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SUPPORTING Information

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Environmentally Benign Strategy for Arylation of Nitronyl Nitroxide Using a Non-Transition Metal Nucleophile

Shuichi Suzuki,* Fumiya Nakamura, and Takeshi Naota*

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ABSTRACT: We have developed a method for the arylation of nitronyl nitroxide without using its transition metal complex as a nucleophile. Various nitronyl nitroxide-substituted π -electronic compounds can be obtained from the parent nitronyl nitroxide and the corresponding aryl iodides using a combination of zero-valent palladium catalysts and a 2-dicyclohexylphosphino-2',4',6'-triiso-propylbiphenyl ligand in the presence of sodium *tert*-butoxide. The utility of the method has been demonstrated by the direct synthesis of open-shell compounds with giant π -electronic systems, such as **10P**.

S table organic radicals are promising components for intriguing electronic and spintronic devices because of their structural and electronic flexibility and processability.¹ Nitronyl nitroxide derivatives having aromatic functionalities with extended π -electronic systems (**NN-Ar**) have been utilized for organic spin sources, and their properties have been investigated in light of negative magnetoresistance,² highspin molecules,³ and hybrid ferrimagnets.⁴ Generally, **NN-Ar** derivatives are synthesized by condensation reactions of various aromatic aldehydes with *N*,*N'*-dihydroxy-2,3-dimethylbutane-2,3-diamine (Scheme 1a).⁵ Recently, the Okada group and our group have developed synthetic methods for **NN-Ar** derivatives from aryl halides and transition metal complexes (Au,⁶ Cu,⁷ and Zn⁸) of NN radical anions (Scheme 1b). These coupling methods serve as powerful tools for the syntheses of

Scheme 1. Synthetic Methods for NN-Ars



functional NN-Ar derivatives, such as diradicals with strong ferromagnetic interactions^{3c,9} and graphene-like π -electronic systems substituted with NN moieties.¹⁰ Most of these derivatives could not be obtained by the previous condensation method due to the difficulty in synthesizing the starting aldehydes and the high reactivity of the aromatic functionalities toward the oxidation process.^{3c,9} These methods require transition metal NN complexes (NN-M) as the NN anion equivalent, because the NN-Ms are moderately reactive but sufficiently robust toward the degradation during these catalytic processes, probably due to stabilization of the C-M bond by the specific $d-\pi$ conjugation. The use of NN anions of alkaline and alkaline-earth metals for a family of the coupling reactions¹¹ may help establish an environmentally benign strategy due to the lack of a need for transition metals and the subsequent wasting process. However, due to the extraordinarily low stability of these "naked" radical anion species, our trials using stoichiometric lithium and magnesium NN species always gave unsatisfactory results.^{5b,12,13} Hence, we adopted a method for the "in situ" generation of the naked NN anions based on a strategy that includes (1) the equilibrated deprotonation of NN by a bulky base such as NaOtBu and (2) the activation of the NN anion in nonpolar solvents such as toluene. In this system, the radical anion species is well protected from inevitable decomposition or disproportionation. The method thus provides a direct and green method for the versatile synthesis of the NN-Ar that proceeds with high efficiency under the mild conditions (Scheme 1c).

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We initially examined various Li, Na, K, and Cs bases and solvents to confirm their suitability for the coupling reaction of 4-iodoacetophenone (1a) with NN-H in the presence of a tetrakis(triphenylphosphine)palladium(0) $[Pd(PPh_3)_4]$ catalyst (10 mol %) for 1–2 h at 70 °C (Table 1). All trials in

Table 1. Cross-Coupling Reaction of 1a with NN-H



the search for suitable conditions for generating the NN radical anion using a typical combination of base and soluble solvents, such as NaOMe and MeOH, NaOtBu and tBuOH, LiHMDS and THF, and NaOtBu and THF, resulted in no reaction or gave trace amounts of the desired compound. This was probably due to fast decomposition or disproportionation of the unstable NN radical anions (entries 1-8). Notably, NaOtBu and KOtBu provided good results when used in combination with toluene (entries 13-15). The successful results can be explained by the low solubility of NaOtBu and KOtBu in toluene, which keeps the concentration of the NN anion low during the catalytic process. This specific equilibration would successfully inhibit the inevitable disproportionation of NN in this particular system. Cs₂CO₃ afforded a trace amount of the product probably due to its weak basicity for the generation of the radical anion (entry 16).

