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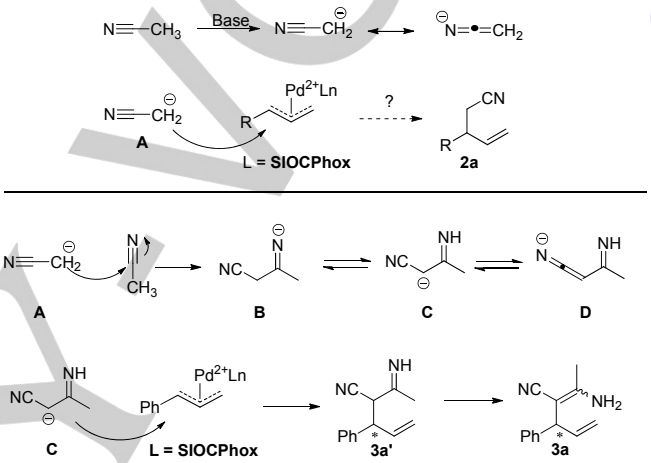
Tandem Thorpe reaction/palladium catalyzed asymmetric allylic alkylation: Access to chiral β-enaminonitriles with excellent enantioselectivity

Da-Chang Bai,[a] Xiu-Yan Liu,[a] Hao Li,[a] Chang-Hua Ding,*[a] and Xue-Long Hou*[a,b]

Abstract: A new type of nucleophile, 3-imino nitrile carbanion generated in-situ by Thorpe reaction of acetonitrile with base, was developed successfully and applied in Pd-catalyzed asymmetric allylic alkylation with mono substituted allyl reagents under Pd/SIOCPhox catalysis, affording β-enaminonitrile products in high yields with excellent regio- and enantioselectivities.

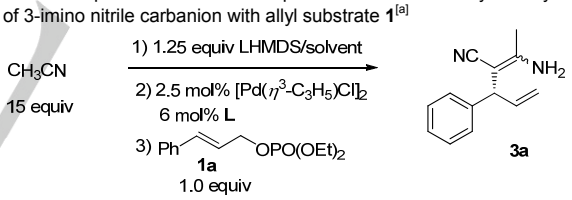
Since its discovery in about 40 years ago, palladium-catalyzed asymmetric allylic alkylation (AAA) has demonstrated its power in enantioselective construction of carbon-carbon and carbon-hetero atom bonds as well as in organic synthesis.[1] To date many efforts have been paid to the development of new type of nucleophiles including carbon nucleophiles.[1-3] Although α-carbanions of ketones and carboxylic acid derivatives have successfully been used as carbon nucleophile in Pd-catalyzed AAA,[2,4e-h,k,l] few reports appeared regarding the use of α-carbanion of nitriles in Pd-catalyzed AAA, probably due to the "hardness" of carbanion and its interconversion between the *C*- and *N*-metalated forms.[3] Because of rich chemistry of nitriles[5] and importance of nitrogen-containing molecules in life science,[6] development of nitrile-containing carbanion as nucleophile in Pd-catalyzed AAA is highly demands. We have been involved in Pd-catalyzed AAA for years and developed some new types of nucleophiles.[4] During the study on the use of "hard" carbanions in the reaction, we found that a novel carbon-nucleophile, 3-imino nitrile carbanion,[7] was formed and corresponding allylic allylation products were afforded in excellent ee when using acetonitrile in Pd-catalyzed AAA. In this communication, we would report this tandem Thorpe reaction/Pd-catalyzed asymmetric allylic alkylation of acetonitrile with mono substituted allyl reagents, affording β-enaminonitrile products in high yields with excellent regio- and enantioselectivities (Scheme 1). Despite the importance of this useful building block,[8,9] only limited methods have been reported for their synthesis.[10]

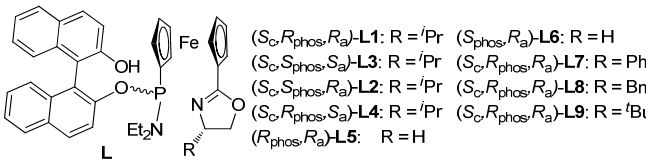
At the beginning, we used acetonitrile to react with cinnamyl phosphate **1a** in the presence of Pd/SIOCPhox catalyst with LHMDS as base to see if α-carbanion of acetonitrile was produced and reacted as nucleophile. However, we could not obtain the expected allylic alkylation product **2a**, instead, we separated allylated nitrile **3a**, which contains β-enaminonitrile group, a useful subunit in the synthesis of heterocycles and polymers as well as in pharmaceutical chemistry.[8,9] Obviously, **3a** should be produced from the reaction of allyl reagent **1a** with nucleophile **C**, a new type of nucleophile formed in situ from two molecules of acetonitrile by attack of α-carbanion of acetonitrile **A** to another acetonitrile followed by isomerization (Scheme 1).



