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Regioselective alkenylation of imidazoles by nickel/Lewis acid catalysis

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ABSTRACT

Nickel/Lewis acid binary catalysis is found effective to direct regioselective alkenylation of imidazoles through C–H bond activation and stereoselective insertion of alkynes. Use of P(*t*-Bu)$_3$ as a ligand allows exclusive regioselective C(2)-alkenylation, while PCyp$_3$ is found effective for C(5)-alkenylation of C(2)-substituted imidazoles. The reaction demonstrates a broad scope of imidazoles and internal alkynes to give trisubstituted ethenes highly regio- and stereoselectively in modest to good yields.

Imidazole ring is an important structural motif encountered in numerous biologically active compounds ranging from natural products to pharmaceuticals.[1] Imidazole derivatives are also widely used as organocatalysts,[2] ionic liquids,[3] and N-heterocyclic carbenes.[4] Consequently, it is not surprising that development of strategies for their synthesis and functionalization has attracted much attention in academia and industry, and continues to be a significant subject in organic synthesis and medicinal chemistry.[1] Most conventional synthetic methods for the imidazole ring involve heteroannulation processes, which frequently require preparation of starting materials through multi-step reactions. Although palladium-catalyzed cross-coupling reactions have also been developed and widely applied to synthesis of imidazole derivatives,[5] these methods require preactivation by stoichiometric halogenation or metallation of imidazoles and therefore result in stoichiometric amounts of waste.

On the other hand, direct functionalization of imidazoles via transition metal-catalyzed C–H bond activation has emerged as a convenient and practical alternative in terms of atom and step economy. Among the reported works, direct arylation has received the most attention.[6] Transition metal-catalyzed carbonylation[7] and alkylation[8] of imidazole derivatives have also been considerably studied. Whereas direct cleavage of imidazole C–H bond followed by insertion of alkynes appears an ideal and straightforward synthetic method for alkenylation of imidazoles,[9] it has remained relatively unexplored. Herein we report the nickel/Lewis acid (LA)-catalyzed regioselective C(2)- and C(5)-alkenylation of imidazole nucleus by means of C–H bond activation followed by stereoselective cis-insertion of an alkyne. In some cases, the initially formed cis-adducts isomerize to give thermodynamically stable trans-isomers in high stereoselectivity.

In the course of our research aimed at C–C bond formation by activation of unreactive C–H bonds followed by insertion of unsaturated C–C bonds,[10] we carried out reactions of imidazoles with alkynes. At the onset, the reaction of 1-methyl-1*H*-imidazole (**1a**, 3.0 mmol) with 4-octyne (**2a**, 1.0 mmol) in the presence of Ni(cod)$_2$ (3 mol %), tricyclopentylphosphine (PCyp$_3$) (12 mol %), and AlMe$_3$ (6 mol %) as a LA catalyst at 100 °C in toluene for 4 h gave (*E*)-1-methyl-2-(4-octen-4-yl)-1*H*-imidazole (**3aa**) and 2,5-dialkenylated adduct **3′aa** in 15% and 24% ^{1}H NMR yields, respectively (Table 1, entry 1). The stereochemistry of the adducts was unambiguously identified based on ^{1}H NMR NOE experiments.[11] Although the use of P(*i*-Pr)$_3$ resulted in almost the same yield but with poorer regioselectivity (entry 2), P(*t*-Bu)$_3$ dramatically improved the regioselectivity to afford C(2)-alkenylated adduct **3aa** exclusively in 70% yield after isolation by silica gel column chromatography (entry 3). P(*n*-Bu)$_3$ and PPh$_3$ ligands resulted in poor yields (entries 4 and 5). ZnMe$_2$ was also effective for the C(2)-alkenylation to a less extent compared with AlMe$_3$ (entry 6). Noteworthy is that a LA-free catalyst was futile: poor yields of the hydroheteroarylation adducts and excessive oligomerization of **2a** resulted (entry 7). A strong σ-donor ligand likely increases electron density on the nickel center to initiate the catalytic cycle, while its bulkiness may accelerate reductive elimination to afford the hydroheteroarylation adduct.

