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Highly Efficient Palladium-Catalyzed Allylic Alkylation of Cyanoacetamides with Controllable and Chemoselective Mono- and Double- Substitutions

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Dedication ((optional))

Abstract: It was found that catalytic allylation of various cyanoacetamides proceeded smoothly and efficiently in environmentally benign PEG-400 (PEG = poly(ethylene glycols)) in the presence of $Pd(OAc)_2$ and novel triazine-derived multifunctional ligand **L1**, in which this reaction could afford the structurally diverse mono- and double- allylated adducts in good to excellent yields as well as good chemo- and regio-selectivity. In addition, this Pd/**L1**/PEG-400 catalyst system could be recycled five runs with good yield and high efficiency, which supported the triazine–containing Schiff base-based phosphine ligand could be a multifunctional and reusable ligand encapsulated in PEG-400.

Introduction

Since the pioneering work of Tsuji and Trost,[1] the palladium-catalyzed allylic alkylations offers one of the most convergent approaches for the construction of complex molecular frameworks, and has become a fundamental carbon-carbon bond-forming reaction in synthetic chemistry.[2] This prestigious reaction has been developed into many synthetically useful variants.[3,4] Despite the use of π-allyl palladium chemistry for the construction of γ-lactams via intramolecular allylic alkylation of a resonance-stabilized carbanion linked with an activated amide and an allylic acetate has been described extensively by several groups,[5] a highly efficient intermolecular allylic alkylation of cyano-activated acetamides is still elusive. Little attention has been dedicated to finding mild and catalytic chemoselective approaches for the allylic alkylation of amide- and cyano-containing functional carbonyl compounds.[6,7] In fact, substituted cyano-containing carbonyl compounds as well as functional amides are useful class of building blocks in organic synthesis, bioactive natural products, drug discovery, and pharmaceutical agents.[5-8] However, it is recognized as a challenge to use cyano-containing acetamides (cyanoacetamides) in environmentally benign and chemoselective allylic alkylation because of low nucleophilic activity and the stabilized nature of Pd-NC coordination derived from cyano moiety with palladium center.

And from the standpoint of green chemistry and industrial applications of expensive palladium catalysts, the development of a recyclable and reusable palladium catalyst system that allows for the highly efficient allylic alkylation is highly desirable. Exceptionally, the exploring of highly efficient and recyclable palladium catalyst systems tolerated various functional groups for this reaction is much valuable.[9] It should be also noted that, one important and practical aspect of synthetic chemistry toward green processes is the development of recyclable palladium catalysts that provide high chemoselectivity and good activity in various chemical reactions. However, the decrease of catalytic activity of recovered metal complex-based catalysts was a common phenomenon in homogeneous catalysis.[10,11] Therefore, it is an important topic in terms of the chemoselectivity and recyclability of palladium catalyst, environmentally benign process, and efficiency of new catalyst system as well as adaptability of allylic alkylation chemistry for the application in industry. Although various reports of catalytic transformations of cyano-containing carbonyl compounds exists,[5-8,11] there remains considerable room for development of green process for allylic alkylation reaction with cyano-containing carbonyl compounds and improvement in terms of functional group tolerance, which could enable an environmentally benign methodology ideal for use in the field of green chemistry and complex molecule synthesis.[12,13]

Notably, among the recyclable and green solvents, poly(ethylene glycols) (PEGs) has been attracted much attentions in homogeneous catalysis and has become one of the suitable choices as reused solvent due to its non-flammable, non-toxic, inexpensive and recoverable nature.[14] So far, PEGs have been successfully employed as reaction media for palladium-catalyzed carbon-carbon bond-forming reaction.[15-18] Surprisingly, there is no report on Pd-catalyzed allylic substitutions in PEGs with a recyclable and efficient manner. Thus we would like to present our findings on controllable mono- and double- allylic substitutions using a palladium catalyst, new triazine-derived ligand, cyano-containing acetamides, simple allylic acetate, and an environmentally benign PEG-400 media, in which a facile preparation of substituted dicarbonyl compounds was finished with excellent chemoselectivities and controllable mono- and double- allylic substitutions via

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environmentally benign process. In addition, our method regarded of allylic alkylation of cyano-containing acetamides is distinguished from earlier reports in terms of new ligands and recyclability of catalyst systems.

