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Palladium−Pincer Complex Catalyzed C−C Coupling of Allyl Nitriles with Tosyl Imines via Regioselective Allylic C−H Bond Functionalization

Juhanes Aydin and Kálmán J. Szabó*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-106 91 Stockhom, Sweden

kalman@organ.su.se

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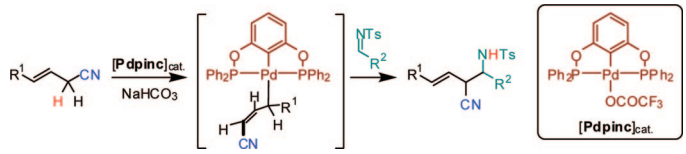
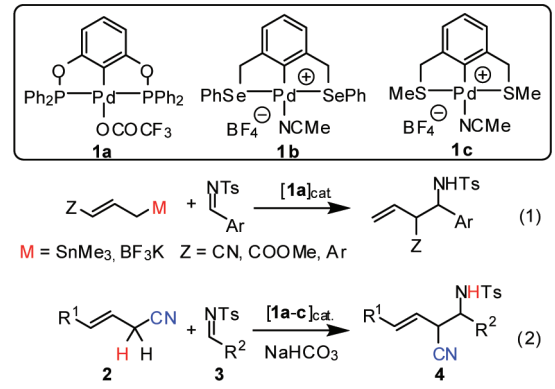
ABSTRACT



A mechanistically new palladium−pincer complex catalyzed allylation of sulfonimines is presented. This reaction involves C−H bond functionalization of allyl nitriles under mild conditions. The reaction proceeds with a high regioselectivity, without allyl rearrangement of the product. Modeling studies indicate that the carbon−carbon bond formation process proceeds via (η^1-allyl)palladium pincer complex intermediates.

Selective palladium-catalyzed allylic C−H bond activation based substitution reactions are attractive synthetic tools, generating a large added value in organic transformations.[1] Although several catalytic methods using nucleophiles to perform allylic C−H bond functionalizations have been reported in the literature,[1f–l] application of carbon electrophiles in these processes remained unexplored.

Electrophilic allylation of imines based on this method is of particular interest, as these transformations would open inexpensive new routes for synthesis of functionalized amines



and amino acids,[2,3] which represent an important class of natural products and drug intermediates.[2e]

Our previous studies[3] have shown that palladium−pincer complexes[4,5] efficiently and selectively catalyze the allylation of imines. However, in these applications organometallic

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substrates,[3] such as stannanes and boronates, were employed as allylating reagents (eq 1).[3] We have now found that allyl nitriles can be used directly for regioselective allylation of sulfonimines using pincer-complex catalysts **1a**−**c**[5] (eq 2) under mild conditions (typically at rt) in the presence of a weak base, $NaHCO_3$, and molecular sieves. Although several pincer complexes with weakly coordinating counterions (entries 1−3) displayed high catalytic activity, we concentrated on exploring the synthetic scope of **1a**,[5a] as a large variety of analogue PCP complexes,[5a,c] including chiral ones,[3c,f,5b] have recently become available and employed in organic synthesis.[3–5]

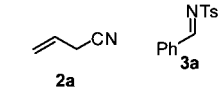
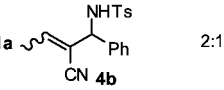
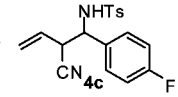
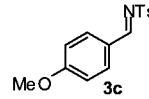
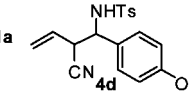
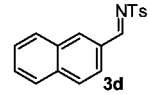
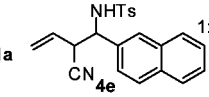
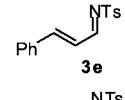
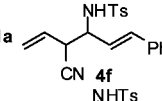
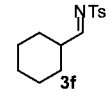
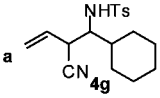
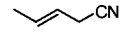
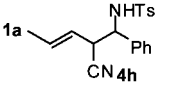
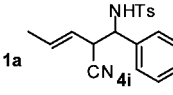
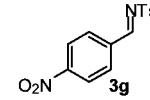
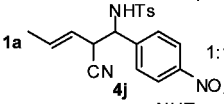
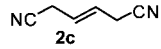
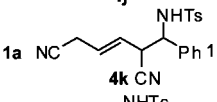
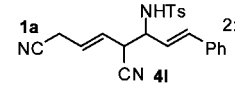
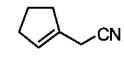
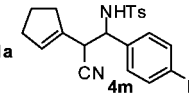
Allyl nitrile (**2a**) reacted rapidly with various aromatic (**3a**−**d**,**g**), vinyl (**3e**), and alkyl (**3f**) sulfonimines (Table 1). The reaction times required to complete the catalytic allylic substitution reactions were strongly dependent on the sulfonimine substrates. Sulfonimines with electron-withdrawing groups (**3b**,**d**) reacted faster than **3a** (cf. entries 1 and 5), while methoxy derivative **3c** (entry 6) was allylated as quickly as the parent compound **3a**. The required reaction times with vinyl and alkyl sulfonimines (**3e** and **3f**) were considerably longer (entries 8 and 9) than with aromatic ones. The regioselectivity of the reaction is excellent, as the branched allylic product is formed exclusively in the substitution reactions.