With the optimized set of a LA and ligand for C(2)-alkenylation in hand, several imidazole derivatives were tested for the reaction with **2a**. Imidazoles with an *N*-benzyl or *N*-phenyl substituent **1b** and **1c** participated in the reaction to give **3ba** and **3ca** highly regio- and stereoselectively in 63% and 42% yields, respectively (entries 1 and 2 of Table 2). A phenyl substituent at the C-4 position in **1d** did not affect the reaction to give **3da** in 63% yield (entry 3). C(2)-alkenylation of **1a** with other alkynes was examined next. Aryl-substituted alkynes **2b**, **2c**, and **2d** underwent the reaction to give triarylethenes in good yields but with reversed stereoselectivity (entries 4–6). In both cases, initially formed cis-adducts apparently isomerized to trans-adducts under the reaction conditions.

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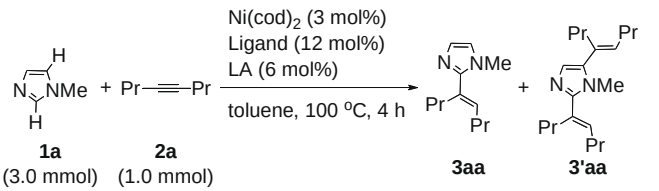
Table 1
Optimization of reaction conditions for C(2)-alkenylation of imidazoles[a]



Entry	Ligand	LA	Yield of **3aa**[b] (%)	Yield of **3′aa**[b] (%)
1	$PCyp_3$	$AlMe_3$	15	24
2	$P(i\text{-}Pr)_3$	$AlMe_3$	16	16
3	$P(t\text{-}Bu)_3$	$AlMe_3$	76 (70)[c]	<1
4	$P(n\text{-}Bu)_3$	$AlMe_3$	6	2
5	PPh_3	$AlMe_3$	7	1
6	$P(t\text{-}Bu)_3$	$ZnMe_2$	40	<1
7[d]	$PCyp_3$	none	5	20

[a] Unless otherwise stated, all the reactions were carried out with **1a** (3.0 mmol) and **2a** (1.0 mmol) in the presence of $Ni(cod)_2$ (3 mol %), a ligand (12 mol %), and LA (6 mol %) in toluene (0.68 mL).
[b] Estimated by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[c] Isolated yield based on **2a** as the limiting reagent, E/Z = 95:5.
[d] The reaction was done with $Ni(cod)_2$ (10 mol %) and $PCyp_3$ (10 mol %).

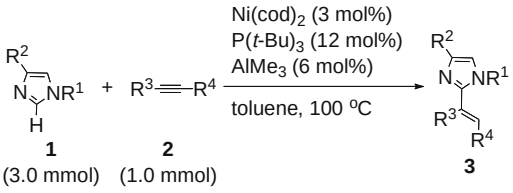
Thus, the E/Z ratios of **3ac** and **3ad** at 1 h were 31:69 and 88:12, respectively. The isomerization was proved further by the fact that reaction of isolated pure *E*-isomer of **3ad** in the presence of $Ni(cod)_2$ (3 mol %), $P(t\text{-}Bu)_3$ (12 mol %), and $AlMe_3$ (6 mol %) in toluene at 100 °C for 6 h induced quantitative isomerization to the *Z*-isomer. Nevertheless, possible formation of the trans-adducts kinetically via isomerization of alkenylnickel intermediates cannot be ruled out (vide infra).[12] The aryl substituents may electronically stabilize intermediates of the isomerization. Unsymmetrical alkyne **2e** underwent the hydroheteroarylation reaction with perfect stereo- and regioselectivity to give the corresponding adduct **3ae**, in which the silyl substituent is located trans to the imidazolyl ring (entry 7), whereas terminal alkynes did not give any trace amount of adducts due to rapid tri- and/or oligomerization of the alkynes under these conditions.

We next turned our attention to optimization of reaction conditions for regioselective alkenylation of C(2)-substituted imidazoles at C(5)-position. $P(t\text{-}Bu)_3$ was ineffective to give expected adduct **3ea** in poor yield (Table 3, entry 3), whereas $PCyp_3$ and $P(i\text{-}Pr)_3$ gave acceptable yields of **3ea** (entries 1 and 2). Use of a mild LA $ZnMe_2$ also provided the hydroheteroarylation adduct in a comparable yield (entry 4). In any case, the alkenylation took place exclusively at the C-5 position, and no trace amount of C(4)-alkenylated imidazole was observed.