Results and Discussion

For initial tests, we chose 2-cyano-*N,N*-diphenylacetamide (**1a**) and simple allylic acetate (**2a**) as model substrates for the allylic alkylation reaction using $Pd(OAc)_2$, DPEPhos, K_2CO_3 and PEG-400 at room temperature. Interestingly, in this preliminary check, only a trace amount of desired product **3a** was observed (Table 1, Entry 1). Other commercially available phosphine ligands, such as XtanPhos and PCy_3, could not promote the palladium catalyzed allylic alkylation to afford the product **3a** (Entries 2 and 3, also see Table S1 of ESI). This observation prompted us to develop novel multifunctional phosphine ligands for the titled reaction. In addition, the design and synthesis of new ligand with highly catalytic efficiency and excellent chemoselectivity is necessary in the catalytic allylation chemistry.

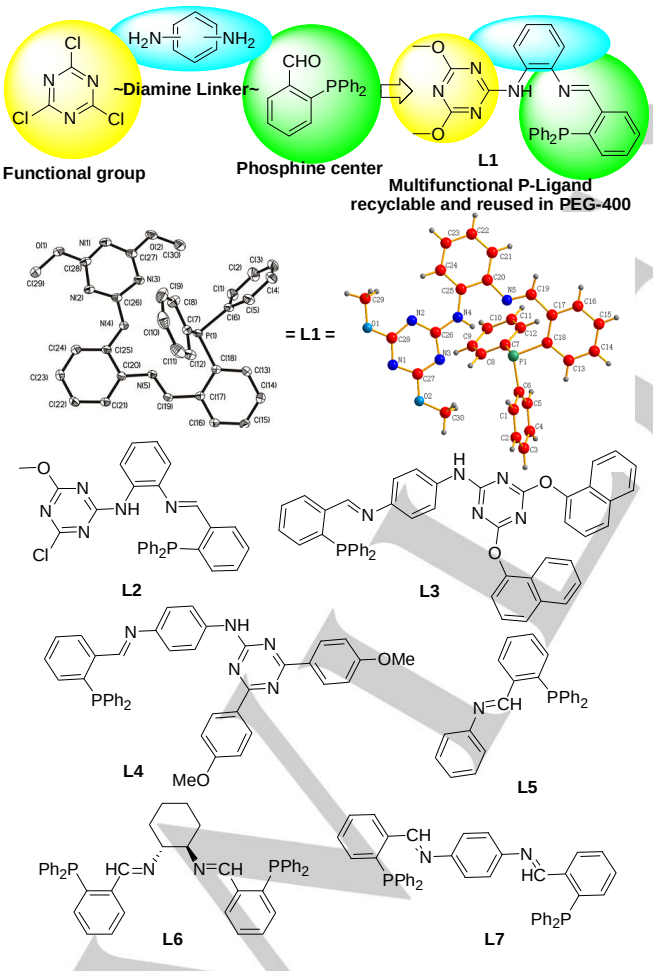
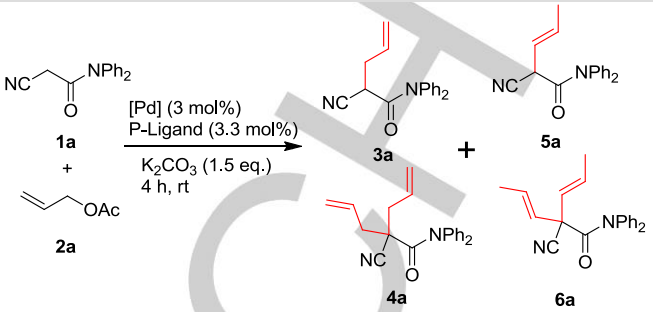


Figure 1. Structures of new ligands **L1-L4** and related P-ligands with Schiff base moiety[19] used in this work. X-ray crystal structure of the ligand **L1** (CCDC 1495547).

Table 1. Optimization of Pd-catalyzed mono-allylation of cyano-containing acetamide **1a** with allylic acetate **2a**[a]



