheme 4. Synthetic Transformations of 2a and Determination of the Absolute Configuration[a]

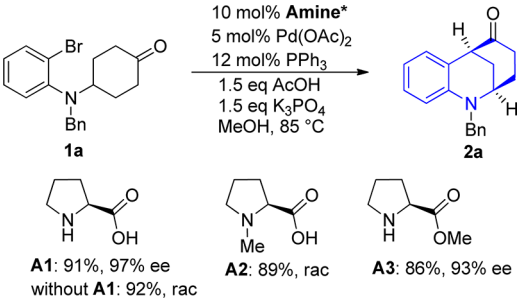


[a]Reaction conditions: (a) 10% Pd/C in EtOH at 30 °C with H_2 balloon for 3 days. (b) **2a** (0.5 mmol), HBr (2.2 equiv), and DMSO (1.1 equiv) in EtOAc (2.0 mL) at 60 °C for 0.5 h. (c) **2a** (0.2 mol) and $NaBH_4$ (0.4 mmol) in MeOH (2.0 mL) at room temperature for 1 h. (d) **2a** (0.2 mmol), phenylhydrazine (1.0 equiv), and TsOH (1.0 equiv) in toluene at 80 °C for 4 h.

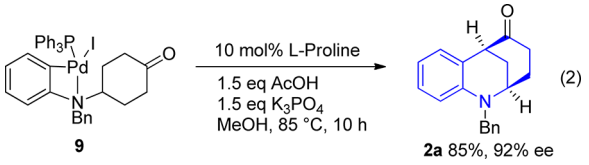
of **2a** in ethanol readily afforded free amine **5** in 81% yield with 98% ee. Bromination of **2a** using HBr/DMSO in EtOAc at room temperature furnished compound **6** in 67% yield with 98% ee. The absolute configuration of **6** was determined to be (2*R*,6*S*) by single-crystal X-ray analysis, which conversely implied the absolute configuration of **2a**. Moreover, facile reduction of **2a** with $NaBH_4$ led to alcohol **7** as a single isomer in 95% yield with 99% ee. A Fischer indolization reaction catalyzed by TsOH produced indole derivative **8** in 95% yield with complete preservation of the enantiopurity.

In order to gain insights into the role of L-proline in this transformation, a few control reactions were conducted. As shown in Scheme 5, racemic product **2a** was isolated in 92%

Scheme 5. Control Experiments



yield in the absence of L-proline (**A1**) and in 89% yield when *N*-methyl-L-proline (**A2**) was used instead. However, excellent enantioselectivity was obtained using (*S*)-methylpyrrolidine-2-carboxylate (**A3**) as a chiral amine. In addition, the reaction of Pd complex **9** (prepared according to the reported method[15]) in the presence of 10 mol % L-proline afforded product **2a** with 92% ee (eq 2). The above results imply that L-proline is more likely to act as an enamine catalyst to activate the ketone.



In conclusion, we have developed a new strategy for the enantioselective α-arylative desymmetrization of cyclohexanones by using palladium/chiral amine catalysis. A series of optically active morphan derivatives bearing α-carbonyl tertiary stereocenters were produced in good yields with excellent enantioselectivities. The present protocol offers new opportunities for the development of enantioselective α-arylation of ketones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01214.

Full experimental and characterization data, including ^1H and ^{13}C NMR spectra for all of the new compounds, chiral HPLC spectra for the products, and crystal data (PDF)

Crystallographic data for **6** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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