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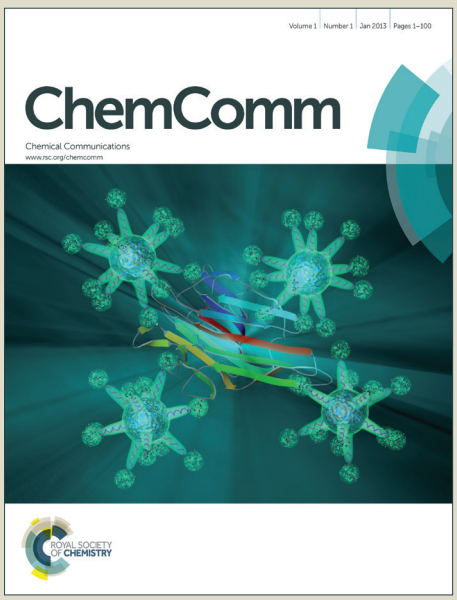

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Nickel-Catalysed *para*-CH Activation of Pyridine with Switchable Regioselective Hydroheteroarylation of Allylarenes

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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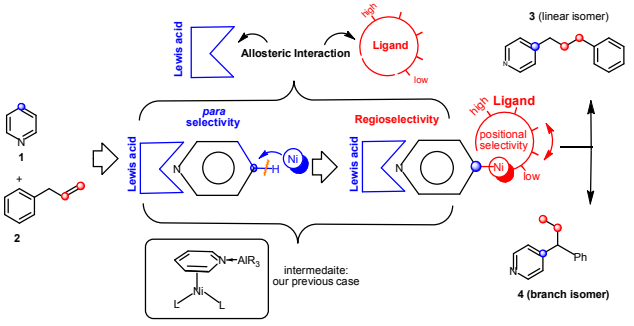
The *para*-CH activation of pyridine with allylbenzene is described by Ni/Al cooperative catalysis with combination of a bulkier NHC ligand and a Lewis acid, leading to the linear hydroheteroarylation products. Interestingly, the branch selectivity can be achieved by using the combination of a less sterically hindered amino-NHC ligand and $AlMe_3$ through tandem reaction of facile alkene isomerization followed by a slow CH bond activation process

Pyridine derivatives are essential molecular motifs, appearing in a myriad of biological and medicinal active products, ligands and functional materials.[1] Thus, synthetic technologies involving functionalization of C-H bonds on pyridine have emerged as attractive paradigms due to atom- and step-economical processes.[2] However, several shortcomings still need to be addressed with regards to π-electron deficiency in the pyridine ring, catalytic deactivation arising from strong binding to metals through the nitrogen atom, and poor positional selectivity. In general, transition metals tend to promote CH activation of pyridine at the C2 position due to the close proximity of the basic nitrogen atom.[3] In contrast, examples related to catalytic CH bond activation of pyridine selectively at the C3 or C4 positions are scarce.[4-6] Thus, further synthetic development towards catalytic CH functionalization selectively at the C3 or C4 positions is highly desirable. In 2010, Hiyama, Nakao and our lab successfully demonstrated the selective *para*-alkylation or alkenylation of pyridine based on bimetallic nickel/Lewis acid catalysis in the absence of directing groups.[4] Similarly, remarkable methods were presented by the groups of Yu and Sames to promote *meta* CH arylation of pyridine using palladium catalysts.[6]

Catalytic enzymatic activity is relatively widespread within the domain of biological phenomena, as globular proteins regulate their catalytic output in response to stimuli from multi-component cooperative interactions, so called allosteric interactions or regulation.[7] Inspired by the working model of an enzyme, we envision a more creative, conceptual line of attack, for which three separate catalytic modules or components work cooperatively in tandem to regulate molecular catalysis: (a) metal center, (b) ligand, and (c) Lewis acid. Encouraged by previous success in our lab on Ni-promoted tandem CH activation and isomerization,[8] we hypothesized that a very sterically demanding ligand and Lewis acid $AlMe_3$ additive would act cooperatively with nickel to impart *para*-C-H alkylation of pyridine with allylbenzene (Scheme 1), in which the linear hydroheteroarylation isomer (1,2-addition) would be favoured. Building on a similar argument, we surmised that a reduction in the steric parameter of the ligand would toggle the isomerization of allylbenzene to allow 1,3-hydroheteroarylation towards the branched product. Herein, we report the regio-switchable *para*-C-H alkylation of pyridine with allylbenzene using bimetallic Ni/Al catalysts. The synthetic scope encompasses a myriad of pyridines and allylbenzenes.

