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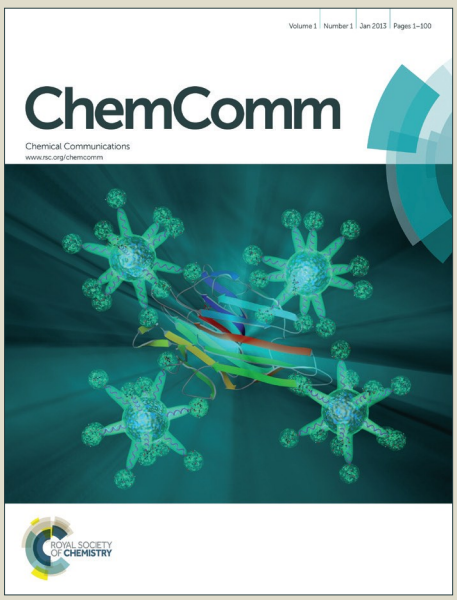

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COMMUNICATION

Ruthenium-Catalyzed *ortho* Alkenylation of Aromatic Nitriles with Activated Alkenes via C-H Bond Activation

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A ruthenium-catalyzed *ortho* alkenylation of substituted aromatic and heteroaromatic nitriles with activated alkenes providing *ortho* alkenylated aromatic and heteroaromatic nitriles in a highly regio- and stereoselective manner is described. Subsequently, *ortho* alkenylated aromatic nitrile was converted into chiral phthalide in the presence of AD-mix-β. Further, by employing nitrile as a directing group, arylation was done at the alkene C-H bond of *ortho* alkenylated aromatic nitriles with aromatic iodides in the presence of palladium catalyst.

Selective transformation of C-H bond of organic moieties into C-C and C-heteroatom bond catalyzed by transition metal complexes via C-H bond activation is one of the most versatile and well-acknowledged methods in organic synthesis.[1] This transformation has gained tremendous attention in chemical and pharmaceutical industries, because it provides step- and atom-economical routes to synthesize useful organic molecules from the readily available starting materials.[2] Particularly, transition metal-catalyzed oxidative cross-coupling of heteroatom substituted aromatics with alkenes has proven to be a highly efficient route to synthesize disubstituted alkenes without having any prefunctionalized starting materials in a highly regio- and stereoselective manner.[3] The selectivity of C-H bond of organic moieties can be controlled by using the suitable directing groups. Mostly, the electron lone pair of nitrogen or oxygen atom of directing groups coordinate with the metal complex through σ-coordination and activate the C-H bond of organic moieties selectively (Figure 1, eq 1).[4-5] The search for new variants to activate the C-H bond of aromatics is highly important to expand the synthetic scope of the alkenylation reaction. Very recently, Cheng's group disclosed an alkene assisted alkenylation of aromatics with activated alkenes in the presence of palladium catalyst via an unusual carbon-carbon π-bond coordination (Figure 1, eq 2).[6]

