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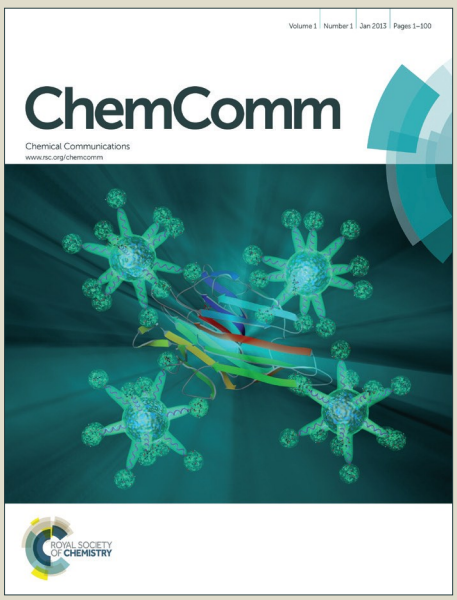

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Rhodium-Catalyzed Selective C–H Functionalization of NNN Tridentate Chelating Compounds via a Rollover Pathway†

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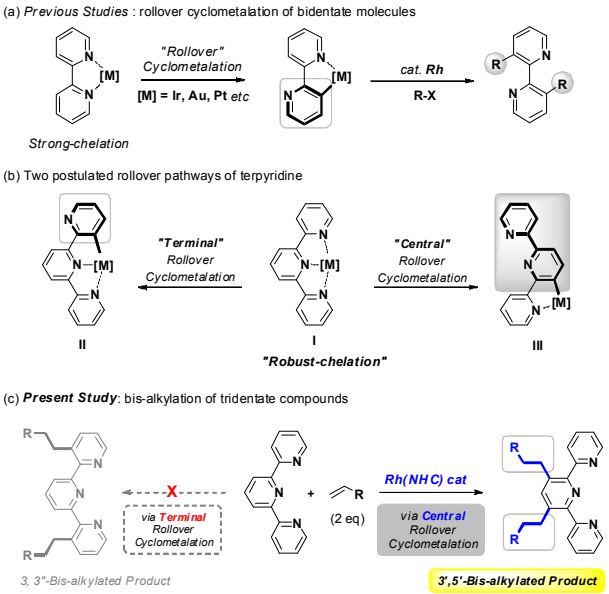
Reported herein is the first example of a Rh(NHC)-catalyzed selective bis C–H alkylation of NNN tridentate chelating compounds in reaction with alkenes. The observed excellent site-selectivity can readily be explained by the postulated rollover pathway in the C–H bond activation step. The reaction is highly facile to afford bis-alkylated tridentate products in high yields over a broad range of versatile heteroarene substrates and alkene reactants including ethylene gas, thus enabling its applications to be feasible in the coordination and synthetic chemistry.

Transition metal-catalyzed direct C–H bond functionalization is a powerful approach to the straightforward construction of new bonds such as C–C, C–N, C–O, or C–X (X: halides) connections.[1] In this strategy, the facile generation of cyclometalated intermediates is regarded as one of the most important factors, thus allowing for efficient and selective catalytic procedures. A classical cyclometalation of molecules bearing one chelating atom (or group) has been well established in coordination and synthetic chemistry.[2] In contrast, when compounds have two coordinating groups at the proper position, the cyclometalation becomes more difficult mainly due to the generation of stable bidentate metal complexes. In order to readily generate a cyclometalated species in this case, a "rollover" pathway has to be operative effectively (Scheme 1a).[3] In fact, growing examples of adapting the rollover concept have appeared for the facile cyclometalation of bidentate compounds.[4] In this line, rollover complexes of 2,2'-bipyridine derivatives are known to be prepared with a *stoichiometric* manner in reaction with certain transition metals, representatively Ir,[5a] Au,[5b] or Pt.[5c]

Not surprisingly, the development of *catalytic* C–H functionalization of bidentate molecules turns out to be challenging mainly due to the difficulty of overcoming the high activation barrier of the postulated rollover pathway *catalytically*. Miura et al. reported a Rh-catalyzed bis-*alkenylation* of 2,2'-bipyridines in reaction with silylacetylene by employing PPh_3 ligand.[6a] More recently, our group has developed a highly efficient and selective catalytic system for the C–H functionalization of various types of bidentate molecules including 2,2'-bipyridines, 2,2'-biquinolines, and 2-(heteroaryl)pyridines.[6b] The key to this success was the use of a NHC ligand[7] that is proposed to exert *trans*-effect to facilitate the desired rollover pathway.

