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COMMUNICATION

C3-Selective Alkenylation of *N*-Acylindoles with Unactivated Internal Alkynes by Cooperative Nickel/Aluminium Catalysis

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

DOI: 10.1039/x0xx00000x

www.rsc.org/

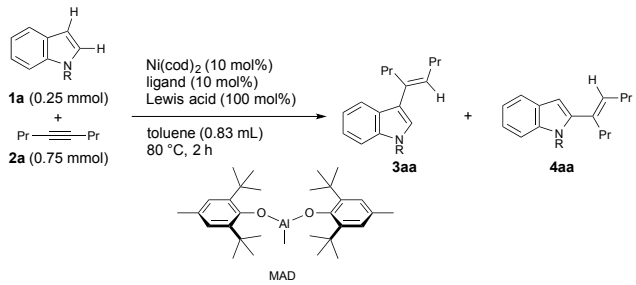
Fumiyoshi Inoue, Teruhiko Saito, Kazuhiko Semba, and Yoshiaki Nakao*

The highly regio- and stereoselective alkenylation of *N*-acylindoles with unactivated internal alkynes has been accomplished by cooperative nickel/aluminium catalysis to afford C3-alkenylated indoles. Coordination of the acyl moiety to a bulky aluminium-based Lewis acid plays a crucial role for the selective functionalization at the C3-position by electron-rich nickel(0) catalysis.

The regioselective alkenylation of indoles is important as alkenylindoles[1] represent useful intermediates in the synthesis of substituted carbazoles,[1a,1b] tetrahydrocarbazoles,[1a,1c] and spiroindolones.[1d,1e] Alkenylindoles are often prepared by cross-coupling reactions using halogenated indoles and organometallic alkenyl reagents,[2] or by the Wittig reaction of the corresponding acylindoles.[3] However, these conventional strategies often suffer from laborious syntheses, whereby every step usually produces stoichiometric amounts of waste. In contrast, transition metal-catalysed direct C–H alkenylation of indoles with alkenes and alkynes are attractive because of their high step- and atom-efficiency as well as ready availability of alkenes and alkynes. Accordingly, several studies on C2-selective alkenylation with alkenes and alkynes have been investigated by metal catalysis.[4] In most of these reactions, indoles carrying an *N*-directing group afford 2-alkenylindoles in high yield and regioselectivity through directed metalation at the C2-position. C7- and C4-selective alkenylations with enones have also been developed with indoles bearing *N*- and C3-directing groups.[5] For C3-selective alkenylation, palladium-catalyzed oxidative Heck-type reactions with enones have been developed.[6] The Friedel–Crafts-type alkenylation of indoles with electrophiles[7] including alkynes[8] also gives 3-alkenylindoles selectively. However, the scope of alkynes has been limited to electron-deficient ones bearing carbonyl and/or aryl groups. Moreover, they sometimes give a mixture of *E/Z* isomers. Herein, we report the C3-selective alkenylation of indoles with unactivated internal alkynes by cooperative nickel/aluminium catalysis. We achieved the highly regio- and stereoselective transformation with the alkynes that have not been suitable substrates for alkenylation of indoles before.

The study was commenced with the reaction of *N*-benzoylindole (**1a**)[4h] and 4-octyne (**2a**) in the presence of $Ni(cod)_2$ (10 mol%) and P^iPr_3 (10 mol%) in toluene at 80 °C to afford a mixture of C3- and C2-substituted *cis*-alkenylation products **3aa** and **4aa** in 8% combined yield (Table 1, entry 1). The stereochemistry of the products were confirmed by the nOe experiments of ^1H NMR (See Supporting Information). As we previously reported the regioselective alkenylation of pyridine by cooperative nickel/Lewis acid catalysis,[9] we subsequently examined the effect of adding Lewis acids (Table 1, entries 2–7). Addition of $AlMe_3$ (100 mol%)

Table 1 Optimisation of the reaction conditions for C3-selective alkenylation of indoles with unactivated internal alkynes.