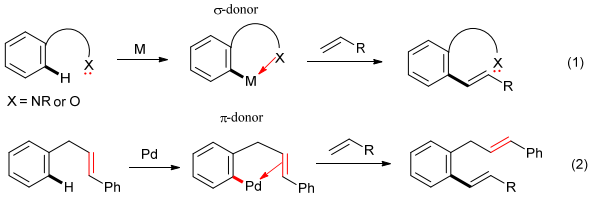


Figure 1 Chelation-assisted C-H bond alkenylation

Nitrile is a versatile functional group which can be efficiently used for various organic transformations.[7] In addition, nitrile group containing organic molecules are used as pharmaceuticals, pesticides and dyes.[8] The strong electron withdrawing nature and better hydrogen bond accepting property of nitrile group, allo… it to use widely in designing drug molecules and till now arou… 30 nitrile-containing drugs are available in market and 20 more nitrile-containing molecules are in the clinical development.[8b] Meanwhile, cyano group can also be used as a directing group fo… the C-H bond activation reaction.[9-11] It is known that the electro… lone pair of nitrogen atom of nitrile group of benzonitrile coordinates with metal complex through σ-coordination, and thi… process leads to the linear metal complex.[9] Also, a less likely C≡N π-bond of benzonitrile coordinates with metal, providing the π-coordinated metal complex.[10] Recently, by employing σ coordination of nitrile moiety, the meta C-H bond of aromatics can be activated efficiently for the alkenylation reaction (Figur… 2, eq 1).[11] Till now, there is no report on the C≡N π-bond assisted alkenylation at the *ortho* position of aromatic nitriles with alkene… due to the difficult coordination of π-bond of C≡N with metal.

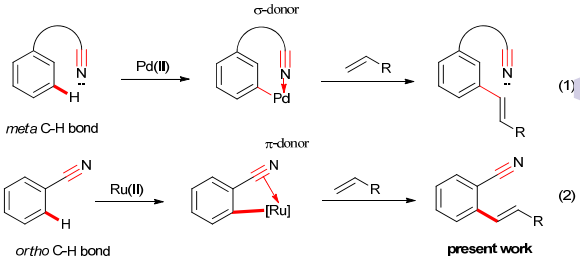
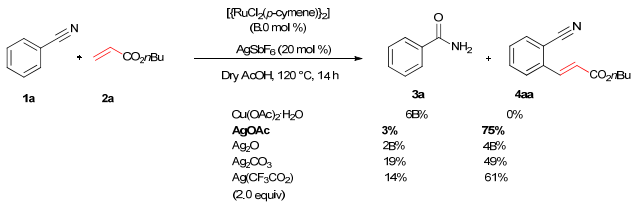


Figure 2 C-H bond alkenylation of aromatic nitriles

Our ongoing interest in the finding of new C-H bon… transformation reaction prompted us to explore the possibility o… C≡N π-bond assisted *ortho* alkenylation of substituted aromati… nitriles with alkenes. Herein, we wish to report for the first time… nitrile as a π-bond coordinating group for the *ortho* alkenylation of aromatic and heteroaromatic nitriles with activated alkenes in the presence of ruthenium catalyst (Figure 2, eq 2). Th… alkenylation reaction was compatible with functional grou… substituted aromatic nitriles. Later, *ortho* alkenylated aromatic nitrile was converted into chiral phthalide in the presence of AD-mix-β. By employing nitrile as a directing group, arylation was done at the alkene C-H bond of *ortho* alkenylated aromati… nitriles with aromatic iodides in the presence of Pd catalyst.

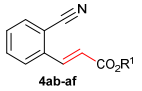
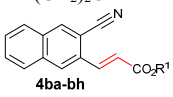
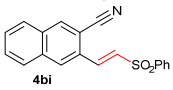