Scheme 1



To test the activity of Ni catalysts for the *para* C-H activation of pyridine, we conducted the reaction of 1 equivalent of pyridine (**1a**) with 2 equivalents of allylbenzene (**2a**) at 130 °C in toluene with 10 mol% $Ni(cod)_2$, various ligands, and a Lewis acid. To our delight, we found complete regioselectivity for the linear hydroheteroarylation isomer **3** at the *para* position in high yield (95 %) using ligand 2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) with methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide (MAD) additive (entry 1, Table 1).

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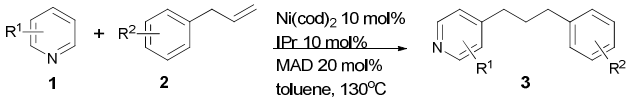
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1. Scope of *para*-CH activation of the pyridine for linear selectivity.



1 2 3

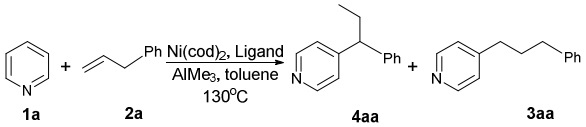
Entry	R	Product	%Yield[b]	3:4
1	**1a** R^1 = H	**3aa**	95	>99:1
2	**1b** R^1 = *m*-Me	**3ba**	57	>99:1
3[c]	**1c** R^1 = *o*-Me	**3ca**	98	>99:1
4	**1d** R^1 = *m*-OMe	**3da**	88	85:13
5	**1j** R^1 = *m*-F	**3ja**	86	>99:1
6[c]	**1l**	**3la**	80	>99[d]:1
7[e]	**2b** R^2 = *o*-Me	**3ab**	83	>99:1
8	**2c** R^2 = *p*-Me	**3ac**	70	>99:1
9[f]	**2e** R^2 = *o*-OMe	**3ae**	57	>99:1
10[f,g]	**2f** R^2 = *p*-OMe	**3af**	23	>99:1
11[f]	**2h** R^2 = *p*-F	**3ah**	65	>99:1
12	**2i**	**3ai**	70	>99:1
13	**2j**	**3aj**	60	>99:1

[a] Reaction condition: **1** (1 mmol), **2** (3 mmol), $Ni(cod)_2$ (10 mol%), IPr (10 mol%), MAD (20 mol%) in toluene (1.0 mL) at 130 °C for 18 h. [b] Isolated yield (%). [c] $AlMe_3$ (20 mol%). [d] *para*:*meta* = 91:9. [e] $Ni(cod)_2$ (3 mol%), IPr (3 mol%). [f] 44 h. [g] $Ni(cod)_2$ (20 mol%), IPr (20 mol%).

With the optimal reaction conditions in hand, a myriad of allylbenzene and pyridine derivatives were examined to evaluate the scope and limitations of this catalytic manifold, as summarised in Table 1. Pyridines bearing a methyl group at the *meta* (**1b**) or *ortho* (**1c**) position reacted efficiently and selectively to afford the *para*-CH functionalized product **3ba** (57 %) and **3ca** (98 %), respectively, with high linear regioselectivity. 3-Methoxypyridine (**1d**) was effectively converted to its corresponding linear product **3da** in 98 % yield. The presence of a strong electron-withdrawing substituent, such as *meta*-fluoro (**1j**) has no adverse effect on the linear regioselectivity (99:1) while maintaining the high yield (86%). Remarkably, quinoline (**1l**), a biologically important motif, reacted successfully with good yield (80%) and high regioselectivity. Next, we systematically examined the effect of allylbenzene derivatives on this reaction (Table 1, entries 7-13). The allylbenzenes bearing electron-donating methyl substituents at the *p*- and *o*-positions afforded the corresponding *para*-CH functionalized pyridine adducts **3ab** and **3ac**, respectively, in good yields (~ 85%) with good linear selectivity. The *ortho*-methoxy derivative **2e** achieves a much better conversion (57%) than its *para*-counterpart **2f** (23%). Nevertheless, regioselectivity of *para*-CH functionalization towards the linear product remained encouragingly high. 1-Allyl-4-fluorobenzene **2h**, an electron-withdrawing group component, and fused allylbenzene substrates like 5-allylbenzodioxole **2j** were suitable in this reaction with a moderate yield of 65%. Finally, we were pleased to observe good yields for the geminal disubstituted allylbenzene **2i** (entry 12) without sacrificing the positional selectivity for the linear product.

