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Lewis Basicity Modulation of *N*-Heterocycles: A Key for Successful Cross-Metathesis

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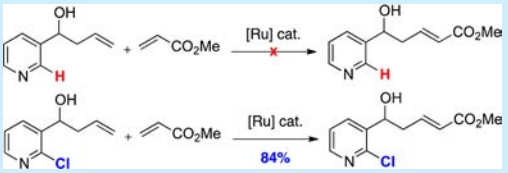
Supporting Information

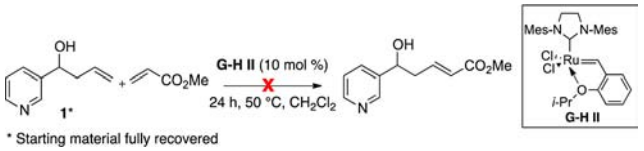
ABSTRACT: Cross-metathesis involving *N*-heteroaromatic olefinic derivatives is disclosed. The introduction of an appropriate substituent on the heteroaromatic ring decreases the Lewis basicity of the nitrogen atom, thus preventing the deactivation of the ruthenium-centered catalyst. The reaction is quite general in terms of both *N*-heterocycles and olefinic partners.



Over the past decades, metathesis reactions have emerged as a powerful tool for the construction of C−C double bonds and is now used for the synthesis of a wide array of compounds such as polymers, petrochemicals, pharmaceuticals, and natural products.[1] The development of well-defined ruthenium carbene complexes has allowed great achievements both in terms of efficiency and chemoselectivity.[2] Thus, a large range of functional groups including alcohols, amides, carbamates, and sulfonamides are well tolerated under metathesis conditions.[3] However, the use of a substrate possessing a strong Lewis base such as a free amine or pyridine remains an issue as the coordination of the nitrogen to the ruthenium center may cause the deactivation of the catalyst.[4] To address this problem, aliphatic amines were protected by electron-withdrawing groups or protonated before the metathesis reactions; alternatively, additives were used.[3a,b,5] The use of pyridine-, quinoline-, or pyrimidine-containing compounds in metathesis remains problematic. Some examples of ring-closing metathesis using *N*-heteroaromatic-containing olefins have already been reported,[6] but in contrast, to the best of our knowledge, only a few examples of cross-metathesis involving olefin possessing a quinoline or a pyridine moiety have been described.[7] Most of these reactions were not optimized as long reaction time or a large excess of the metathesis partner were required. In addition, these reactions are quite limited, and no general study has been conducted. As part of our efforts toward the development of attractive synthetic tools, our group is interested in cross-metathesis.[8] In particular, we have described the functionalization of vinyloxazoles[9] and -thiazoles[10] by cross-metathesis, and the method was successfully applied to the synthesis of several myxobacterial antibiotics.[10] Pyridine, pyrimidine, or imidazole moieties are ubiquitous in bioactive compounds.[11] Thus, we decided to embark on the development of cross-metathesis involving *N*-heteroaromatic-containing olefinic substrates. Herein, we report that a suitable choice of the C2-substituent on the heteroaromatic ring enables the use of alkenes bearing a pyridine motif in ruthenium-catalyzed cross-metathesis. The study was further extended to olefinic partners which incorporated a pyrimidine as well as an imidazole group.

The cross-metathesis between the C3-monosubstituted pyridine **1** and methyl acrylate was first investigated. Because of its performance in cross-metathesis, the second-generation Grubbs−Hoveyda catalyst (**G−H II**) was chosen, and the reaction was carried out at 50 °C in CH_2Cl_2 (Scheme 1).[12] After 24 h, no conversion was observed, and the starting material was fully recovered. This result was not surprising as pyridines were found to poison the ruthenium catalyst by coordination to the metal center.[4]

Scheme 1. Absence of Cross-Metathesis between Pyridine 1 and Methyl Acrylate



* Starting material fully recovered

In order to reduce the Lewis basicity of the nitrogen atom of the pyridine, we decided to introduce an electron-withdrawing substituent on the pyridine ring (Table 1). Pleasingly, in the presence of the **G−H II** catalyst, the 2-chloropyridine derivative **2a** reacted with methyl acrylate to give the cross-metathesis product **3** in 64% yield (Table 1, entry 1). An increase of the concentration from 0.1 to 1 M allowed the reaction to reach an excellent yield of 84% in **3** (Table 1, entry 2). The use of toluene at 80 °C instead of CH_2Cl_2 resulted in a lower yield of **3** (35%) (Table 1, entry 3), and the Grubbs II catalyst (**G II**) appeared to be less effective for this transformation (65%) (Table 1, entry 4).