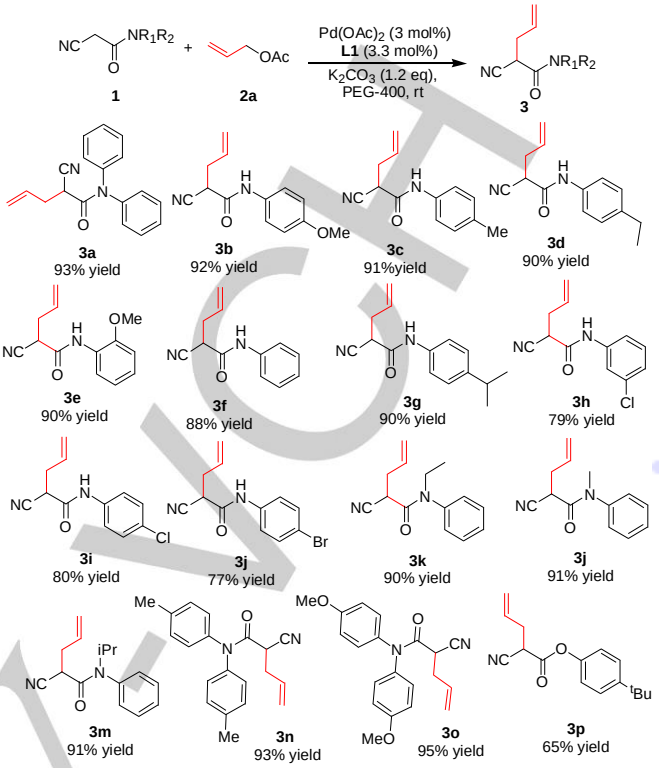
Entry	Ligand	Solvent	Yield of **3a** (%)[b]	**3a**/**4a**/**5a**/**6a**[c]
1	DPEPhos	PEG-400	trace	--
2	XtanPhos	PEG-400	N.D	--
3	PCy_3	PEG-400	N.D	--
4	**L5**	PEG-400	71	75/0/25/0
5	**L6**	PEG-400	72	72/0/28/0
6	**L7**	PEG-400	71	65/0/35/0
7	**L1**	PEG-400	93	98/0/2/0
8	**L2**	PEG-400	22	55/0/45/0
9	**L3**	PEG-400	77	88/4/5/3
10	**L1**	H_2O	N.D	--
11	**L1**	DMSO	72	85/12/5/3
12	**L5**	DMF	77	84/0/13/3
13	**L6**	DMAc	77	85/0/12/3
14	**L7**	DCM	77	90/0/10/0

[a] The reaction conditions: **1a** (1 equiv.), **2a** (1.5 equiv.), $Pd(OAc)_2$ (3 mol%), P-ligand (3.3 mol%), K_2CO_3 (1.5 eq.) and PEG-400 (1 mL) at room temperature for 4h. [b] Isolated yield. [c] Ratio of **3a**:**4a**:**5a**:**6a** was determined by ^{1}H-NMR analysis of crude mixture.

Then we focused on a modularly synthetic strategy to triazine-based multifunctional *N,P*-ligands on the basis of our previous findings in Schiff base and phosphine ligand chemistry.[20] As shown in Figure 1, our approach provided a convergent, and

highly modular means for the construction of rigid and multifunctional Schiff base containing one phosphorous and five nitrogen atoms in most cases (Figure 1, **L1**-**L4**). The structure of new ligand **L1** was confirmed by X-ray crystallography (CCDC 1495547). Importantly, the multiple heteroatom-containing ligands **L1**-**L4** presented in this work were derived from the aromatic diamine and triazine respectively. The phosphorous atom or -PPh_2 can be easily introduced by 2-diphenylphosphanyl-benzaldehyde (The detailed synthetic procedures for the synthesis of new ligands **L1**-**L4** were provided in Supporting Information), in which the linked reaction is the simple condensation of aldehyde and primary amine to construct the Schiff base moiety. Notably, we hypothesized that triazine core would be beneficial to the encapsulation of palladium catalyst in PEG-400, especially for the ether-containing triazine-derived ligands **L1**-**L4**. To support the importance of triazine moiety in this work, other simple Schiff base-based phosphine ligands, for example, ligand **L6**,[19] were also used for comparison in the palladium catalyzed allylic alkylation of cyano-containing acetamide.

With phosphine ligands **L1**-**L4** (Figure 1) in hand, we then test the performance of these Schiff-base phosphine ligands in the titled reaction. Notably, the allylic alkylation of cyano-containing acetamide **1a** with allylic acetate **2a** is not so simple as imagined because four possible product could be formed in the presence of palladium catalyst. Gratifyingly, triazine-linked multifunctional phosphine ligand **L1** could promote the palladium-catalyzed allylic substitution to afford 93% yield of **3a** and exhibited both excellent chemo- and regio-selectivity, with 98:2 of **3a**/**5a** and without the observation of double allylated product either **4a** or **6a**. Unexpectedly, when **L2** and **L4** bearing a chloride group around the triazinal core were individually tested in the allylic alkylation reaction, the yield and chemoselectivity were significantly decreased obviously, only to give 22% and 58% yield of **3a** respectively (Entries 8 and 9). Interestingly, the simple phosphine ligand **L5-L7** with Schiff base-based afforded decreased yield of desired product **3a** with lower chemo-selectivity (Entries 4-7). In addition, undesired isomerization reaction of **3a** occurred to give **5a**, which was detected based on ^{1}H-NMR analysis of the reaction mixture. Next, solvents were also tested under identical conditions in the presence of $Pd(OAc)_2$ and **L1**. It was found that other solvents, such as DMSO, DMF, DCM, and DMAc, afforded the moderate yield of desired **3a** and exhibited poor selectivity (Entries 10-14). Although the high efficiency and good selectivity could be also achieved in MeCN, THF, and Toluene (Table S3-S5 of ESI), PEG-400 is still the ideal choice of solvent due to the environmentally friendly property, inexpensive and recyclability nature. Then, different bases and Pd-catalysts were tested and series of experiments were carried out to examine the effect of various reaction parameters (See Table S2 and Table S6 of ESI respectively), such as bases, catalyst loading on the yield of the desired product and the equivalent of substrates, which supported the optimized reaction conditions provided in Entry 1 of Table 1. Notably, in the absence of triazine-derived phosphine ligand **L1**, the reaction did not occur and the starting materials were recovered completely.