Scheme 1. 3-Imino nitrile carbanion prepared in situ from acetonitrile

Table 1. Optimization of reaction parameters for Pd-catalyzed allylic alkylation of 3-imino nitrile carbanion with allyl substrate **1**[a]





entry	L	solvent	Yield (%)[b]	B/L[c]	*E*/*Z*[c]	ee (*E*/*Z*)(%)[d]
1	**L1**	THF	82	97/3	89/11	85/91
2	**L4**	THF	78	91/9	89/11	55/60
3	**L3**	THF	30	90/10	88/12	-65/--
4	**L2**	THF	26	91/9	88/12	ND
5	**L5**	THF	75	97/3	89/11	85/83
6	**L6**	THF	84	93/7	85/15	-24/0
7[e]	**L1**	THF	51	95/5	89/11	73/--
8[f]	**L1**	THF	40	36/64	--	33 /--

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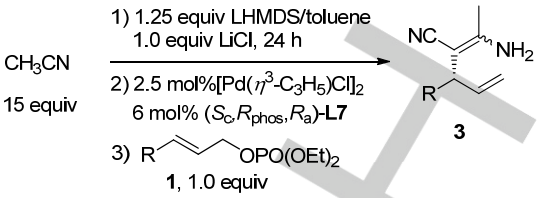
9	**L1**	DME	73	95/5	88/12	87/84
10	**L1**	Et_2O	89	97/3	88/12	89/91
11	**L1**	dioxane	72	99/1	86/14	88/90
12	**L1**	toluene	95	95/5	89/11	91/93
13	**L1**	CH_2Cl_2	NR	--	--	--
14	**L7**	toluene	96	96/4	89/11	94/93
15	**L8**	toluene	74	95/5	83/17	62/66
16	**L9**	toluene	73	95/5	80/20	87/90
17[g]	**L7**	toluene	88	96/4	89/11	88/90
18[h]	**L7**	toluene	99	98/2	89/11	94/97
19[i]	**L7**	toluene	99	96/4	90/10	95/95
20[j]	**L7**	toluene	90	>99/1	90/10	96/98

[a] Reaction conditions: **1a**/LiHMDS/[Pd(η^3-C_3H_5)Cl]$_2$/**L** = 100/125/2.5/6, 0.25 mL CH_3CN, 0.2 mmol **1** in solvent (3.0 mL), CH_3CN reacted with base for 1.5 h, room temperature, monitored by TLC. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC. [e] **1b** with OCO_2Me as leaving group was used instead of **1a**. [f] **1c** with Cl as leaving group was used instead of **1a**. [g] 0 °C. [h] 40 °C. [i] LiCl (1.0 equiv). [j] LiCl (1.0 equiv), CH_3CN reacted with base for 24 h at room temperature.

To understand better this tandem reaction and to improve its efficiency, the influence of the reaction parameters on the reaction was investigated. SIOCPhox ligands developed by us[4] were adopted as they showed excellent regio- and enantioselectivities in the Pd-catalyzed AAA. When cinnamyl phosphate **1a** was reacted with acetonitrile using LHMDS as base in the presence of [Pd(η^3-C_3H_5)Cl]$_2$ and (S_c,R_{phos},R_a)-SIOCPhox (**L1**) in THF at room temperature, allylation product **3a** was obtained in 82% yield with B/L ratio of 97/3, *E*/*Z* ratio of 89/11, and ee of 85% for *E* isomer (Table 1, entry 1). The evaluation of SIOCPhox ligands revealed the importance of their structure in controlling the yield and enantioselectivities of the product (Table 1, entries 1-6). The examination of leaving group (LG) of allyl substrate **1** showed that the phosphate ester was best (Table 1, entry 1 *vs* entries7 and 8). The screen of solvent effect indicated that toluene was the choice among tested solvents since the reactivity and the enantioselectivity is better than other solvents (Table 1, entry 1 *vs* entries 9-13). With toluene as solvent, the substituent of oxazoline in SIOCPhox ligand was examined (Table 1, entries 14-16). When the (S_c,R_{phos},R_a)-SIOCPhox (**L7**) with Ph as substituent was used, the ee increased to 94% while the yield and the *E*/*Z*-selectivity was maintained (Table 1, entry 14). When the reaction temperature was 0 °C , the ee of the major product decreased to 88% while it was 40 °C, the ee of the major product was same as that at room temperature (Table 1, entry 14 vs entries 17-18). It was found that the use of LiCl as additive benefited the reactivity and selectivity (Table 1, entry 19). When the reaction time of CH_3CN with base was extended, the ee of the major product increased to 96% with excellent regio- and *E*/*Z*-selectivities (Table 1, entry 20).