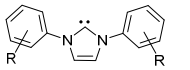
Reducing the steric congestion around the metal centre should in principle facilitate π coordination of the allylbenzene to the metal centre, encouraging the facile isomerization of allylbenzene to the more thermodynamically stable β-methylstyrene, which would eventually lead to the branched product **4** via hydroheteroarylation of pyridine. With a goal of switching the reaction towards branched selectivity, we selected IMes and $AlMe_3$, less sterically encumbered components than IPr and MAD, for a similar CH activation reaction resulting in an increase ratio of branch/linear to 1:1 in 87 % yield (Table 2, entry 1). We next attempted to employ a less bulky, unsymmetrical NHC-bearing secondary *t*-butyl-amino pendant arm (**L1**, entry 6). Branch selectivity was observed exclusively while a lower yield (40 %) was obtained. Nevertheless, the efficiency of the reaction could be further improved to 88% without scarifying much of its selectivity by using the tertiary amino-NHC (**L2**) and increasing amount of $AlMe_3$ additive to 1 equivalent (entry 10).

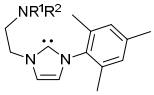
Table 2. Optimization process for branch selectivity.



1a **2a** **4aa** **3aa**

Entry	Ligand (eq)	$AlMe_3$ (eq)	Yield (%)[b]	4aa:3aa
1	IMes (0.1)	0.2	87	55 : 45
2	IPr (0.1)	0.2	63	trace : 99
3	**L1** (0.2)	0.2	18	99 : trace
4	PCy_3 (0.2)	0.2	0	-
5	PPh_3 (0.2)	0.2	0	-
6	**L1** (0.3)	0.3	40	99 : trace
7[cd]	**L2** (0.3)	0.3	70	79 : 21
8[cde]	**L2** (0.3)	0.3	59	82 : 18
9[cde]	**L2** (0.3)	0.5	76	82 : 18
10[cde]	**L2** (0.3)	1.0	88	84 : 16


R = 2,4,6-Me_3 (IMes)
R = 2,6-iPr_2 (IPr)

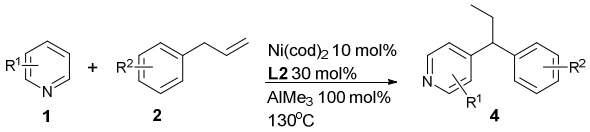

R^1 = H, R^2 = *t*Bu (**L1**)
R^1 = R^2 = Me (**L2**)

[a] Reaction condition: **1a** (1 mmol), **2a** (2 mmol), $Ni(cod)_2$ (10 mol%), ligand and $AlMe_3$ in toluene (1 mL) at 130 °C for 18 h. [b] Isolated yield (%). [c] **L2** was prepared in situ. See SI for details. [d] **1a** (1 mmol), **2a** (3 mmol). [e] Neat condition.

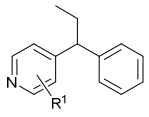
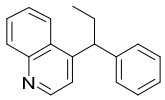
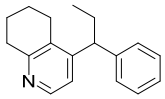
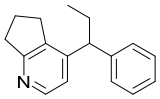
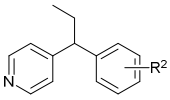
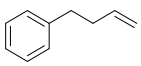
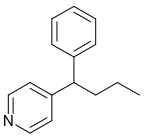
With the optimal reaction conditions for branch selectivity, several pyridine candidates were first examined to evaluate the scope of this catalytic reaction. The results are listed in Table 3. Pyridines bearing electron-donating methyl substituents at the *m*- and *o*-positions afforded the corresponding *para*-CH functionalized product of **4ba** and **4ca**, respectively, in excellent yields with high branch regioselectivity (~99:1, entries 2-3). Average yields were also witnessed for *o,m*-dimethyl, and *m*-phenyl derivatives (entries 4 & 6) with high regioselectivity. Compounds **1g** and **1i** gave low yields (~30 %, entries 5 and 7) while high selectivity towards the branched isomer remained. We attributed these low conversions to steric reason, for which the methyl substituents at the *meta* position or the phenyl group at the *ortho* position might partially block substrate binding to Ni or Al. For the fused pyridines, tetrahydroquinoline (**1m**) was found to be more suitable than quinoline (**1l**) for *para*-CH functionalization. High yield with excellent regioselectivity was also observed for **1n**, a pyridine with a fused 5-membered ring. Next, we systematically examined the effect of the allylbenzene on this reaction (entries 11-17, Table 3). A general observation is that methyl or methoxy groups at different positions of the allylbenzene (**2b-f**) did not have an adverse effect