It is envisaged that molecules bearing tris-coordinating groups will provide more challenges in the development of facile catalytic transformations. In fact, more robust tridentate metal complexes of terpyridines compared to bidentate bipyridine species have been well known.[8,9] Another critical issue is in the site-selectivity during the course of the rollover C–H activation step.[10] For instance, a terpyridine metal complex is expected to have two rollover cyclometalation routes: from **I** to **II** or **III** (Scheme 1b). While a former process (**I** → **II**) leads to a κ^3N,N',C-cyclometalate at the *terminal* pyridyl moiety, the latter one (**I** → **III**) gives rise to a κ^2N,C-rollover metal complex at the *central* pyridyl group. To our best knowledge, no report has appeared to reveal a selective catalytic C–H functionalization of NNN tridentate chelating compounds. Herein, we report the successful application of the rollover cyclometalation strategy for this purpose (Scheme 1c).



Scheme 1 Rollover cyclometalation of multidentate molecules.

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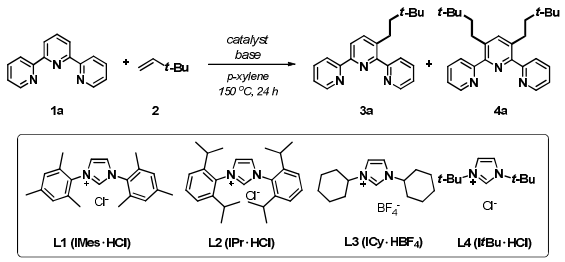
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data. CCDC 1440161 (**4e**) and CCDC 1440160 (**6a**). See DOI: 10.1039/x0xx00000x

Table 1 Optimization of the Rh-catalyzed alkylation of terpyridine[a]



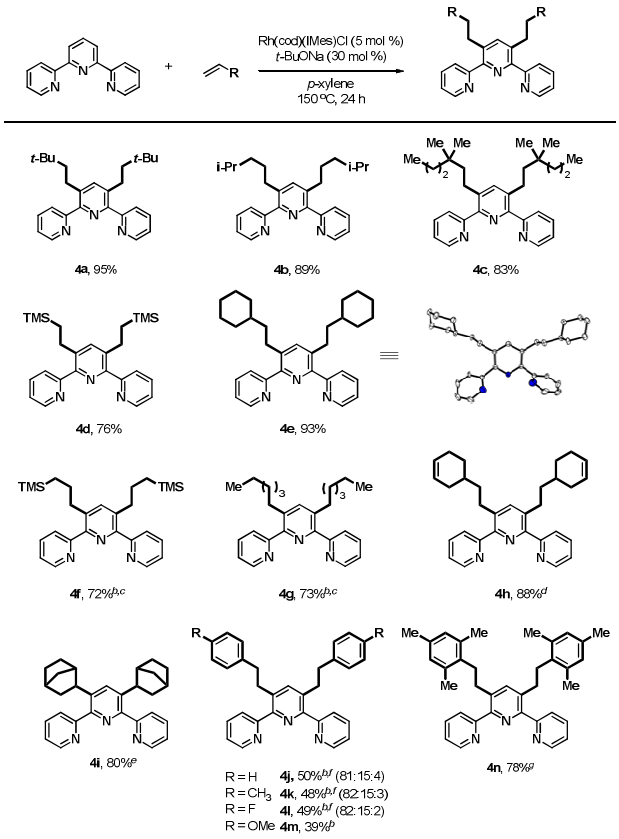
Entry	Catalytic system (mol %)	Base (equiv)	**3a**[b] (%)	**4a**[b] (%)
1[c]	Rh(cod)(IMes)Cl (3)	*t*-BuONa (0.3)	24	16
2[c]	Rh(cod)(IMes)Cl (10)	*t*-BuONa (1.5)	20	55
3	Rh(cod)(IMes)Cl (5)	*t*-BuONa (1.5)	**<5**	**95**
4	Rh(cod)(IMes)Cl (5)	*t*-BuONa (0.3)	**<5**	**99(95)**
5	Rh(cod)(IMes)Cl (5)	Cs_2CO_3 (0.3)	<5	**95**
6	Rh(cod)(IMes)Cl (5)	–	<5	**<5**
7	$[Rh(cod)Cl]_2$ (2.5) + **L1** (5)	*t*-BuONa (0.35)	<5	**95**
8	$[Rh(cod)Cl]_2$ (2.5) + **L2** (5)	*t*-BuONa (0.35)	11	–
9	$[Rh(cod)Cl]_2$ (2.5) + **L3** (5)	*t*-BuONa (0.35)	–	–
10	$[Rh(cod)Cl]_2$ (2.5) + **L4** (5)	*t*-BuONa (0.35)	–	–