The catalytic activity of various palladium complexes was examined for the coupling reaction of **1a** with **NN-H** (1 equiv) in the presence of NaOtBu (1 equiv) in toluene (Table 2). Pd(PPh₃)₄ was the best catalyst among the catalysts examined (entries 1–7). The addition of 1,1'-bis(diphenylphosphino)ferrocene (dppf), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos), or 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos) effectively increased the product yield (entry 5, 6, or 7, respectively), while the addition of other phosphines, 1,2-bis(diphenylphosphino)ethane (dppe), 1,2bis(dicyclohexylphosphino)ethane (dcype), or 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl (BINAP), did not lead to any significant additive (or ligand) effect (entries 1–4, Table 2. Catalytic Activity of Various Palladium Complexesand Ligands for the Reaction of 1a with NN

	1a (1 equiv) NaO/Bu (1 equiv) Pd catalyst (10 mol%) additive toluene, 1–2 h, 70 °C		(° 1P	
catalyst		additive		,

entry	catalyst	additive	yield (%) ^a	
1	$Pd(PPh_3)_4$	none	63	
2	$Pd(PPh_3)_4$	dppe (10 mol %)	62	
3	$Pd(PPh_3)_4$	dcype (10 mol %)	60	
4	$Pd(PPh_3)_4$	BINAP (10 mol %)	65	
5	$Pd(PPh_3)_4$	dppf (10 mol %)	79	
6	$Pd(PPh_3)_4$	XPhos (20 mol %)	83	
7	$Pd(PPh_3)_4$	SPhos (20 mol %)	73	
8	Pd ₂ (dba) ₃ ·CHCl ₃	none	7	
9	Pd ₂ (dba) ₃ ·CHCl ₃	XPhos (20 mol %)	31	
10	PdCl ₂	dppf (10 mol %)	0 ^b	
11	$Pd(PPh_3)_2Cl_2$	none	trace ^b	
12	$Pd(OAc)_2$	XPhos (20 mol %)	trace ^b	
13	Pd-PEPPSI-iPr	none	0 ^b	
14	none	none	0 ^b	
^a Isolated yield based on NN-H . ^b Monitored by TLC.				

respectively). Tris(dibenzylideneacetone)dipalladium(0)– chloroform adduct $[Pd_2(dba)_3 \cdot CHCl_3]$ and various divalent palladium complexes, $PdCl_2$ -bis(triphenylphosphine) [Pd-(PPh_3)_2Cl_2], $PdCl_2$ -[1,1'-bis(diphenylphosphino)ferrocene (dppf)], $[Pd(OAc)_2]$ -[2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos)], and $PdCl_2$ -[1,3-bis(2,6diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl) [Pd-PEPPSI-*i*Pr], showed almost no catalytic activity (entries 8, 10–13, respectively). It is noteworthy that the yield of the corresponding **NN-Ar** in this catalytic process (entry 6) was higher than those obtained upon similar treatment with transition metal NN nucleophiles such as NN-Au(PPh_3)⁶ and NN-ZnCl⁸ (Tables S1 and S2).

The acceleration effect of XPhos was also observed by timedependent changes in the concentration of the starting material NN-H, which can be monitored at λ_{max} maxima of 549 nm by means of UV-vis spectrometry (Figure S1). The initial rate constants k_{obs} ($k_{obs} = -d[NN-H]/dt$) were determined to be 5.50 × 10⁻⁴ s⁻¹ for the Pd(PPh₃)₄ (10 mol %)-XPhos (20 mol %) catalyst and 3.42 × 10⁻⁴ s⁻¹ for the Pd(PPh₃)₄ catalyst (10 mol %) (Figure 1), which indicated that the reaction with XPhos proceeds 1.6 times faster than that without the ligand. The linear time dependence of the concentration of NN-H in the reaction with the Pd(PPh₃)₄-XPhos catalyst (Figure 1a and Figure S1) indicated that the addition effect of XPhos is ascribed to the acceleration of the rate-determining step in the catalytic process instead of the inhibition of the deactivation of the catalytically active species.

To gain information about the reaction mechanism, we monitored the coupling reaction of **NN-H** and **1a** under the optimized condition by means of electron spin resonance (ESR) spectroscopy (Figure 1b). The 10-line ESR signal for **NN-H** $[la^{N}]$ (hyperfine coupling of ¹⁴N nuclei) = 0.74 mT, and $la^{H}|$ (hyperfine coupling of ¹H nucleus) = 0.36 mT],⁶ observed at the initial stage of the reaction, was gradually converted into a five-line signal ($la^{N}| = 0.75$ mT) that was assigned to **1P**. In spite of the lack of detection of ESR signals assigned to **NN-Na** during the catalytic reaction, the formation of a stoichiometric



Figure 1. Time-dependent changes in (a) absorbance at 549 nm and (b) ESR spectra during the reaction of **1a** $(1.32 \times 10^{-2} \text{ M})$ and **NN-H** (1 equiv) with the Pd(PPh₃)₄ (10 mol %)–XPhos (20 mol %) catalyst in the presence of NaOtBu (1 equiv) in toluene at 70 °C. Filled and empty squares denote the reactions with and without XPhos as an additive, respectively. The red and blue solid lines show the fitting lines by the first-order equation. The observed rate constants (k_{obs}) of the reaction with and without the additive were estimated to be 5.50 × 10⁻⁴ and 3.42 × 10⁻⁴ s⁻¹, respectively.