on the yield or selectivity of the reaction. Pleased by the successful tandem alkene isomerization and CH activation process for pyridine, we tested the viability of the reaction using 1-phenyl-3-butene **2m**, a non-conjugated olefin with an additional sp^3 type carbon. Positively, olefin isomerization followed by hydroheteroarylation occurred to afford the branch product **4am**. Finally, we expanded the scope of this Ni-Al bimetallic protocol with styrene derivatives to demonstrate the viability of the catalytic system (Table 4). Excellent yields with high *para* and branch selectivity were observed with various styrenes (**5a-f**, entries 1-6). Likewise, a high branch positional selectivity and yield were consistently observed with a myriad of pyridines bearing different functional groups.

Table 3. Scope of *para*-CH activation of pyridine for branch selectivity.

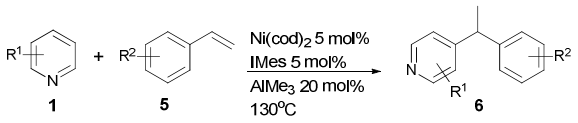


1 2 4

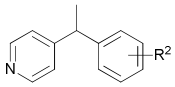
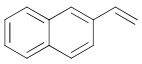
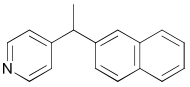
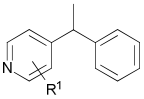
Entry		R	Major Product		Yield (%)[b]	4:3
1	**1a**	R^1 = H		**4aa**	88	84:16
2	**1b**	R^1 = *m*-Me		**4ba**	78	>99:1
3	**1c**	R^1 = *o*-Me		**4ca**	81	>99:1
4	**1f**	R^1 = *o*,*m*-Me_2		**4fa**	50	>99:1
5	**1g**	R^1 = *m*-Me_2		**4ga**	36	81:19
6	**1h**	R^1 = *m*-Ph		**4ha**	54	85:15
7	**1i**	R^1 = *o*-Ph		**4ia**	36	>99[c]:1
8[d]	**1l**			**4la**	28	55:45[e]
9[d]	**1m**			**4ma**	40	>99:1
10	**1n**			**4na**	80	>99:1
11	**2b**	R^2 = *o*-Me		**4ab**	77	87:13
12	**2c**	R^2 = *p*-Me		**4ac**	70	86:14
13	**2d**	R^2 = *m*-Me		**4ad**	71	87:13
14	**2e**	R^2 = *o*-OMe		**4ae**	78	95:5
15	**2f**	R^2 = *p*-OMe		**4af**	69	>99:1
16	**2g**	R^2 = *m*,*p*-$(OMe)_2$		**4ag**	43	>99:1
17	**2m**			**4am**	67	>99:1

[a] Reaction condition : **1** (1 mmol), **2** (3 mmol), $Ni(cod)_2$ (10 mol%), **L2** (30 mol%), $AlMe_3$ (1 equiv) at 130 °C for 18 h. **L2** was prepared in situ; see SI for details. [b] Isolated yield (%, **3**+**4**). [c] *para*:*meta* = 1:1. [d] $Ni(cod)_2$ (20 mol%), **L2** (60 mol%), 66 h. [e] Determined by NMR.

Table 4. Scope of pyridines and styrenes.

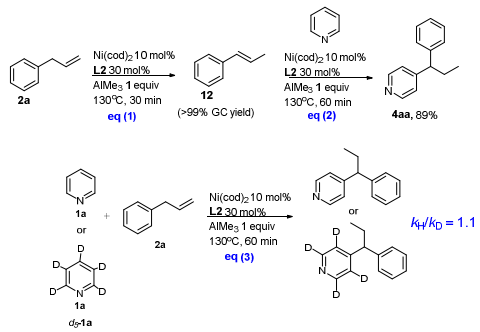


1 5 6

Entry		R	Major Product		Yield (%)[b]
1	**5a**	R^2 = H		**6aa**	95
2	**5b**	R^2 = *o*-Me		**6ab**	94
3	**5c**	R^2 = *p*-Me		**6ac**	69
4	**5d**	R^2 = *p*-OMe		**6ad**	76
5[cd]	**5e**	R^2 = *p*-F		**6ae**	79
6	**5f**			**6af**	50
7	**1b**	R^1 = *m*-Me		**6ba**	63
8	**1d**	R^1 = *m*-OMe		**6da**	85

[a] Reaction condition : **1** (1 mmol), **5** (3 mmol), $Ni(cod)_2$ (5 mol%), IMes (5 mol%), $AlMe_3$ (20 mol%) at 130 °C for 18 h. [b] Isolated yield (%). [c] $Ni(cod)_2$ (10 mol%), IMes (10 mol%). [d] 44 h.