[a] Conditions: **1** (0.2 mmol) and **2** (1.0 mmol) in *p*-xylene (0.4 mL) at 150 °C. [b] ^{1}H-NMR yield of the crude reaction mixture (internal standard: 1,1,2,2-tetrachloroethane). [c] At 130 °C in toluene.

At the outset of our studies, we examined the reaction parameters to obtain optimal conditions in a Rh-catalyzed alkylation of 2,2':6',2"-terpyridine (**1a**) with 3,3-dimethyl-1-butene (**2**, Table 1). The use of Rh(cod)(IMes)Cl, the most effective catalyst in our previous study of bipyridines,[6b] afforded a mixture of mono- (**3a**) and dialkylated (**4a**) products in low combined yield at 130 °C in the presence of catalytic amount of *t*-BuONa (entry 1). Importantly, this reaction was highly site-selective to introduce the alkyl group exclusively at the central pyridyl group, and regioisomeric products alkylated at the terminal pyridine were not observed. This result implies that the reaction occurred probably by a central rollover pathway rather than the alternative terminal rollover route.[10a] Whereas higher loadings of catalyst and base provided only a slight increase in yields (entry 2), the reaction became more efficient at higher temperature even with lower amounts of rhodium catalyst to give a bis-alkylated product (**4a**) selectively in high yield (entry 3).

We were pleased to see that the reaction efficiency was maintained still high even with the catalytic amount of external base (entry 4). Moreover, the use of carbonate bases (e.g. Cs_2CO_3) was also satisfactory (entry 5) while no reaction proceeded in the absence of those bases (entry 6). When a Rh(IMes) species was prepared *in situ* by the separate addition of a Rh(I) precursor and NHC ligand **L1**, similar product yield was obtained (entry 7). On the other hand, the employment of NHC ligands (**L2**–**L4**) other than IMes (**L1**) was almost or completely ineffective (entries 8–10).

Table 2 Substrate scope of olefins[a]



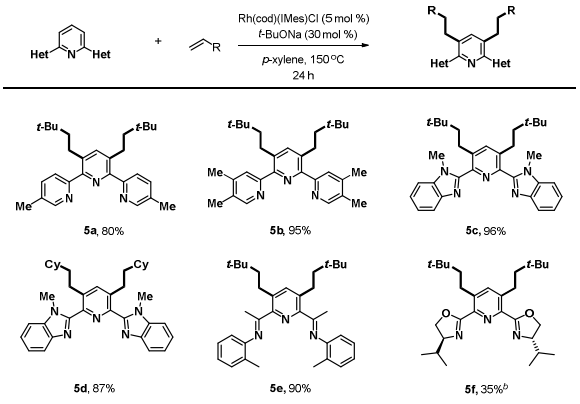
[a] Conditions: substrate (0.2 mmol), olefin (5.0 equiv), Rh(cod)(IMes)Cl (5 mol %), and *t*-BuONa (30 mol %) in *p*-xylene (0.4 mL) at 150 °C for 24 h: isolated yields are indicated. [b] 10 Mol % of catalyst was used. [c] 1 Equiv of base was used. [d] Mixture of double bond isomerized compounds, and only major product is shown. [e] Mixture of *endo*- and *exo*-products. [f] Ratio in parentheses are linear + linear, linear + branched, and branched + branched isomers, respectively, and only major products are shown. [g] For 48 h.