Entry	Lewis acid	Ligand	R	Yield **3aa**+**4aa**[a] (**3aa**/**4aa**)[a]
1	None	P^iPr_3	C(O)Ph (**1a**)	8% (58:42)
2	$AlMe_3$	P^iPr_3	C(O)Ph	9% (94:6)
3	$Al(C_8H_{17})_3$	P^iPr_3	C(O)Ph	17% (93:7)
4	MAD	P^iPr_3	C(O)Ph	94% (99:1)
5	MAD[b]	P^iPr_3	C(O)Ph	84% (93:7)[c]
6	$B(C_6F_5)_3$	P^iPr_3	C(O)Ph	<5%
7	$ZnEt_2$	P^iPr_3	C(O)Ph	<5%
8	MAD	P^nPr_3	C(O)Ph	<5%
9	MAD	P^tBu_3	C(O)Ph	<5%
10	MAD[b]	P^iPr_3	C(O)Me	29% (86:14)[c]
11	MAD[b]	P^iPr_3	C(O)Cy	56% (88:12)[c]
12	MAD[b]	P^iPr_3	C(O)Ph	27% (>99:1)[c]
13	MAD[b]	P^iPr_3	Me (**1a'**)	32% (>99:1)[d]

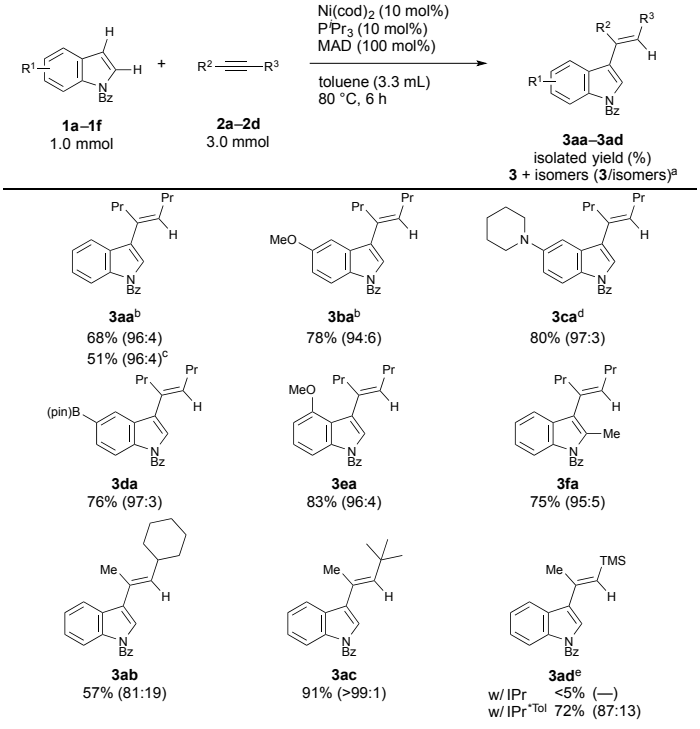
[a]Determined by GC analysis of the crude reaction mixture GC yields including isomers are given in this table. [b]20 mol% of MAD were used. [c]NMR yield. [d]Isolated yield with a 1.0 mmol scale.

Department of Material Chemistry, Graduate School of Engineering, Kyoto University Katsura, Nishikyo-ku, Kyoto 615-8510 (Japan)
E-mail: nakao.yoshiaki.8n@kyoto-u.ac.jp
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

improved the C3 selectivity (**3aa**:**4aa** = 94:6), albeit in poor overall yield (entry 2). Comparable yield and regioselectivity was also observed with $Al(C_8H_{17})_3$ (entry 3), while methylaluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[10] dramatically improved the yield (94%) and regioselectivity (**3aa**:**4aa** = 99:1) (entry 4). A catalytic amount of MAD (20 mol%) still gave **3aa** in high yield (entry 5), while other Lewis acids such as $B(C_6F_5)_3$ and $ZnEt_2$ were not effective (entries 6 and 7). Other phosphines such as P^nPr_3 and P^tBu_3 did not promote this reaction, even in the presence of MAD (entries 8 and 9). The *N*-acyl group that would coordinate to MAD was found to be crucial to control the regioselectivity and yield (entry 5 vs. entries 10–12). Better regioselectivity was observed with sterically bulkier *N*-substituents, although alkanoyl groups generally afforded merely modest yields. The benzoyl group was considered to be the best in terms of yield and regioselectivity. *N*-Boc-indole decomposed under these reaction conditions and gave a complex mixture. When *N*-methylindole (**1a'**) was used under these reaction conditions, the alkenylation proceeded at the most acidic C(2)–H bond to give 2-alkenylindole **4aa'** was obtained selectively in 32% yield (entry 13).