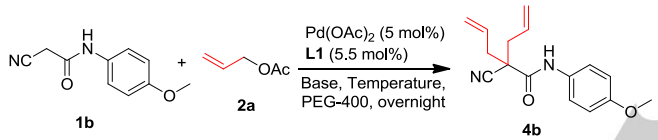
Scheme 1. Palladium-catalyzed allylic substitution of different cyanoacetamides with allylic acetate **2a**.

Encouraged by above results, we evaluated a series of different substrates to determine the specificity and scope of substrates for this Pd/**L1** catalyst system. Experimental probing the substrate scope of mono-substituted allylic alkylation are summarized in Scheme 1. Both electron-donating group and halide group on the cyano-containing aromatic amides reacted with allylic acetate in good to excellent yields (up to 95%). The different cyano-containind amides bearing either *N*-aryl or *O*-aryl residues on the amide and ester moieties[21] were examined and showed that there is no significant difference among various amides. Although yield can be further improved, this method was found to be effective for cyano-containing ester, affording the corresponding mono-allylic product **3p** in high regioselectivity with moderate yield. Generally, all these allylic alkylation reactions give excellent chemoselectivities (**3**/**5** ≥ 98:2) Notably, the double allylated product **4** was not detected under the optimized reaction conditions.

It is important to note that there is no report on the diallylation of cyano-containing carbonyl compounds, and the triazine-derived ligand -involved palladium catalyst system described here shows exceptional functional cyano group tolerance and high chemoselectvities under mild reaction conditions, encompassing a remarkably wide substrate scope. After establishing the Pd/**L1** catalyst system in the mono-allylation of cyano-containing acetamides, we envisioned that this catalytic system could be employed in the one-pot double-allylation of cyano-containing acetamides with simple allylic acetate **2a** directly. On the basis

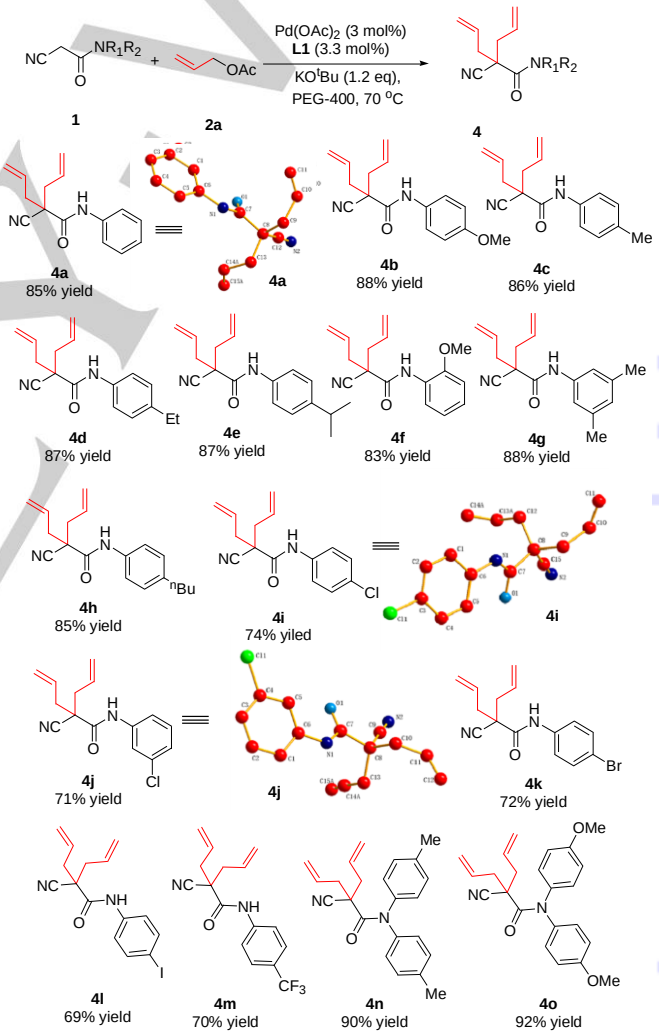
of the above findings with Pd/**L1** system in THF (Table S4 of ESI), we hypothesized that the double-allylation was a thermodynamic process and could be achieved by elevating the reaction temperature and changing the bases. Initially, we conducted the reaction of **1b** (1 equiv.) and **2a** (2.2 equiv.) in PEG-400 at 70 ^{o}C overnight under 3 mol% of $Pd(OAc)_2$, 3.3 mol% of **L1**, and K_2CO_3 (2.2 equiv.). To our delight, 25% yield of double-allylated product **4b** was obtained in this case (Table 2, Entry 1). Then, strong inorganic bases were further tested in this reaction (Table 2, and Table S8-S9 of ESI). Interestingly, it was found that KO^{t}Bu under the same conditions afforded the desired product **4b** in good yield (Entry 6) and only a trace amount of mono-allylated product was detected. We also checked the effect of the solvents on the catalytic performance of Pd/**L1** catalyst in this reaction (Entries 10-17). As shown in Table 2, it was found that PEG-400 is still the best media for palladium/**L1** –catalyzed double-allylation of **1b** with allylic acetate (**2a**).