With the optimized conditions in hand, we scrutinized the generality of this selective alkylation of 2,2':6',2"-terpyridine (**1a**) in the reaction with a range of olefins (Table 2). Aliphatic terminal alkenes were efficiently reacted to give the corresponding products in excellent yields (**4a**–**4c**) irrespective of the steric environment on the double bonds. Reactions of vinylsilane and vinylcyclohexane were also facile under the optimized conditions (**4d** and **4e**, respectively). The structure of **4e** was unambiguously confirmed by an X-ray crystallographic analysis. Terpyridine underwent the desired bis-alkylation with allylsilane and 1-hexene in satisfactory yields albeit with higher loadings of catalyst and base (**4e** and **4f**, respectively). Interestingly, when 4-vinylcyclohex-1-ene was allowed to react with terpyridine, the desired product **4h** was obtained in high yield accompanied by small amounts of double bond-isomerized isomers. This result indicates that terminal double bonds react faster than internal ones. However, not surprisingly, ring-stained internal olefins were found to readily participate in the desired reaction as demonstrated by norbornene (**4i**).

While the alkylation of terpyridine with aliphatic olefins afforded only *anti*-Markovnikov linear products, reaction with styrenes provided a mixture of linear and branched products, but still favouring the linear isomers.[11] For instance, styrene was reacted to give linear/linear, linear/branched, and branched/branched isomeric products with ratio of about 20:4:1

(**4j**: a major isomeric product). This selectivity pattern was also observed with styrene derivatives having methyl- or fluoro substituents at the 4-position (**4k** and **4l**, respectively). However, 4-methoxystyrene was reacted to afford only a linear product (**4m**) although the exact reason for this unique selectivity is not understood at the present stage. In addition, as anticipated, a linear product was exclusively formed with a sterically hindered styrene derivative (**4n**).

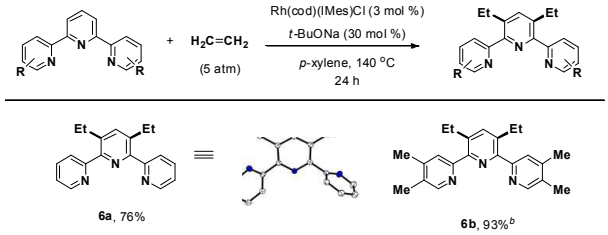
Table 3 Substrate scope of NNN tridentate chelating compounds[a]



[a] Conditions: substrates (0.2 mmol), olefins (5.0 equiv), Rh(cod)(IMes)Cl (5 mol %), *t*-BuONa (30 mol %) in *p*-xylene (0.4 mL) at 150 °C for 24 h. [b] $[Rh(coe)_2Cl]_2$ (10 mol %) + IMes (20 mol %) without *t*-BuONa.

We found that the present selective C–H alkylation procedure could successfully be expanded to various types of tridentate heteroarenes (Table 3). For instance, terpyridines substituted with 5,5"-dimethyl or 4,4',5,5"-tetramethyl groups were efficiently reacted with 3,3-dimethyl-1-butene to afford the corresponding dialkylated products in excellent yields (**5a** and **5b**, respectively). Notably, the reactions of a tridentate heteroarene containing benzimidazole moieties were highly facile under the present conditions (**5c** and **5d,** respectively). Furthermore, diiminopyridine (DIP), a widely employed NNN pincer ligand,[12] was alkylated smoothly leading to **5e** in high yield. This result is significant in that the present procedure can provide a library of ligand derivatives in a highly efficient way, thus being immediately applicable in coordination chemistry. In addition, a reaction of a pybox ligand[13] resulted in a dialkylated product in moderate yield (**5f**) without using *t*-BuONa mainly due to the decomposition of substrate.