The only exception is application of Cs_2CO_3 (or other strong bases) instead of $NaHCO_3$ (entry 4), where the primary coupling product (**4a**) undergoes allylic rearrangement to give **4b**.

The allylation reactions could be extended to substituted allyl nitriles **2b**−**d** incorporating internal double bonds (entries 10−16). The catalytic process with **2b** and **2d** (entries 10−13 and 16) proceeded slower than with **2a** and **2c**. However, the high regioselectivity and the integrity of the allyl system could be maintained. For symmetrical substrate **2c**, the catalytic reaction could be stopped after substitution of one of the allylic carbons. Thus, desymmetrization of **2c** (entries 14 and 15) could be achieved, affording **4k**,**l** in high yields. Because of the mild conditions, the reaction tolerates many functional groups (CN, NTs, F) including even the nitro group (entry 13).

Application of $NaHCO_3$ (1 equiv) is a very attractive feature of the process, as stronger bases induce allylic rearrangement of the product (e.g., entry 4) and degradation

Table 1. Palladium−Pincer Complex Catalyzed Coupling of Allyl Nitriles with Sulfonimines[a]

Entry	Substrates	T[°C]/ t[h]	Cat.	Products	dr[b]	Yield[c]
1	 **2a** **3a**	20/5	**1a**	**4a**	3:2	90
2	**2a** **3a**	20/4	**1b**	**4a**	1:1	81
3	**2a** **3a**	20/5	**1c**	**4a**	3:2	83
4[d]	**2a** **3a**	20/12	**1a**	 **4b**	2:1[e]	88
5	**2a**  **3b**	20/1	**1a**	 **4c**	3:2	91
6	**2a**  **3c**	20/5	**1a**	 **4d**	3:2	91
7	**2a**  **3d**	20/2	**1a**	 **4e**	1:1	87
8	**2a**  **3e**	20/14	**1a**	 **4f**	2:1	93
9	**2a**  **3f**	20/12	**1a**	 **4g**	1:1	90
10	 **2b** **3a**	40/14	**1a**	 **4h**	1:1	98
11	**2b** **3a**	40/14	**1b**	**4h**	1:1	90
12	**2b** **3b**	20/3	**1a**	 **4i**	1:1	98
13	**2b**  **3g**	20/18	**1a**	 **4j**	1:1	57
14	 **2c** **3a**	20/4	**1a**	 **4k**	1:1	97
15	**2c** **3e**	20/3	**1a**	 **4l**	2:1	83
16	 **2d** **3b**	20/20	**1a**	 **4m**	3:2	94

[a] Catalyst **1** (5 mol %), $NaHCO_3$, **2**, and **3** in THF were reacted at the given temperatures and reaction times. [b] Diastereomeric ratio. [c] Isolated yield (%). [d] Cs_2CO_3 was employed as base. [e] *E*/*Z* ratio.

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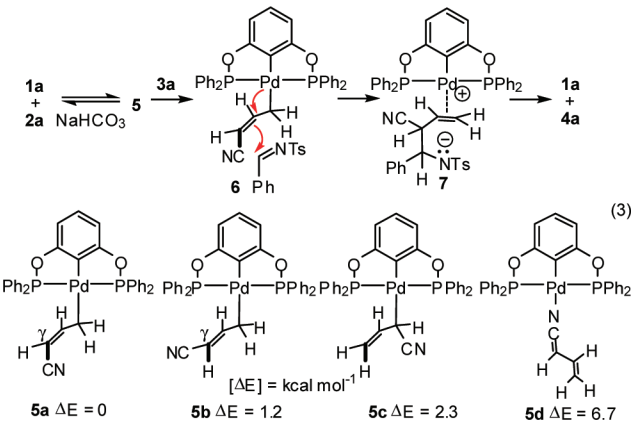
of sensitive substrates, such as **3f**,**g**.[6] In fact, functionalized allyl nitriles and related compounds extremely easily undergo base-catalyzed allylic rearrangement.[6] The applied $NaHCO_3$ is one of the few very weak bases which does not induce such a rearrangement, and therefore, the integrity of the allyl system in **4a**,**c**−**m** can be maintained under the applied reaction conditions. The reactions proved to be rather sensitive to moisture, and therefore, we employed molecular sieves, which efficiently dried the reaction medium. The catalytic transformations still proceed in the absence of molecular sieves or with substoichiometric amounts of $NaHCO_3$. However, the reaction times are elongated. In fact, the reaction of allyl nitrile (**2a**) and imine **3a** (c.f., entry 1) could also be achieved in the absence of base; however, these reactions were very slow and poorly reproducible.