Scheme 1 *ortho* Alkenylation of benzonitrile

Initially, the ruthenium-catalyzed alkenylation reaction was examined with benzonitrile (**1a**) and *n*-butyl acrylate (**2a**) (Scheme 1). It is expected that the nitrogen atom of **1a** prefers to coordinate with metal via lone pair electron rather than π-coordination. But, to success the *ortho* C-H bond activation, π-coordination of nitrile is crucial. Meanwhile, metal acetate base is needed for the deprotonation of C-H bond of weak coordinating group substituted aromatics. Thus, a combination of ruthenium catalyst and metal acetate having Lewis acidic nature was selected. The main idea behind the selection of Lewis acid metal acetate is that the lone pair of nitrogen of nitrile moiety would coordinate with Lewis acid prior to the ruthenium catalyst and block the corresponding site. Therefore, a possibility is created for the π-bond coordination of nitrile moiety into ruthenium catalyst and initiates the C-H bond activation. With this idea, a combination of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv) was used for the reaction. As a nitrile is weak coordinating group, $AgSbF_6$ was used to generate a cationic ruthenium species for the C-H bond reaction. However, in the reaction, hydration takes place at nitrile group and only benzamide (**3a**) was observed. If the same reaction is run for a long time, a cyclic isoindolin-1-one derivative was observed.[12] Later, the reaction was examined with various Lewis acids such as $Co(OAc)_2$, $Mn(OAc)_2$, Ag_2O, AgOAc, Ag_2CO_3, $Ag(CF_3CO_2)$ and $Fe(OAc)_2$ (2.0 equiv). Very interestingly, in AgOAc, the *ortho* C-H bond activation takes place selectively and further reacted with *n*-butyl acrylate (**2a**) providing *ortho* alkenylated benzonitrile **4aa** in 75% isolated yield. In the reaction, benzamide **3a** was observed only in very minor 3% yield. In other silver salts such as Ag_2O, Ag_2CO_3, $Ag(CF_3CO_2)$, product **4aa** was observed in 45%, 49% and 61% yields. Benzamide **3a** was observed in 25%, 19% and 14% yields, respectively. But, in $Co(OAc)_2$ and $Mn(OAc)_2$, benzamide **3a** was observed in more 45% and 51% yields and product **4aa** was observed in 15% and 19% yields, respectively. Meanwhile, acidic solvent AcOH is crucial for the reaction. Other solvents such as 1,2-dichloroethane, THF, 1,4-dioxane, DMF, toluene and CF_3COOH were not suitable for the reaction. But, in *iso*-PrOH, product **4aa** was observed only in 10% yield without benzamide **3a** formation.

The scope of alkenylation reaction was examined with various activated alkenes **2** under the optimized reaction conditions (Table 1). Ethyl acrylate (**2b**), cyclohexyl acrylate (**2c**), phenyl acrylate (**2d**), benzyl acrylate (**2e**) and 2-phenoxyethyl acrylate (**2f**) reacted efficiently with **1a**, providing the expected *ortho* alkenylated benzonitriles **4ab-ae** in 64%, 79%, 69%, 67% and 59% yields, respectively (entries 1-5). Further, *n*-butyl acrylate (**2a**), ethyl acrylate (**2b**), methyl acrylate (**2g**) and 2,2,2-trifluoroethyl acrylate (**2h**) also efficiently reacted with 2-naphthonitrile (**1b**), yielding *ortho* alkenylated 2-naphthonitriles **4ba-bh** in 75%, 65%, 62% and 57% yields, respectively (entries 6-9). In the reaction, C-H bond activation selectively takes place at the C3 position of 2-naphthonitrile (**1b**). Interestingly, phenyl vinyl sulphone (**2i**) was also efficiently involved in the reaction, providing product **4bi** in 52% yield (entry 10).

Table 1 Reaction of benzonitrile **(1a)** or 2-naphthonitrile **(1b)** with activated alkenes **2b-i**[a]

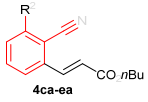
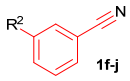
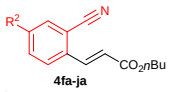
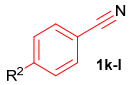
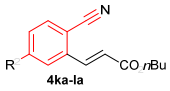
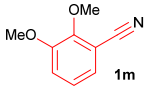
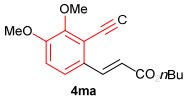
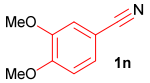
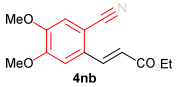
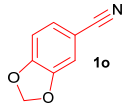
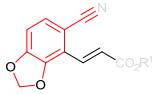
Entry	Alkenes**2**	Product **4**	Yield (%)[b]
	 2b-f	 4ab-af	
1	**2b**: R^1 = Et	**4ab**: R^1 = Et	64
2	**2c**: R^1 = cyclohexyl	**4ac**: R^1 = cyclohexyl	79
3	**2d**: R^1 = Ph	**4ad**: R^1 = Ph	69
4	**2e**: R^1 = CH_2Ph	**4ae**: R^1 = CH_2Ph	67
5	**2f**: R^1 = $(CH_2)_2OPh$	**4af**: R^1 = $(CH_2)_2OPh$	59
	 2a-h	 4ba-bh	
6	**2a**: R^1 = *n*-Bu	**4ba**: R^1 = *n*-Bu	75
7	**2b**: R^1 = Et	**4bb**: R^1 = Et	65
8	**2g**: R^1 = Me	**4bg**: R^1 = Me	62
9	**2h**: R^1 = CH_2CF_3	**4bh**: R^1 = CH_2CF_3	57
10	 2i	 4bi	52[c]

