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Asymmetric Construction of Quaternary α-Nitro Amides by Palladium-Catalyzed C(sp³)–H Arylation

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Pd-catalyzed enantioselective C(sp³)-H arylation of *N*-(*o*-Br-aryl) anilides has been disclosed, and quaternary α -nitro amides were constructed with up to 98% ee. The presence of the nitro group on the substrate enables the progress of the reaction and the ready transformation of the product to optically active quaternary amino acid derivatives.

Quaternary α , α -disubstituted α -amino acids are important and valuable chemicals that have been widely utilized as enzyme inhibitors, ligands in catalysis, and key units for the preparation of modified peptides and proteins not found in nature.¹ Compared to natural peptides, peptides made from quaternary α -amino acids often show enhanced stability against chemical and enzymatic degradation.² Consequently synthetic methodologies for quaternary α -amino acids have been explored for decades.³ The main reported methods include the alkylation or addition of a glycine ester and its equivalents to electrophiles under phase transfer catalysis,⁴ the asymmetric addition of cyanides to ketonimines,⁵ and the allylic alkylation of glycine esters under transition-metal catalysis.⁶ Despite this expressive progress, considering the wide utility of quaternary amino acid derivatives, the development of new synthetic methodologies is still a high necessity.

Cleavage and transformation of the C-H bond is a direct pathway for the preparation of functionalized molecules, and numerous methods have been developed recently with the use of various metal catalysts.⁷ Asymmetric C-H activation has also received much attention but with limited success.^{8,9} The palladium-catalyzed asymmetric intramolecular arylation reaction is a direct and efficient route for the generation of fused carbocycles and heterocycles. Cramer et al. first reported a seminal example on the enantioselective intramolecular C(sp²)-H arylation of alkenyl triflates,¹⁰ and this catalytic system has been extended to construct a wide variety of compounds with carbon-11 and phosphorous-centered chirality, 12 planar chirality,¹³ and axial chirality¹⁴. With respect to palladiumcatalyzed intramolecular asymmetric C(sp³)-H activation, only a few successful examples¹⁵⁻¹⁸ were disclosed and the reactions were usually carried out at high temperature (>135 °C) to break the strong C(sp³)-H bond and complete the entire reaction process via a concerted metalation deprotonation¹⁹ (CMD) mechanism (Scheme 1). In this regard, Kündig has first disclosed a palladium/chiral N-heterocyclic carbene catalyst for the enantioselective construction of indolines with excellent enantioselectivities.¹⁵ Soon after that, Kagan,¹⁶ and Cramer¹⁷ also reported their protocols for the same reaction independently by using different chiral phosphine ligands. We wondered that asymmetric C(sp³)-H reaction could happen at relatively mild conditions by introducing a strong electronwithdrawing group into the substrate, which may reduce the required activation energy for the C(sp³)-H bond cleavage according to CMD mechanism.²⁰ On the basis of this hypothesis, to continue our interest in the enantioselective C-H activation reaction,^{12a,21} we reported an intramolecular arylation for the construction of optically active guaternary α -nitro amides with excellent enantioselectivities, which are suitable precursors for the preparation of quaternary amino acid derivatives.





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This reaction was initiated with substrate 1a N-(obromophenyl)-*N*-methyl-isobutyramide having a α -nitro group in the presence of a palladium catalyst and phosphorus ligand (Table 1). First, screening achiral phosphine ligands indicated that PCy₃ is an effective ligand (Entry 1). As we expected, the racemic reaction occurred with 81% yield at 100 °C, which is much lower than the reported 160 °C for the C-H arylation of the amide having α -methyl moiety.²² Next, chiral phosphorus ligands were further investigated, and neither the well-known BINAP L1 nor the BINOL skeleton-based phosphoramidite L2 gave the product (Entries 2 and 3), (S,S,S)-SKP ligand²³ L3 developed by Ding et al. afforded the product with 50% ee (Entry 4). The use of (S)-Methoxy-MOP²⁴ generated 36% ee of 2a in 80% yield (Entry 5). Taddol-derived phosphoramidites (L5-L9) have also been examined (Entries 6-15).²⁵ The results revealed that ligand L9 bearing a 3,5-(bis-tertbutyl)phenyl substituent afforded product 2a with the highest enantioselectivity (93% ee) with 32% yield (Entry 10). Switching the palladium acetate to the Pd(Cp)allyl complex17a,26 and increasing the amount of ligand to 25 mol% resulted in an increase in the yield to 70% with the same level of enantiomeric excess (Entry 11). Interestingly, by changing the methyl group on the nitrogen atom to a 4-methoxyl benzyl (PMB) substituent, the use of starting compound 1b led to the formation of desired compound 2b with an improvement in both the enantioselectivity and yield (Entry 12, 98% ee and 85% yield). In contrast, the use of PCy_3 as the ligand resulted in the formation of N-Acyl-5,6-dihydrophenanthridine 2b' (43% yield) as the major product along with 2b (35% yield), and NH substrate without the PMB substituent on the nitrogen atom has no reactivity under the same reaction conditions (Entry 12).27 These results suggest that ligand L9 plays an important role both in the control of enantioselectivity of the C(sp³)-H product and in the suppression of the formation of the byproduct via relatively easy C(sp²)-H activation on the PMB aryl ring. Finally, the screening of solvents did not further improve the yield and enantiomeric excess of the product 2b (Entries 13 to 15).