This positive result prompted us to investigate the influence of the nature of the C2 substituent on the pyridyl moiety. Thus, a variety of 2,5-disubstituted pyridine derivatives **4a−g** were

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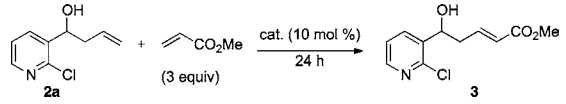
Table 1. Optimization of the Conditions with 2-Chloropyridine Derivative 2a

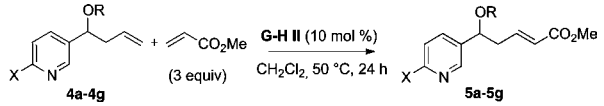


entry	cat.	solvent	temp (°C)	[C] (M)	**3**, yield[a] (%)
1	**G–H II**	CH_2Cl_2	50	0.1	64
2	**G–H II**	CH_2Cl_2	50	1	84
3	**G–H II**	toluene	80	1	35
4	**G II**	CH_2Cl_2	50	1	65

[a]Isolated yields.

reacted with methyl acrylate under the above optimized conditions (Table 2).[13] When a halogen atoms was present at C2 on the pyridine ring (X = Br, Cl, F), the reaction proceeded smoothly delivering the desired olefins in 67–73% yields (Table 2, entries 1–3). A trifluoromethyl group was also suitable for the CM, and the corresponding cross-metathesis product **5d** was obtained in 73% yield (Table 2, entry 4). The best result was obtained with **4e** bearing a triflate at C2 as olefin **5e** was isolated with an excellent 85% yield (Table 2, entry 5).[14] In the presence of a (−*I*, +*M*) methoxy substituent at C2, a lower yield of 51% in **5f** was observed (Table 2, entry 6). Similarly, when a *tert*-butyl group was introduced at the C2 position, the cross-metathesis proceeded in a moderate 52% yield in **5g** (Table 2, entry 7).

Table 2. Influence of the C2 Pyridine Substituent



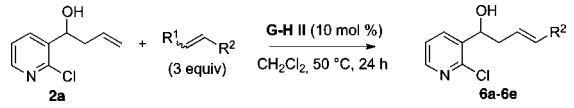
entry	**4**	R	X	**5** (yield,[a] %)
1	**4a**	H	Br	**5a** (73)
2	**4b**	H	Cl	**5b** (67)
3	**4c**	H	F	**5c** (68)
4	**4d**	H	CF_3	**5d** (73)
5	**4e**	Ac	OTf	**5e** (85)
6	**4f**	H	OMe	**5f** (51)
7	**4g**	H	*t*-Bu	**5g** (52)

[a]Isolated yields.

In order to evaluate the scope and limitations of the cross-metathesis, pyridine derivative **2a** was reacted with a range of alkenes under the optimized reaction conditions. Encouraged by the successful cross-metathesis between **2a** and methyl acrylate (Table 1, entry 2), we first turned our attention to electron-poor olefinic partners (Table 3). When 3-buten-2-one was used, the cross-metathesis product **6a** was isolated in 78% yield (Table 3, entry 1). The conditions were compatible with the use of a disubstituted alkene as the cross-metathesis between **2a**, and crotonaldehyde delivered the expected product albeit in a moderate 52% yield (Table 3, entry 2). Triethoxyvinylsilane was also a suitable partner for the metathesis as a good yield in **6c** was obtained (62%) (Table 3, entry 3). Disappointingly, vinyl phosphonates and vinyl boronates proved unreactive under the reaction conditions (Table 3, entries 4 and 5).

Styrenic partners were next tested, and when the cross-metathesis was performed between **2a** and 4-vinylanisole the

Table 3. Evaluation of Electron-Poor Olefinic Partners

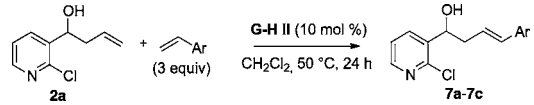


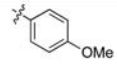
entry	R^1	R^2	**6** (yield,[a] %)
1	H	Ac	**6a** (78)
2[b]	Me	CHO	**6b** (52)
3	H	$Si(OEt)_3$	**6c** (62)
4	H	$P(O)(OEt)_2$	**6d** (0)
5[c]	H	B(pin)	**6e** (0)

[a]Isolated yields. [b]Crotonaldehyde was used as a 1/20 *cis*/*trans* mixture. [c]pin = pinacol.

expected product was isolated in a low 37% yield (Table 4, entry 1).[15] Similarly, the product of the metathesis between **2a** and 4-fluorostyrene could not be purified, thus disabling the determination of the isolated yield (Table 4, entry 2). In contrast, the use of 2-chloro-3-vinylpyridine led to the cross-metathesis product in 55% yield (Table 4, entry 3).