[a]All reactions were carried out using **1a** or **1b** (75 mg), alkenes **2a-h** (4.0 equiv) and **2i** (2.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and AgOAc (2.0 equiv) in dry acetic acid (3.0 mL) at 120 °C for 14 h. [b]Isolated yield. [c]In the reaction, DCE (3.0 mL) + pivalic acid (0.5 mL) was used instead of AcOH.

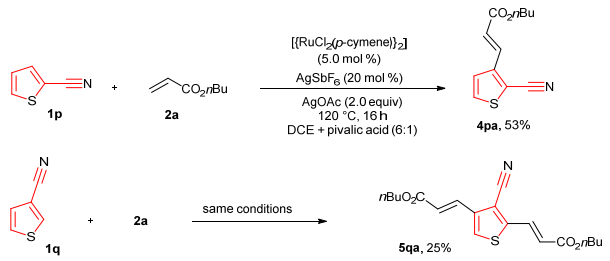
The alkenylation reaction was compatible with a variety of sensitive functional groups such as Br, Cl, I, OMe, SMe and CO_2Me substituted aromatic nitriles (Table 2). *ortho* Bromo (**1c**), chloro (**1d**) and methoxy (**1e**) substituted benzonitriles reacted efficiently with *n*-butyl acrylate (**2a**), providing the corresponding *ortho* alkenylated aromatic nitriles **4ca-ea** in 51%, 50% and 47% yields, respectively (entries 1-3). Subsequently, *meta* methylester (**1f**), iodo (**1g**), bromo (**1h**), chloro (**1i**) and methoxy (**1j**) benzonitriles also efficiently participated in the reaction providing the corresponding *ortho* alkenylated benzonitriles **4fa-ja** in 53%, 48%, 45%, 44% and 42% yields, respectively, in a highly regioselective manner (entries 4-8). In all these reactions, C-H bond activation takes place at a less hindered *ortho* C6-H bond of benzonitriles **1f-j**. 4-Methoxy (**1k**) and 4-SMe (**1l**) substituted benzonitriles provided the corresponding alkenylation products **4ka** and **4la** in 42% and 57% yields, respectively (entries 9 and 10). The alkenylation reaction was also examined with disubstituted benzonitriles **1m-o**. 2,3-Dimethoxy (**1m**) and 3,4-dimethoxy (**1n**) benzonitriles reacted with **2a** or **2b**, affording *ortho* alkenylated benzonitriles **4ma** and **4nb** in moderate 38% and 29% yields, respectively (entries 11 and 12). In the substrate **1n**, C-H bond activation takes place at a less hindered *ortho* C6-H bond. In contrast, a sterically hindered *ortho* C-H bond of piperonylonitrile (**1o**) reacted with **2a** or **2g** providing products **4oa** and **4og** in 52% and 48% yields, respectively (entries 13 and 14). The present result clearly reveals that a strong electron donating OMe group substituent on the benzonitrile decreases the yield of the product and SMe, halogen and electron withdrawing substituent on the benzonitrile moderately increases the yield. In

unsubstituted benzonitrile and 2-naphthonitrile substrates, good yields were observed.