The substrate scope was examined under the optimized conditions obtained (Table 2). Compound 1, which has diverse electron-rich or -deficient moieties, such as methyl, methoxyl, fluoro, chloro, trifluoromethyl, nitrile, and trifluoromethoxyl, on the aryl ring at the 3-, 4-, 5-, and 6-positions were all tolerated, and the corresponding products 2a-2q were constructed in excellent enantioselectivity (88 to 98% ee). The absolute configuration of product 2 was assigned to be S according to X-ray crystal diffraction analysis of product 2k.28 In addition, a double C-H arylation reaction was conducted by employing substrate 1r, and the fused four-membered ring 2r was isolated in 90% ee and 50% yield (Scheme 2). To further elucidate the effect of the α -substituent group, the reaction was conducted with compounds (1s-1u) containing trifluoromethyl, ethyl ester, and ethyl moieties (Scheme 3). The progress of the reaction was significantly affected by the electron density of the α -substituent. The presence of an electron-deficient group facilitated the progress of the reaction. The reaction of substrate 2u, with an ethyl moiety under the current reaction conditions, did not proceed at all at 120 °C and required a higher

temperature of 160 °C to achieve 60% yield with 52% ee. These results imply that the current reaction also 1070 lso 1070 ceeds 0.016 concerted metalation deprotonation (CMD) mechanism.

To demonstrate the utility of the developed methods, the nitro group of product **2b** can be readily reduced to the amine moiety (Scheme 4a), and the 4-PMB group on the nitrogen atom can also be removed under mild conditions to generate the desired compound **2w** in 90% yield (Scheme 4b).



entry	Pd. Salt	ligand	solvent	yield	ee
		(mol%)		(%) ^b	(%) ^c
1	$Pd(OAc)_2$	PCy ₃	toluene	81	-
2	$Pd(OAc)_2$	(R)-L1	toluene	0	-
3	$Pd(OAc)_2$	(S)-L2	toluene	0	-
4	$Pd(OAc)_2$	(<i>S</i> , <i>S</i> , <i>S</i>)-L3	toluene	6	50
5	$Pd(OAc)_2$	(S)-L4	toluene	80	36
6	$Pd(OAc)_2$	(R,R)-L5	toluene	19	70
7	$Pd(OAc)_2$	(R,R) -L6	toluene	9	46
8	$Pd(OAc)_2$	(<i>R</i> , <i>R</i>)-L7	toluene	13	80
9	$Pd(OAc)_2$	(R,R)- L8	toluene	20	90
10	$Pd(OAc)_2$	(R,R)-L9	toluene	32	93
11^{d}	$Pd(Cp)(C_3H_5)$	(R,R)-L9	toluene	70	93
12^{e}	$Pd(Cp)(C_3H_5)$	(R,R)-L9	toluene	85	98
13^{e}	$Pd(Cp)(C_3H_5)$	(R,R)-L9	1,4-dioxane	40	98
14^{e}	$Pd(Cp)(C_3H_5)$	(R,R)-L9	DMF	0	-
15^{e}	$Pd(Cp)(C_3H_5)$	(R,R)-L9	t-amyl-OH	60	98

^{*a*}Reaction conditions unless otherwise noted: **1a** (0.10 mmol), catalyst (0.01 mmol), ligand (0.02 mmol), K₂CO₃ (0.15 mmol), 1-AdCOOH (0.03 mmol), toluene (1 mL) under a N₂ atmosphere at 100 °C for 24 h. ^{*b*}Isolated yields. ^{*c*}Determined by chiral HPLC. ^{*d*}With Ligand (0.025 mmol), K₂CO₃ (0.20 mmol), 1-AdCOOH (0.05 mmol). ^{*c*}**1b** (0.1 mmol), Catalyst (0.01 mmol), Ligand (0.025 mmol), K₂CO₃ (0.20 mmol), 1-AdCOOH (0.05 mmol), toluene (1 mL) under a N₂ atmosphere at 100 °C for 24 h.



Scheme 2. Enantioselective Double C-H Arylation of 1r.

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Scheme 3. Investigations on α -Substituent Effect of 1.



^{*a*}Reaction conditions unless otherwise noted: **1** (0.10 mmol), $[PdCp(C_3H_5)]$ (0.01 mmol), **L9** (0.025 mmol), K₂CO₃ (0.20 mmol), 1-AdCOOH (0.05 mmol), in toluene (1 mL) under a N₂ atmosphere at 100 °C for 24 h. ^{*b*}Yield of the isolated product. ^{*c*}The *ee* was determined by HPLC.



Scheme 4. The Product Transformation.

Conclusions

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In summary, we have disclosed a direct method reference the construction of quaternary α -nitro and α and

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Conflicts of interest

There are no conflicts to declare".

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