Table 2. Optimization of Pd-catalyzed double-allylation of **1b** with allylic acetate (**2a**).



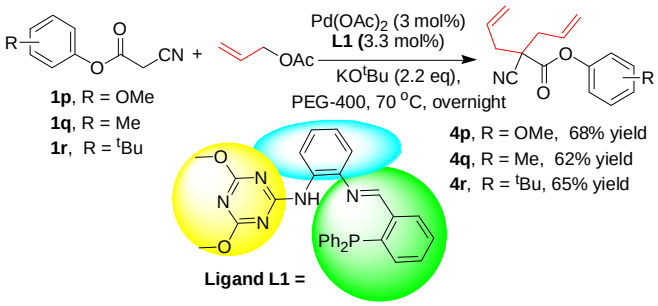
Entry[a]	Base	Solvent	Yield (%)[b]
1	K_2CO_3	PEG-400	25
2	Cs_2CO_3	PEG-400	37
3	NaOH	PEG-400	32
4	KOH	PEG-400	40
5	NaO^{t}Bu	PEG-400	81
6	KO^{t}Bu	PEG-400	88
7	DIPEA	PEG-400	trace
8	DABCO	PEG-400	trace
9	DBU	PEG-400	7
10	KO^{t}Bu	DMSO	trace
11	KO^{t}Bu	DMF	trace
12	KO^{t}Bu	DCM	41
13	KO^{t}Bu	$CHCl_3$	37
14	KO^{t}Bu	Toluene	57
15	KO^{t}Bu	H_2O	N.D
16	KO^{t}Bu	THF	80
17	KO^{t}Bu	MeCN	82

[a] The reaction conditions: **1b** (1 equiv.), **2a** (2.5 equiv.), $Pd(OAc)_2$ (5 mol%), ligand **L1** (5.5 mol%), base (2.2 equiv) and PEG-400 (1 mL) at 70 ^{o}C for overnight unless otherwise noted. [b] Isolated yield.



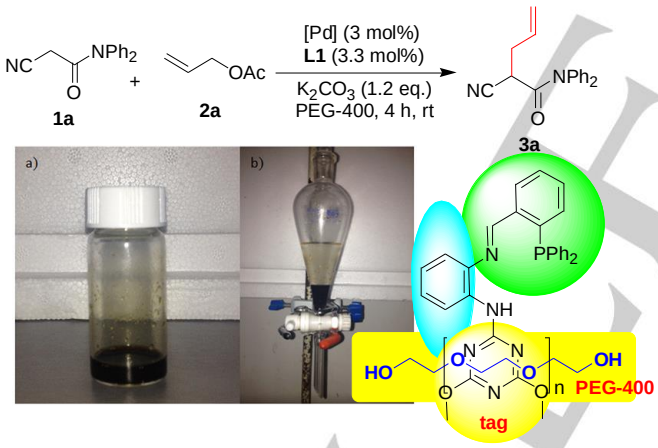
Scheme 2. Pd-catalyzed double-allylation of different cyanoacetamides with allylic acetate. X-Ray structure of double-allylic products **4a**, **4i**, and **4j** (CCDC: 1497436, 1497437, 1497438). H atom was omitted for clarity. Red-C, dark blue-N, sky blue- O, and green- Cl.