Although the reaction proceeds with excellent regioselectivity (entries 1−16) and trans stereoselectivity for the double bond (entries 10−15), the diastereoselectivity is poor. A similarly low diastereoselectivity was reported[3g] for the related allylstannane based-reactions (eq 1), when the allylating reagent incorporated a nitrile functional group. The low diastereoselectivity can be explained by either the low level of stereodiscrimination in the coupling step or by epimerization of product **4** under the applied reaction conditions. When a diastereomerically enriched product (such as **4l**) was exposed to the reaction conditions of the coupling reaction, further change of the diastereomeric ratio could not be observed. Therefore, it can be concluded that the low diastereoselectivity of the reaction can be ascribed to the similar activation energy of the formation of the two diastereomers of **4** under the pincer-complex catalyzed coupling reaction.

Interestingly, under the applied mild reaction conditions (e.g., entry 1) formation of **4a** could not be detected at all when pincer-complex catalyst **1a** was replaced by traditional palladium catalysts, such as $Pd(OCOCF_3)_2$, $Pd(OAc)_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$. The absence of the reaction with $Pd(OCOCF_3)_2$ is particularly important from a mechanistic point of view, as it indicates that the activation effects of trifluoroacetate complex **1a** cannot be explained simply by its Lewis acid activity. If Lewis acid activation would be sufficient for coupling of **2a** with **3a**, then $Pd(OCOCF_3)_2$ and pincer complex **1a** should have displayed a similar catalytic activity.

There are a few examples in the literature for transition metal catalyzed C−H bond activation of nitriles.[1a,7] In these literature studies ruthenium,[7a] rhodium,[7b] and palladium[7c] catalysts were employed to perform Michael addition of activated alkyl nitriles. As shown above, commonly used palladium sources are not efficient to catalyze the allylation of sulfonimine **3** with allyl nitriles **2** under the employed mild conditions. Thus, application of pincer complex **1** is a prerequisite of the successful coupling reaction. The mechanism of the coupling reaction (eq 3) probably involves coordination of the allyl cyanide to the pincer complex catalyst affording complex **5**. This process is certainly aided by $NaHCO_3$, facilitating the deprotonation of **2a**. Strong bases are known to deprotonate allyl nitriles and related species.[6] However, $NaHCO_3$ alone is not able to deprotonate **2a** (even less **2b** or **2d**), and therefore, the deprotonation process is assisted by palladium. We have considered **5a**−**d** as possible structures for the allyl nitrile anion coordinated pincer complex intermediates. DFT modeling studies (B3PW91/6-31G(d) level) indicate that the η^1-allylpalladium structures (**5a**−**c**) are much more stable (up to 6.7 kcal·mol^{-1}) than the N-coordinated form **5d**. Considering that in the most stable forms (**5a**,**b**), the nitrile group is in the terminal position, the new C−C bond is created[3e] between the substituted γ-carbon of the allyl moiety and **3** (**6**), which explains the observed regiochemistry of the process. The mechanism and selectivity of η^1-allylpalladium complex mediated electrophilic substitutions is well established.[3a,d,e,5e,h] In these processes other potential electrophiles may also react with **5**.[3a] Therefore, it is very important to exclude moisture from these processes, which can be achieved by using molecular sieves.



Our previous DFT modeling studies[3e] on the C−C bond formation between the allyl moiety of palladium pincer complexes (such as **5a**−**c**) and sulfonimines revealed that the stereoselectivity of the reaction is dependent on the geometry of the double bond in the functionalized (e.g., CN) allyl moiety. On the basis of these results, the relatively small energy difference between **5a** and **5b** may account for the poor stereoselectivity of the allylation process. Accordingly, a possible way of increasing the stereoselectivity of this C−C coupling is the optimization of the ligand size in the side arms of **1** to increase the energy difference between the **5a** and **5b** type of intermediates. Formation of (η^1-allyl)palladium complexes **5a**,**b** (required for reaction with electrophiles[3a,e]) is favored by the terdentate pincer ligand architecture,[3a,b,e] which explains the fact that traditional palladium (i.e., nonpincer, $Pd(OCOCF_3)_2$) catalysts are inefficient in the presented transformations. The allylation process is terminated by formation of **7**, which after decomplexation affords product **4a** and regenerates the catalyst.

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In summary, we have presented the first palladium pincer-complex catalyzed C−H bond activation based allylation reaction. The experimental findings, the modeling studies, and the fact that traditional palladium sources are ineffective as catalysts suggest that the key intermediate of the reaction is an (η^1-allyl)palladium pincer complex. The presented mechanistically new catalytic process opens novel synthetic routes to palladium pincer-complex catalyzed C−H bond activation reactions.

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Supporting Information Available: Experimental procedures, NMR data, as well as ^{1}H and ^{13}C NMR spectra of products **7a**−**m**, **8**, and **10a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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