amount of NN-D from the reaction of NN-H with NaOtBu was confirmed by the ESR analysis of the control reaction in CD₃OD and toluene (Figure S2), which strongly suggests that the NN-Na intermediate generated from NN-H and NaOtBu is consumed immediately upon the subsequent reaction with the $ArPdIL_n$ species during this catalytic coupling reaction. This mechanistic assumption rationally explains the experimental result showing that the present coupling reaction using NN-Na as the nucleophile proceeded specifically when NaOtBu and toluene were used as a combination of base and solvent (Scheme S1). NN-H undergoes equilibrated proton abstraction with the bulky NaOtBu to give a trace amount of NN-Na. NN-Na acts as an efficient nucleophile for this coupling reaction, undergoing rapid transmetalation with the ArPdIL_n species formed by the oxidative addition of the catalytically active PdL_n species to Ar-I. The reaction would proceed smoothly without any degradation of the unstable NN-Na, despite the low concentration and low stability of this intermediate, because highly diluted NN-Na is protected from self-degradation but sufficiently activated as an effective nucleophile in a noncoordinating solvent such as toluene. The unsatisfactory results obtained when using NaH and NaHMDS (entries 10 and 12, respectively, of Table 1) would be caused by the stoichiometric formation of NN-Na and its subsequent rapid self-degradation. The acceleration effect of dppf and Xphos (entries 5 and 6, respectively, of Table 2) can be explained by the strong electron-donating nature of these ligands,¹⁴ which would accelerate the rate-determining step for the oxidative addition of PdL_n to Ar-I.

Table 3 summarizes the representative results for the coupling reaction using catalytic amounts of $Pd(PPh_3)_4$ and XPhos as the optimal condition.¹⁵ Various aryl iodides could be efficiently converted into the corresponding NN-Ar derivatives (entries 4, 5, 7–10, 12, and 14–17), while a similar treatment of aryl bromides and triflate gave unsatisfactory results (entries 1–3, 6, 11, and 13). Phenyl iodides with various electron-donating and electron-with-drawing groups (4a–7a) could be converted into the desired NN derivatives (4P–7P, respectively) (entries 7–10, respectively). π -Extended NNs (8P–10P) and heteroaromatic NNs (11P and 12P) except for pyridine derivative 13P could also be obtained with high efficiency (entries 12 and 14–18). The NN functionality in the NN-Ar products was confirmed

Table 3. Cross-Coupling Reaction of Various Ar-X Substrates



^{*a*}For a, X = I. For b, X = Br. For c, X = OTf. ^{*b*}Isolated yield based on NN-H. ^{*c*}Detected by TLC.

by single-crystal XRD analysis of the **10P** crystal obtained by recrystallization from a dichloromethane/hexane mixture,¹⁶ as shown in Figure 2. This catalytic reaction allows for the facile and versatile syntheses of **NN-Ar** compounds with giant π -electronic systems, which have been recognized as candidates



Figure 2. (a) Top and (b) side ORTEP views of 10P (50% probabilities). Hydrogen atoms have been omitted for the sake of clarity.

for molecular graphene nanoribbons functionalized with magnetic edges.¹⁰

We developed a new direct functionalization of NN-H to NN-Ar derivatives using catalytic amounts of palladium complexes. The method can be applied to various π -electronic systems, including benzene moieties, heteroaromatic moieties, and fused benzene species. We also demonstrated that this method is a simpler alternative to the conventional multistep methods using stoichiometric amounts of transition metal sources for the preparation of new open-shell molecules.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04655.

Experimental procedure, UV-vis spectra of NN-H and 1P, effects of phosphine ligand for other coupling reaction, ESR spectra of NN-H in CD_3OD -toluene, proposed reaction mechanism, and ESR spectra of 10P and 11P (PDF)

Accession Codes

CCDC 1973888 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

- Shuichi Suzuki Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560-8531, Japan; orcid.org/0000-0001-6294-9084; Email: suzuki-s@chem.es.osaka-u.ac.jp
- Takeshi Naota Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560-8531, Japan; orcid.org/0000-0001-5348-3390; Email: naota@chem.es.osaka-u.ac.jp

Author

Fumiya Nakamura – Department of Chemistry, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560-8531, Japan

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.9b04655

Notes

The authors declare no competing financial interest.

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(15) The yields of products did not increase even with a longer reaction time or a higher temperature (100 $^{\circ}$ C).

(16) CCDC 1973888 (10P) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc. cam.ac.uk/data_request/cif.