With the optimized conditions in hand (Pd/**L1** catalyst system, KO^{t}Bu as base, PEG-400 as solvent, 70 ^{o}C), we then studied the scope of various cyano-containing acetamides and allylic acetate. As shown in Scheme 2, most of amides afforded the desired double-allylated products in good to excellent yields (up to 92%) with excellent chemoselectivity. High reactivity was consistently observed when secondary amides and tertiary amides were used as electrophiles. Moreover, the structure of new products, such as **4a**, **4i**, and **4j**, were confirmed by X-ray crystallography (Scheme 2).



Scheme 3. Palladium catalyzed double-allylation of cyanoesters.

Table 3. Recyclability of Pd/**L1**/PEG-400 for the monoallylic alkylation of 2-cyano-*N*,*N*-diphenylacetamide.

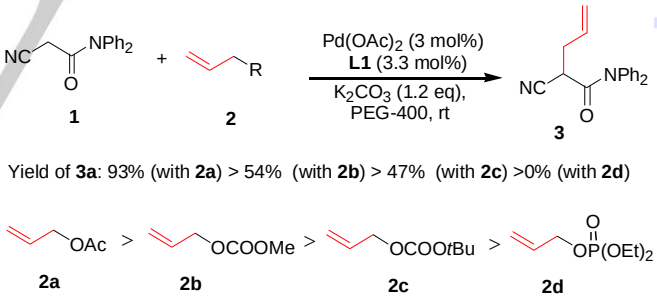


Runs	1	2	3	4	5
Yield (%)	93%	93%	91%	91%	88%

The described reactions could also, in principle, be extended to a catalytic allylic alkylation of cyanoesters. To further evaluate the reaction, we next examined the double allylation of cyanoesters with allylic acetate. As shown in Scheme 3, the use of cyano-containing ester bearing electron-donating groups at the phenyl ring as substrates resulted into corresponding double-allylated products with moderate yields (62-68%). However, cyano-ester bearing electron-donating groups, such as –CF_3 ,-NO_2, -F only undergo the hydrolysis to give the corresponding phenols, without observation of desired allylic products.

To check the recyclability of the catalyst Pd(OAc)$_2$/**L1** in PEG-400, the mono-allylation of 2-cyano-*N*,*N*-diphenylacetamide was examined in the presence of 3 mol% of Pd(OAc)$_2$ and 3.3 mol% of **L1**. After initial test, the reaction mixture was extracted with diethyl ether, and the PEG-400 –encapsulated Pd/**L1** system was subjected to a second run by charging with the same substrates and addition of K_2CO_3. We were gratified to observe that the Pd(OAc)$_2$/**L1** catalyst system could be immobilized in PEG-400 phase. As shown in the Table 3, the catalytic system could be recycled and reused five times with only slightly loss of activity. The yields of **3a** in every runs were 93%, 93%, 91%, 91%, and 88% for 4 h, respectively. We believed that PEG-400 might chelate Pd and good solubility with methyl ether-tagged triazine linked Schiff base/phosphine ligand, hasten the formation of recyclable Pd/**L1**/PEG-400 catalyst system.

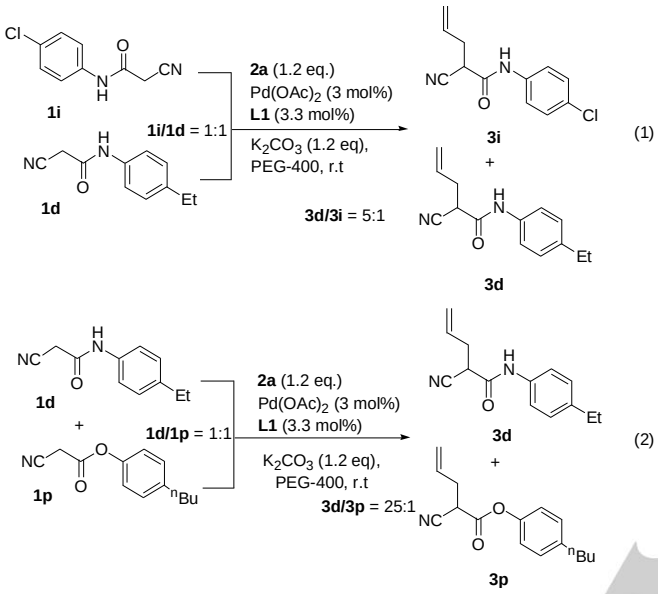
In order to understand the reaction mechanism as well as the detection of activated species involving in the mono-allylation process, we conducted series of controlled experiments. Initially, various allylic ethers with different leaving groups were tested. As described above, allylic acetate **2a** could afford the desired mono-substitution in 93% yield with both good chemoselectivity (98:2) and regioselectivity. However, when allylic carbonate **2b** or **2c** was employed instead of **2a** as allylic sources, the yield of **3a** was decreased obviously, giving 54% or 47% yield respectively. The poor chemoselectivity and regioselectivity were also observed in these cases (Entries 2 and 3 of Table S7) In addition, vinyl phosphate **2d** is not a suitable allylic substrate in this reaction (Scheme 4).