Table 2 Reaction of benzonitrile **(1a)** or 2-naphthonitrile **(1b)** with activated alkenes **2b-i**[a]

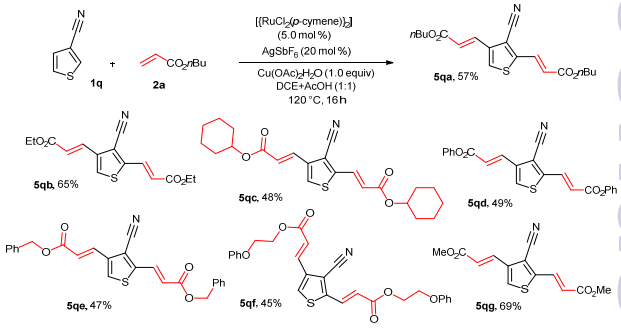
Entry	Alkenes **2**	Product **4**	Yield (%)[b]
			
1	**1c**: R^2 = Br	**4ca**: R^2 = Br	51
2	**1d**: R^2 = Cl	**4da**: R^2 = Cl	50
3	**1e**: R^2 = OMe	**4ea**: R^2 = OMe	47
			
4	**1f**: R^2 = CO_2Me	**4fa**: R^2 = CO_2Me	53
5	**1g**: R^2 = I	**4ga**: R^2 = I	48
6	**1h**: R^2 = Br	**4ha**: R^2 = Br	45
7	**1i**: R^2 = Cl	**4ia**: R^2 = Cl	44
8	**1j**: R^2 = OMe	**4ja**: R^2 = OMe	42
			
9	**1k**: R^2 = OMe	**4ka**: R^2 = OMe	42[c]
10	**1l**: R^2 = SMe	**4la**: R^2 = SMe	57
11			38[c]
12			29[c]
			
13		**4oa**: R^2 = *n*-Bu	52[c]
14		**4og**: R^2 = Me	48[c]

[a]All reactions were carried out using **1c-o** (75 mg), alkenes **2** (4.0 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and AgOAc (2.0 equiv) in dry acetic acid (3.0 mL) at 120 °C for 14 h. [b]Isolated yield. [c]The reaction time was 16 h.

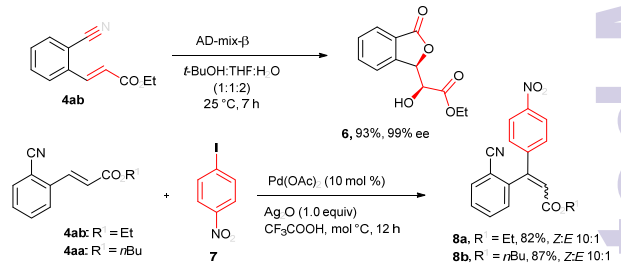


Scheme 2 Alkenylation of 2-cyano and 3-cyanothiophenes

The alkenylation reaction was also successfully extended with heteroaromatic nitriles (Scheme 2). Treatment of 2-nitrile thiophene (**1p**) with *n*-butyl acrylate (**2a**) in the presence of [{$RuCl_2$(*p*-cymene)}$_2$] (5 mol %), $AgSbF_6$ (20 mol %) and AgOAc (2.0 equiv) at 120 °C for 16 h provided 2-alkenyl-3-nitrile thiophene (**4pa**) in 53% yield. 3-Nitrile thiophene (**1q**) reacted with *n*-butyl acrylate (**2a**) affording *bis* alkenylated 3-nitrile thiophene **5qa** in 25% yield. Next, the same reaction was examined with $Cu(OAc)_2{\cdot}H_2O$ without AgOAc. Interestingly, in the reaction, *bis* alkenylated 3-nitrile thiophene **5qa** was observed in 57% yield (Scheme 3). Similar, *n*-ethyl acrylate (**2b**), cyclohexyl acrylate (**2c**), phenyl acrylate (**2d**), benzyl acrylate (**2e**), 2-phenoxyethyl acrylate (**2f**) and methyl acrylate (**2g**) also reacted with **1q**, affording *bis* alkenylated 3-nitrile thiophenes **5qb-qg** in 65%, 48%, 49%, 47%, 45% and 69% yields respectively (Scheme 3).