Table 4. Evaluation of Styrenic Partners



entry	Ar	**7** (yield)[a]
1		**7a** (37%)
2		**7b** (0%)
3		**7c** (55%)

[a]Isolated yields.

Finally, several electron-rich olefins were evaluated, and to our delight, the cross-metathesis between **2a** and *cis*-1,4-diacetoxy-2-butene proceeded smoothly providing the desired product in 79% yield (Table 5, entry 1). Similar results were obtained when the unsaturated acetate **2b** (Table 5, entry 2) or the TBS ether **2c** (Table 5, entry 3) were involved in the CM. Unfortunately, a low yield of 38% was observed for the formation of the allylic chloride **8d** resulting from the cross-metathesis between **2a** and *cis*-1,4-dichloro-2-butene (Table 5, entry 4). By contrast, 1-phenylallyl acetate reacted with **2a** to give the corresponding product in 68% yield (Table 5, entry 5). When the cross-metathesis was conducted between **2a** and allyltrimethylsilane or allyl bromide, a mixture of compounds with no trace of the desired product was observed (Table 5, entries 6 and 7).

The reactivity of 2-chloro-3-vinylpyridines was then investigated (Table 6). Surprisingly, under the optimized conditions, the cross-metathesis between **9a** and methyl acrylate was sluggish, and after 24 h, **9a**, **10a**, and **11** were obtained as a 2/2/1 mixture. A better result was obtained by using *cis*-1,4-diacetoxy-2-butene as the cross-metathesis product **10b** was isolated albeit in a moderate yield of 56%.

When the olefinic substituent was moved to the C5 position on the pyridine ring, the cross-metathesis with *cis*-1,4-diacetoxy-2-butene provided the expected product **13a** in 61% yield

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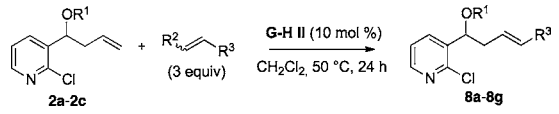
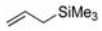
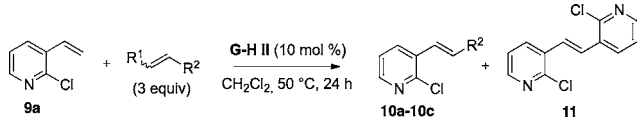
Table 5. Evaluation of Electron-Rich Olefins



entry	2	R^1	partner	8 (yield)[a]
1	**2a**	H		**8a** (79%)
2	**2b**	Ac		**8b** (80%)
3	**2c**	TBS		**8c** (71%)
4	**2a**	H		**8d** (38%)[b]
5	**2a**	H		**8e** (68%)[c]
6	**2a**	H		**8f** (0%)
7	**2a**	H		**8g** (0%)

[a]Isolated yields. [b]Isolated together with some impurities. [c]*syn*/*anti* = 50/50.

Table 6. Reaction of 2-Chloro-3-vinylpyridine

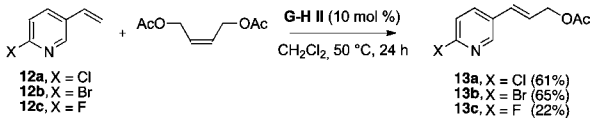


entry	R^1	R^2	9a/10/11[a]	10 (yield,[b] %)
1	H	CO_2Me	40:40:20	**10a** (31)
2	CH_2OAc	CH_2OAc	20:80:—	**10b** (56)

[a]Determined by ^{1}H NMR on the crude mixture. [b]Isolated yield.

(Scheme 2). Replacing the chlorine atom by a bromine did not lead to significant improvement of the yield whereas the presence of a fluorine atom was detrimental to the reaction (Scheme 2).

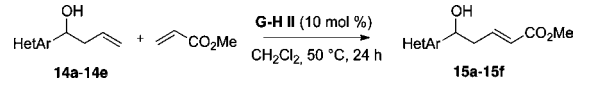
Scheme 2. Influence of the Substituent on Vinylpyridine Reactivity

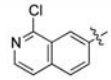
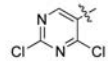
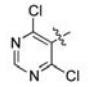
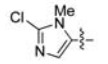
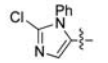
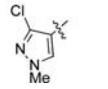


The cross-metathesis reaction with methyl acrylate was then generalized to a range of *N*-heteroaromatic-containing alkenes (Table 7). When olefin **14a** possessing a 2-chloroisoquinoline moiety was used, the corresponding product **15a** was delivered in a moderate yield of 53% (Table 7, entry 1). To our delight, in the presence of dichloropyrimidines, the expected products were isolated in 70% and 82% yields (Table 7, entries 2 and 3). When a *N*-methyl-2-chloro imidazole ring was present, a low yield of 21% for the cross-metathesis product was obtained- (Table 7, entry 4). Gratifyingly, an increased yield of 71% was reached by replacing the methyl group on the nitrogen by a phenyl substituent (Table 7, entry 5). Finally, compound **15f** possessing a pyrazole ring was obtained in good yield (82%) (Table 7, entry 6).