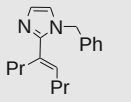
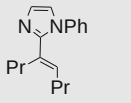
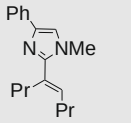
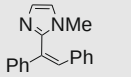
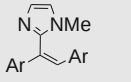
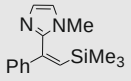
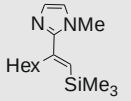
With the conditions for C(5)-alkenylation in hand, we examined the scope of 2-substituted imidazoles and alkynes. The reaction of 1-methyl-2-phenyl-1*H*-imidazole (**1f**) with **2a** also proceeded smoothly to give the corresponding C(5)-alkenylated product **3fa** in 81% yield (Table 4, entry 1), whereas *tert*-butyldimethylsilyl substituted one **1g** reacted sluggishly to give **3ga** in 42% yield. The hydroheteroarylation of other alkynes such as 1-trimethylsilyl-1-octyne (**2e**), 4-methyl-2-pentyne (**2f**), and 4,4-dimethyl-2-pentyne (**2g**) with **1e** also proceeded smoothly in excellent regio- and stereoselectivities to give the corresponding adducts with a bulkier substituent located trans to the imidazolyl ring (entries 3–5).

Following is a plausible mechanism. We consider that nickel(0) species **A**[13] and imidazolium species **B**[14] are initially formed in situ by coordination of an alkyne to nickel and the lone pair electrons of nitrogen in imidazole nucleus to $AlMe_3$, respectively (Scheme 1).

Table 2
Nickel/$AlMe_3$-catalyzed C-2 alkenylation of imidazoles[a]



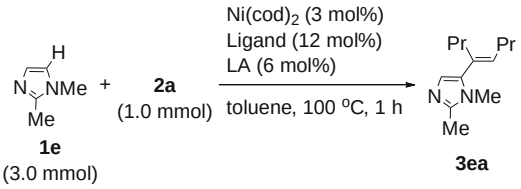
R^1, R^2 = Bn, H (**1b**); Ph, H (**1c**); Me, Ph (**1d**)
R^3, R^4 = Ph (**2b**); 4-MeO–C_6H_4 (**2c**); Ph, $SiMe_3$ (**2d**); Hex, $SiMe_3$ (**2e**)

Entry	1	2	Time (h)	Major product	Yield[b] (%)	E/Z[c]
1	**1b**	**2a**	3		63 (**3ba**)	93:7
2	**1c**	**2a**	10		42 (**3ca**)	92:8
3	**1d**	**2a**	2		63 (**3da**)	>99:1
4	**1a**	**2b**	10		75 (**3ab**)	<1:99
5[d]	**1a**	**2c**	18		53 (**3ac**)	<1:99
6	**1a**	**2d**	20		69 (**3ad**)	20:80
7[e]	**1a**	**2e**	26		60 (**3ae**)	>99:1

[a] Unless otherwise stated, all the reactions were carried out with **1** (3.0 mmol) and **2** (1.0 mmol) in the presence of $Ni(cod)_2$ (3 mol %), $P(t\text{-}Bu)_3$ (12 mol %), and $AlMe_3$ (6 mol %) in toluene (0.68 mL).
[b] Isolated yields of isomerically pure products based on **2** as the limiting reagent.
[c] Estimated by ^1H NMR analysis of a crude product.
[d] Ar = 4-MeO–C_6H_4.
[e] $Ni(cod)_2$ (10 mol %), $P(t\text{-}Bu)_3$ (40 mol %), and $AlMe_3$ (20 mol %) were used.

Oxidative addition of the imidazolium C–H bond to the nickel species affords alkyne-coordinating Ar–Ni(II)–H intermediates **C** or **C′**.[15] Hydronickelation across the coordinating alkyne takes place in a direction that minimizes steric repulsion between a bulkier R^3 group and the imidazoyl ring in **C** or **C′** to give Ar–Ni(II)–alkenyl intermediates **D** or **D′**, respectively. Subsequent reductive elimination gives *cis*-hydroheteroarylation products **3** or **3′**, respectively, and regenerates nickel(0) species **A**. Exclusive C(5)–H activation with 2-substituted imidazoles may be ascribed to resonance structure **B**, wherein the C(5)–H bond locates α to the formally positively charged nitrogen. The origin of the observed preferences for ligands depending on the site of alkenylation is yet to be clarified.