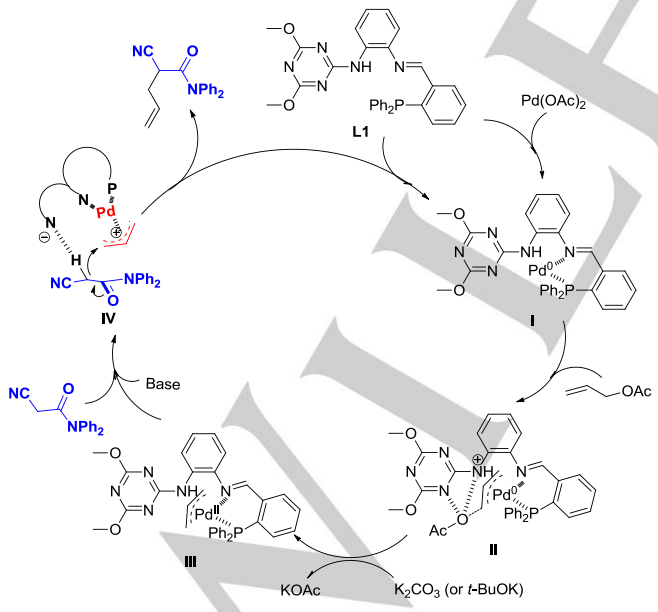
Scheme 4. Palladium-catalyzed monoallylation of cyanoacetamide **1a** with various allylic substrates **2a-2d**.

Then, we conducted several competing experiments between different cyano-containing carbonyl substrates with allylic acetate **2a** (Scheme 5 and S1-S2, see Supporting Information). Cyano-containing acetamide bearing ethyl group at the terminals (**1d**) appeared to react with **2a** much faster than that bearing chloride group at the terminals (**1i**), with 5:1 molecular ratio of the desired product **3d**/**3i** (Scheme 5, equation 1). These results were consistent with the fact that the yield of mono-allylate product was influenced by substituted pattern at the phenyl units in a sequence: electron-donating groups > halide groups. We

also tested the activity of cyanoacetamide **1d** with ester **1p**. The high selectivity was obtained with 25:1 molecular ratio of **3d**:**3p**, suggesting that cyanoacetamide is more reactive to undergo allylation than that of corresponding cyanoesters.[21] At last, we monitored the reaction by the ESI-MS and NMR analysis, including ^{1}H NMR spectroscopy in d^3- MeCN (Scheme S3).

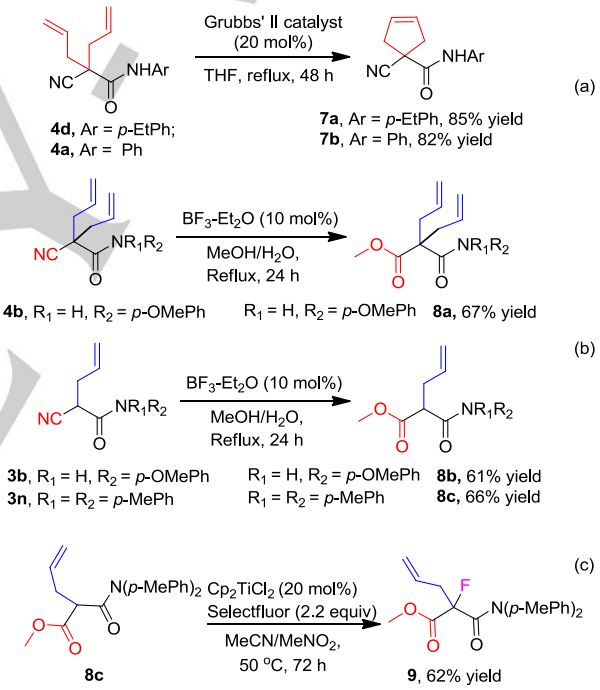


Scheme 5. Competitive monoallylation with allylic acetate **2a** between different cyanoacetamides: The electronic effect of substituents on the aryl ring of cyanoacetamides.