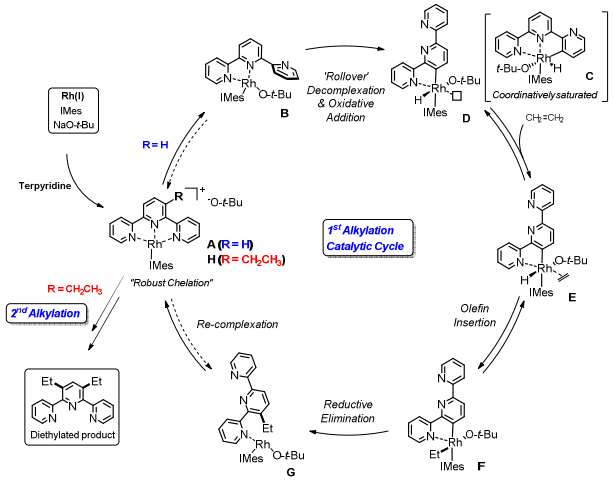
Table 4 Alkylation of terpyridines with ethylene gas[a]



[a] Conditions: substrate (2.0 mmol), ethylene (5.0 atm), Rh(cod)(IMes)Cl (3 mol %), and *t*-BuONa (30 mol %) in *p*-xylene (4.0 mL). [b] Substrate (0.5 mmol).

To our delight, we also observed that the Rh(IMes)-catalyzed bis-alkylation protocol worked well with ethylene gas (Table 4).[13] Indeed, terpyridine was bis-ethylated at the 3'- and 5'-positions (**6a**) with 5 atm of ethylene even under slightly milder conditions (3 mol % of Rh catalyst at 140 °C). The structure of **6a** was unambiguously characterized by an X-ray crystallographic analysis. A substituted terpyridine substrate was also radily applicable under these conditions (**6b**).

A mechansitic pathway of the present Rh(IMes)-catalyzed alkylation of tridentate compounds is proposed in Scheme 2.[6b,15] First, a cationic Rh-terpyridine complex (**A**)[8] will be generated from tepyridine and Rh(NHC) species (NHC = IMes herein) which can be generated in situ from Rh(I) precursor and NHC in the presence of an external base (*t*-BuONa). We then propose that a successive decomplexation of **A** is operative leading to a species **B** that will undergo a key initial rollover cyclometalation[3] *via* an oxidative addition pathway leading to a metal hydride intermediate **D**.[16,17,18] In fact, this type of pathway was previously elucidated by us in the case of bipyridne substrates.[6b] Although a direct oxidative addition of **B** at the terminal pyridyl moiety would also be possible to give a metal hydride complex **C**, this is believed to be less likely due to the coordinative saturatation of this species that does not proceed further. Olefin (herein ethylene) coordination to the more plausbile inetrmediate **D** followed by an insertion will lead to the formation of an ethyl rhodium complex **F**.[18] Reductive elimination of **F** will afford a mono-alkylated product (**H**) that enters into the subseqeunt catalytic cycle eventually to afford the bis-alkylated product.



Scheme 2 Proposed catalytic cycle.

In conclusion, we, for the first time, have developed a Rh(NHC)-catalyzed bis-alkylation reaction of NNN tridentate chelating molecules. The observed regioselectivity in this C–H functionalization can be reasoned by a rollover cyclometalation pathway favoring the central pyridine site. The reaction was found to be highly facile to afford a library of functionalized tridentate compounds in high yields over a broad range of versatile heteroarene substrates and alkene reactants including ethylene gas, thus enabling its applications to be feasible in the coordination and synthetic chemistry.

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