Table 2. Substrate scope of Pd-catalyzed allylic alkylation of 3-imino nitrile carbanion with allyl substrate **1**[a]



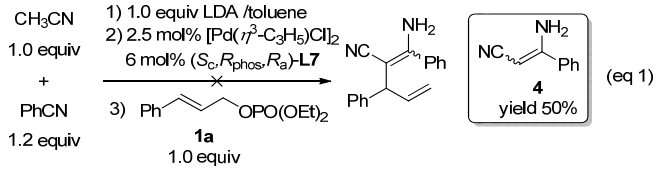
entry	R	yield (%)[b]	B/L[c]	*E*/*Z*[c]	ee (*E*/*Z*) (%)[d]
1[e]	Ph (**1a**)	**3a**, 90	>99/1	90/10	96/98
2[e]	4-MeC_6H_4 (**1d**)	**3d**, 94	95/5	90/10	88/--
3	4-^{i}PrC_6H_4 (**1e**)	**3e**, 94	>99/1	90/10	93/--
4	4-FC_6H_4 (**1f**)	**3f**, 73	95/5	89/11	95/--
5	4-ClC_6H_4 (**1g**)	**3g**, 99	95/5	90/10	87/--
6	4-BrC_6H_4 (**1h**)	**3h**, 99	94/6	90/10	89/--
7	4-$CF_3C_6H_4$ (**1i**)	**3i**, 81	>99/1	90/10	90/--
8[e]	3-MeC_6H_4 (**1j**)	**3j**, 88	99/1	90/10	93/--
9	3-$MeOC_6H_4$ (**1k**)	**3k**, 90	>99/1	88/12	95/--
10	2-MeC_6H_4 (**1l**)	**3l**, 98	98/2	90/10	95/--
11	2-Naphthyl (**1m**)	**3m**, 81	94/6	88/12	94/--
12	Cyclohexyl (**1n**)	NR	--	--	--

[a] Reaction conditions: **1**/LiHMDS/[Pd(η^3-C_3H_5)Cl]$_2$/**L7** = 100/125/2.5/6, 0.25 mL CH_3CN, 0.2 mmol **1** in solvent (3.0 mL), 30 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by HPLC. The ee of *Z*-product except for **3a** was not determined. [e] Room temperature.

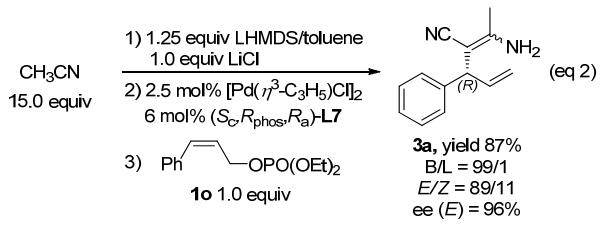
Under the optimized reaction conditions, the scope of the substrates was examined (Table 2). The reaction proceeded well for a wide range of cases, affording alkylation products in 73-99% yields with branched/linear ratio of 94/6-99/1, *E*/*Z* ratio of 88/12-90/10 and 87-96% ee for (*E*)-products. In all cases excellent regioselectivity was obtained. A little bit lower ee were obtained for **3d** and **3e** with methyl- and isopropyl- on the para-position of the phenyl ring (Table 2, entries 2 and 3). Fluoro, chloro, bromo and trifluoromethyl at the *para*-position of the phenyl ring were tolerated (Table 2, entries 4-7). The reaction also worked well for allyl substrates **1** with *m*-methyl, *m*-methoxy and *o*-methyl as substituent on phenyl ring, affording allyl products with excellent enantioselectivity (Table 2, entries 8-10). The yield was slightly lower when 2-naphthyl allyl substrate **1m** was used (Table 2, entry 11). No desired product was obtained when cyclohexyl allyl reagent **1n** was used because β-H elimination took place (Table 2, entry 12).

It is known that various nucleophiles can be obtained with different nitrile by Thorpe reaction, so we tried some other nitriles in this Pd-catalyzed AAA. When acetonitrile and benzonitrile were used in our system, only Thorpe reaction occurred but no palladium catalyzed allylic alkylation product

was obtained (eq 1), probably due to the steric hindrance of the nucleophile generated by Thorpe reaction.



When (*Z*)-allyl reagent **1o** was used in the reaction, similar results with that using (*E*)-allyl reagent were obtained, which indicated this reaction proceeded through the same π-allylpalladium intermediate (eq 2). All of these results support the proposed pathway depicted in Scheme 1.[1,11]



The absolute configuration of product **3h** was assigned as (*R*) and the alkene configuration was determined as *E* by X-ray analysis of its single crystal.[12]

In summary, a new type of carbon-nucleophile has been developed from the reaction of acetonitrile with base and used in Pd-catalyzed AAA with monosubstituted allyl reagents successfully, affording β-enaminonitrile products in high yields with high regio- and enantioselectivities. These results not only show the formation and application of new type of nucleophile in Pd-catalyzed AAA but also provide some information, which should be useful in the development of new type of nucleophile.

Acknowledgements

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Keywords: palladium · allylic alkylation ·3-imino nitrile ·asymmetric catalysis ·Thorpe reaction

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[12] Crystallographic data of compound **3h** have been deposited at the Cambridge Crystallographic Data Centre with CCDC 1510786. For its structural detail, see the Supporting Information.

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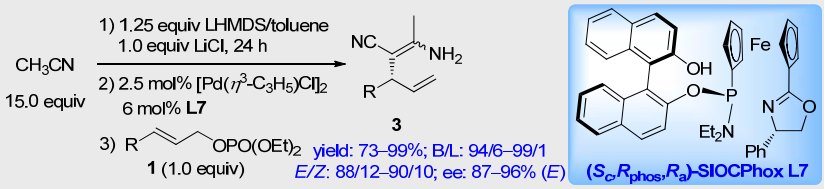

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