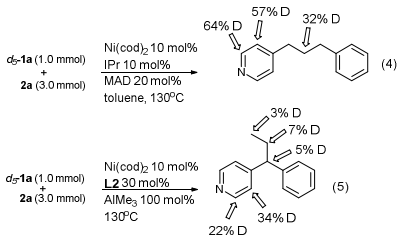
Scheme 2. Reactions pertaining mechanistic investigation



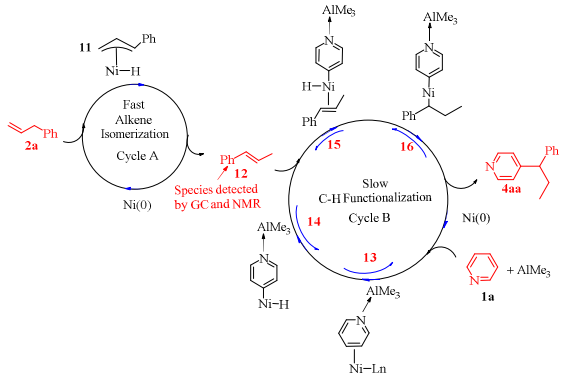
We conducted several control reactions in order to understand the mechanistic nature of the reaction. First, allylbenzene (**2a**) was isomerized to *trans*-β-methylstyrene (**12**) by the nickel catalyst in the absence of pyridine (eq 1, Scheme 2). Under the standard catalytic conditions, reaction of **1a** and **12** also successfully gave the branch product **4aa** (eq 2) in high yield. The GC analysis of the reaction process (see supporting information, Figure S1) further corroborated that rapid isomerization of allylbenzene exclusively occurred prior to the CH activation of pyridine. We also conducted kinetic isotope effect (KIE) experiments by examining the intermolecular competition reaction between pyridine and d_5-pyridine (eq 3). A primary KIE value of 1.1 was obtained; indicating the C-H bond cleavage of pyridine is not significant with respect to the rate-determining step. In addition, reaction of d_5-**1a** and **2a** using both linear or branch standard conditions was independently examined (Scheme 3) with both products containing some loss of deuterium at the *ortho*- and *meta*-positions of pyridine (eq 4 & 5). The results suggest the possibility that both the CH bonds of pyridine were also cleaved reversibly. Yet, the absence of hydroheteroarylation observed at the *ortho*- and *meta*-positions of pyridine was probably due to the steric hindrance imposed by ligand and Lewis acid, disfavoring the insertion or reductive elimination process at these positions. Similar results have been previously discussed.[4] A possible reaction pathway consisting of

two operating catalytic cycles can be proposed based on the results described above and the available literature: a facile double chain-walking isomerization mechanism (Scheme 4, cycle A) and a rather slow C-H functionalization mechanism (Scheme 4, cycle B). In cycle A, **2a** is isomerized via a formal 1,3-hydride shift through an η^3-allyl Ni hydride intermediate **11** to afford the more thermodynamically stable **12**. In the slow catalytic cycle B, the C-H functionalization process most likely proceeds through the following steps: (1) oxidative addition of the C-H bond to afford the Ni-H species, (2) migratory insertion of **12** into the Ni-H to give **16**, and (3) reductive elimination of **16** to afford **4aa**. However, the rate-determining step is most likely the π-coordination of pyridine onto the metal prior to the C-H bond cleavage or reductive elimination step.

Scheme 3. The reaction of d_5-pyridine with allylbenzenes.



Scheme 4. Proposed mechanism



Conclusions

In summary, without installing directing groups on the substrate, we have disclosed a novel regiodivergent C-H bond functionalization of pyridines with allylbenzenes. The catalytic method features a cooperative interaction between Ni and Al to invoke remote *para* C-H activation via hydroheteroarylation towards branched and linear isomers, which is unprecedented. Ongoing work seeks to gain a detailed mechanistic understanding of the synergy offered by Ni-Al bimetallic catalysis. Such mechanistic insights will be crucial for the future development of bimetallic catalysts.

This work was financially supported by the Ministry of Science & Technology of Taiwan (MOST-104-2628-M-001-005-MY4 grant) and Academia Sinica Career Development Award (104-CDA-M08).

Notes and references

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