Scheme 6. Possible mechanism for the monoallylation of cyanoacetamide **1a** with allylic acetate **2a**.

Thus on the basis of experimental results and the commonly accepted mechanism for the Pd-catalyzed allylic alkylation involves four discrete steps,[22] including metal-allyl coordination, ionization, nucleophilic addition, and decomplexation, we proposed the possible mechanism for the palladium–catalyzed allylic alkylation of activated amides (Scheme 6). As shown in Scheme 4, the nucleophilic addition of the *in-situ* formed enolate to the π-allylpalladium complex leads to the formation of an alkylated products associated with re-generation of the palladium catalyst. In this mechanistic rationale, the in-situ formed palladium/**L1** complex give a tetra-coordinated Pd(II) species (**I**), followed by ligand exchange process to give a palladium intermediate (**II**) with allylic acetate (**2a**). Then with the assistance of 1,3,5-triazinal core and K_2CO_3, the intermediates II underwent oxidation to form Pd/**L1** π-allylpalladium intermediate (**III**), followed by nucleophilic attack on the allyl terminus, resulting into reductive elimination of the palladium center to afford the desired α-allylated product.



Scheme 7. Studies on the synthesis of cyanoacetamide derivatives from allylated cyanoacetamides.

Moreover, with the two types of alkylated cyanoacetamides in hand, we devoted to the chemoselective transformations of these structurally diverse allylated cyanoacetamides under different circumstances, including hydrolysis/esterification of cyano group and fluorination. As shown in Scheme 7, double-allylated amide **4d** or **4g** underwent metathesis under catalytic amount of Grubbs' II catalyst in THF leading to novel cyclopentene derivatives. In addition, it is well-known that introduction of fluoride atom(s) into a molecule brings out valuable properties.[23] Accordingly, mono-fluorinated 1,3-

dicarbonyl compounds, are widely used in asymmetric synthesis and construction of biologically active molecules.[24] With the mono-allylated cyanoacetamide and corresponding allylated dicarbonyl product in hand , we obtained the desired fluorinated carbonyl compound **9** in good yield under new reaction conditions (Cp_2TiCl_2 as catalyst). In addition, further efforts to develop new synthetic methods for the catalytic application of allylated cyanoacetamides, and on the basis of above findings descried in this work, the development of chiral triazine-derived *N,P*-ligand for recyclable Pd-catalyzed enatioselective allylation are underway in our laboratory.

Conclusions

In summary, an efficient and recyclable triazine-linked *N,P*-ligand for Pd-catalyzed controllable allylation reaction has been developed in this work, providing a direct and effective route to a variety of substituted cyanoacetamides, in which the resulting homogenous palladium catalyst and liquid/liquid separation also featured with facile recovery and reuse, easy preparation, and high selectivity. In the presence of $Pd(OAc)_2$ and novel triazine-derived ligand **L1**, catalytic allylation of various kinds of cyano-containing acetamides proceeded smoothly and efficiently with the assistance of base in environmentally benign PEG-400 to afford the desired mono- and double- substitutes in good to excellent yields as well as good chemo- and regio-selectivity. This catalytic system could be recycled five runs with slightly loss of catalytic activity. Thus the triazine–containing Schiff base-based phosphine ligand was proved to a multifunctional and important ligand encapsulated in PEG-400, and in other word, environmentally benign PEG-400 could be catalyst support in homogeneous reaction and heterogeneous separation, in which the combinational use of triazine–derived phosphine ligand and palladium catalyst combined with PEG-400 was also shown to be recyclable up to 5 times with good yield and efficiency. Studies are ongoing to gain insight into the catalytic relationship between structures and properties of the triazine-derived phosphine ligand and expanding its further applications to green chemistry and asymmetric catalysis.

Acknowledgements ((optional))

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Keywords: Palladium • Cyanoacetamide • Triazine • Phosphine ligand • Allylic substitution

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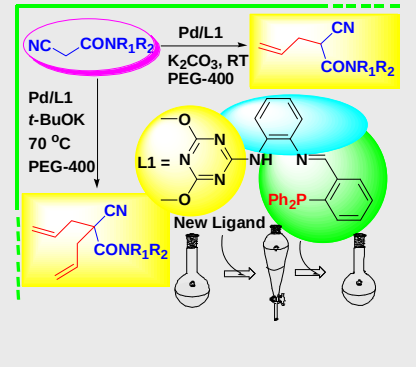

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Highly Efficient Palladium-Catalyzed Allylic Alkylation of Cyanoacetamides with Controllable and Chemoselective Mono- and Double-Substitutions