Scheme 3 *bis* Alkenylation of 3-cyanothiophene

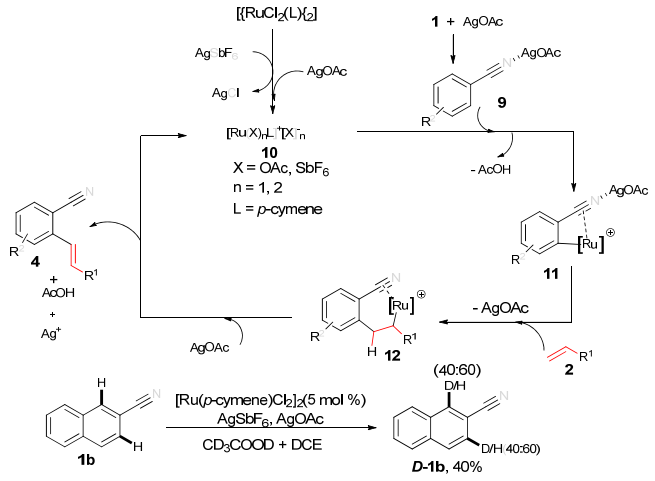


Scheme 4 Transformation of *ortho* Alkenyl Benzonitriles 4

Substituted *ortho* alkenyl aromatic nitrile is a versatile synthetic intermediate which can be used for synthesizing various useful organic molecules.[7-8] *ortho* Alkenyl benzonitrile **4ab** underwent intramolecular cyclization in the presence of AD-mix-β, yielding chiral phthalide **6** in 93% yield in 99 ee% (Scheme 4).[13] By using AD-mix-α, the reverse chiral phthalide derivative can be prepared in a highly enantioselective manner.[13] Further, by employing nitrile as a directing group, arylation was done at alkene C-H bond of **4ab** and **4aa** with 4-iodo nitrobenzene (**7**) in the presence of $Pd(OAc)_2$ and Ag_2O in CF_3COOH at 110 °C for 12 h, giving trisubstituted alkenes **8a** and **8b** in 82% and 87% yields in a 10:1 *Z*:*E* ratio.

A possible reaction mechanism is proposed to account for the present alkenylation reaction in Scheme 5. It is strongly believed that first the lone electron pair of nitrogen atom of benzonitrile coordinates with Lewis acid AgOAc, providing a linear benzonitrile silver complex **9**. A similar observation is strongly supported by DFT calculation.[14] Subsequently, $AgSbF_6$ likely removes the Cl^- ligand from [{$RuCl_2$(*p*-cymene)}$_2$] complex providing a cationic ruthenium species **10**. Coordination of the C≡N π-bond of **9** into the ruthenium species**10** followed by *ortho*-metalation provides intermediate **11**. Coordinative insertion of activated alkene **2** into the Ru–carbon bond of intermediate **11** affords intermediate **12**. Subsequent β-hydride elimination of intermediate **12** in the presence of AgOAc gives product **4** and regenerates the active ruthenium species **10**. To support the *ortho* C-H bond cleavage of **9** is a reversible and rate determining process, the reaction of **1b** was done in the presence of

CD_3COOD under similar reaction conditions. In the reaction, product ***D*-1b** was observed in 40% yield, in which 40% of deuterium incorporation was observed at both C-1 as well as C-3 carbons of **1b**.



Scheme 5 Proposed mechanism

In conclusion, We have demonstrated a ruthenium-catalyzed C≡N π-bond assisted *ortho* alkenylation of substituted aromatic and heteroaromatic nitriles with activated alkenes providing *ortho* alkenylated aromatic and heteroaromatic nitriles in good to moderate yields in a highly regio- and stereoselective manner. Later, *ortho* alkenylated aromatic nitrile was converted into chiral phthalide in the presence of AD-mix-β. Additional, by employing nitrile as a directing group, arylation was done at the alkene C-H bond of *ortho* alkenylated aromatic nitriles with aromatic iodides in the presence of palladium catalyst.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectroscopic data. See DOI: 10.1039/b000000x/

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