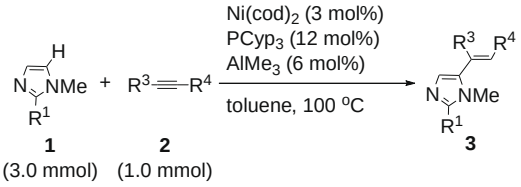
Table 3
Optimization of reaction conditions for C(5)-alkenylation of imidazoles[a]



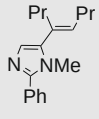
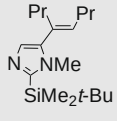
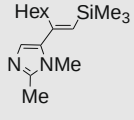
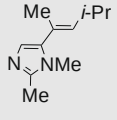
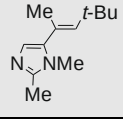
Entry	Ligand	LA	Yield of **3ea**[b] (%)
1	$PCyp_3$	$AlMe_3$	59 (55)[c]
2	$P(i\text{-}Pr)_3$	$AlMe_3$	59
3	$P(t\text{-}Bu)_3$	$AlMe_3$	12
4	$PCyp_3$	$ZnMe_2$	51

[a] All the reactions were carried out with **1e** (3.0 mmol) and **2a** (1.0 mmol) in the presence of $Ni(cod)_2$ (3 mol %), a ligand (12 mol %), and LA (6 mol %) in toluene (0.68 mL).
[b] Estimated by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[c] Isolated yield after 1.5 h, E/Z = >99:1.

Table 4
Nickel/$AlMe_3$-catalyzed C(5)-alkenylation of 2-substituted imidazoles[a]

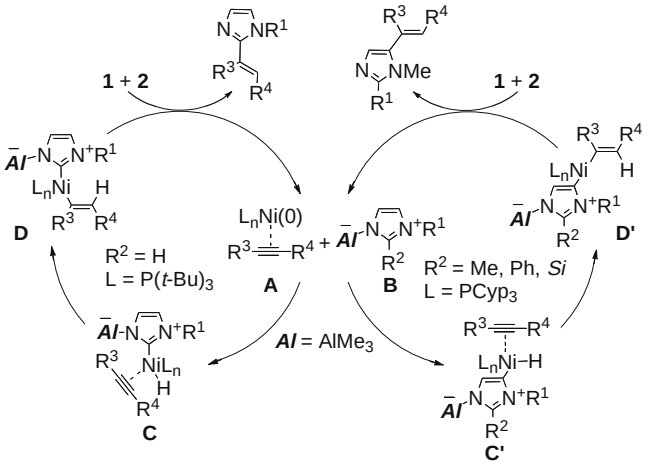


R^1 = Ph (**1f**), $SiMe_2t$-Bu (**1g**); R^3, R^4 = Me, *i*-Pr (**2f**), Me, *t*-Bu (**2g**)

Entry	1	2	Time (h)	Major product	Yield[b] (%)	E/Z[c]
1	**1f**	**2a**	2		81 (**3fa**)	>95:5
2	**1g**	**2a**	1		42 (**3ga**)	96:4
3[d]	**1e**	**2e**	31		63 (**3ee**)	>95:5
4	**1e**	**2f**	4		75 (**3ef**)	>95:5
5	**1e**	**2g**	4		71 (**3eg**)	>95:5

[a] Unless otherwise stated, all the reactions were carried out with **1** (3.0 mmol) and **2** (1.0 mmol) in the presence of $Ni(cod)_2$ (3 mol %), $PCyp_3$ (12 mol %), and $AlMe_3$ (6 mol %) in toluene (0.68 mL).
[b] Isolated yields of isomerically pure products based on **2** as the limiting reagent.
[c] Estimated by ^1H NMR analysis of a crude product.
[d] $Ni(cod)_2$ (10 mol %), $PCyp_3$ (40 mol %), and $AlMe_3$ (20 mol %) were used.

In conclusion, we have demonstrated regio- and stereoselective alkenylation of imidazoles by nickel/LA binary catalysis. The present alkenylation reactions allow efficient synthesis of a diverse range of substituted imidazoles with high atom economy. Current efforts are directed to develop direct C–H functionalization reactions of other substrates by the cooperative catalysis.



Scheme 1. Plausible mechanism.

Acknowledgments

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Supplementary data

Supplementary data associated (detailed experimental procedures including spectroscopic and analytical data) with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.195.

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