In order to explain the difference of reactivity between nonsubstituted and C2-substituted *N*-heterocycles in the cross-metathesis, we hypothesized that Lewis basic *N*-heterocycles

Table 7. Variation of the *N*-Heterocycles

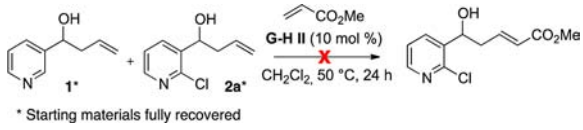


entry	14,	HetAr	15 (yield)[a]
1	**14a,**		**15a** (53%)
2	**14b,**		**15b** (70%)
3	**14c,**		**15c** (82%)
4	**14d,**		**15d** (21%)
5	**14e,**		**15e** (71%)
6	**14f,**		**15f** (82%)

[a]Isolated yields.

could inhibit the Grubbs–Hoveyda catalyst by strongly coordinating the ruthenium metal center thus disabling its reactivity with olefins.[4] The introduction of an electron-withdrawing group at C2 on the *N*-heteroaromatic ring could reduce its Lewis basicity facilitating the dissociation step essential to the activity of the catalyst.[16,17] Similarly, the presence of an hindered substituent such as a *tert*-butyl group render the coordination of the nitrogen to the catalyst more difficult, thus enabling a moderate reactivity (Table 2, entry 7). To verify our hypothesis, a competitive experiment was carried out (Scheme 3). Monosubstituted pyridine **1** and 2-chlorosubstituted pyridine derivative **2a** were mixed (1 equiv of each) in the presence of methyl acrylate (3 equiv) and **G–H II** catalyst (10 mol %). Interestingly, no reaction took place and both olefins **1** and **2a** were fully recovered. This result suggests that pyridine **1** could deactivate the ruthenium catalyst thus totally inhibiting the cross-metathesis reaction.

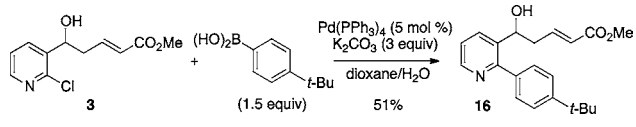
Scheme 3. Competitive Experiment



* Starting materials fully recovered

The presence of a substituent at C2 could offer opportunities for further functionalization. As an example, the 2-chloropyridine **3** was used in a Suzuki cross-coupling with *p*-*tert*-butylphenylboronic acid to afford the expected product in a nonoptimized 51% yield (Scheme 4).

Scheme 4. Suzuki Coupling with Chloropyridine 3



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In summary, we have shown that the presence of an electron-withdrawing substituent enables the use of *N*-heteroaromatic-containing olefins in cross-metathesis reactions. The reaction is quite general both in terms of *N*-heterocycles and olefinic partners. The presence of (pseudo)halogeno substituents could be profitable for further functionalization of aromatic rings. Thus, this method appears as a promising synthetic tool which could find application in the preparation of natural products, agrochemicals, or pharmaceuticals.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(3) For selected examples, see: (a) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829. (b) Woodward, C. P.; Spiccia, N. D.; Jackson, W. R.; Robinson, A. J. *Chem. Commun.* **2011**, *47*, 779. (c) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (d) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123. (e) Lin, Y. A.; Davis, B. G. *Beilstein J. Org. Chem.* **2010**, *6*, 1219. (f) Yun, J. I.; Kim, H. R.; Kim, S. K.; Kim, D.; Lee, J. *Tetrahedron* **2012**, *68*, 117. (g) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277. (h) Hoveyda, H. R.; Vézina, M. *Org. Lett.* **2005**, *7*, 2113. (i) Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2007**, *12*, 4094.

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(12) A sealed tube was used.

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(14) Protection of the alcohol was necessary to access the desired substrate.

(15) Several consecutive purifications were necessary for the separation of the expected product from the homodimer of vinylanisole.

(16) In an experiment, pyridine (20 mol %) was shown to inhibit the cross-metathesis between hex-5-en-1-yl acetate and methyl acrylate,-whereas 2-chloropyridine (20 mol %) did not.

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