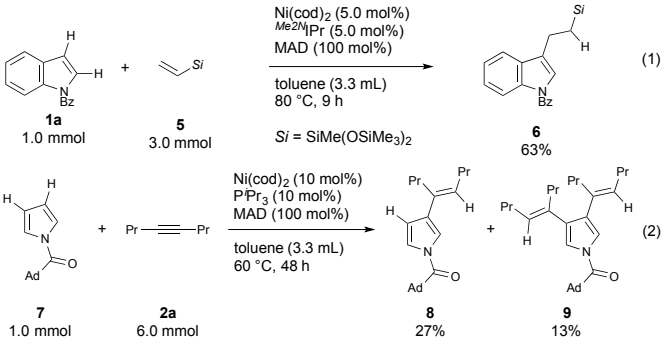
Under the optimised reaction conditions, various indoles (**1a–1f**) and internal alkynes (**2a–2d**) were examined (Table 2). The alkenylation of **1a** with **2a** with a 1.0 mmol-scale successfully proceeded to afford **3aa** in 68%. The reaction could also be performed on a gram-scale to give **3aa** in 51% yield. All *N*-benzoylindoles substituted at the C5 position (**1b–d**) were converted into the corresponding alkenylindoles (**3ba**, **3ca**, and **3da**)

Table 2 Scope of substrates.

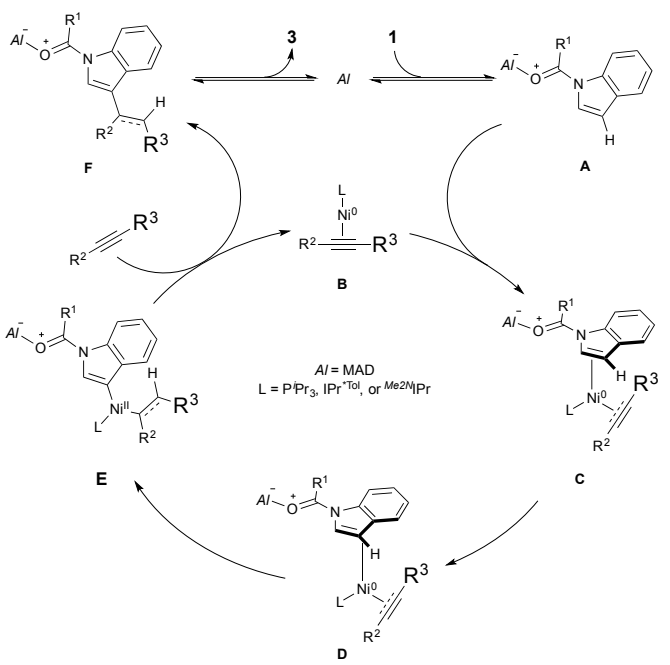


[a]The product mixtures were consisted mainly of the C2-substituted isomer, but other isomers were also detected. Isolated yields of mixtures of isomers are given. [b]20 mol% of MAD were used. [c]**1a** (1.5 g, 6.8 mmol) and **2a** (1.7 g, 16 mmol) were used. [d]The reaction was carried out on a 0.50 mmol scale for 24 h. [e]IPr^{*Tol} was used instead of P^iPr_3 at 50 °C.

in good yields. Functional groups such as amino and pinacolate boryl moieties remained unaffected under reaction conditions involving strong Lewis acids, whereas other functionalities such as chloro, alkoxycarbonyl, and nitro groups were most likely not tolerated, resulting in low conversions. 5-Cyanoindole was susceptible to an alkyne-arylcyanation reaction.[11] Substituents at the C4 and C2 position did not interfere with the C3 selectivity of this alkenylation and afforded **3ea** and **3fa** in high yield. Sterically biased unsymmetrical internal alkynes could also be converted in this hydroheteroarylation to afford adducts (**3ab** and **3ac**), in which the indolyl group was introduced selectively *trans* with respect to the bulky alkyne substituent. In the reaction with 1-trimethylsilylpropyne (**2d**), NHC ligand IPr^{*Tol},[12] was able to successfully replace P^iPr_3 at 50 °C, while 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) gave less than 5% of **3ad**. Aryl-substituted alkynes, enynes, and terminal alkynes did not afford the products due to rapid oligomerization. The use of another NHC ligand, ^{Me2N}IPr,[13] that would have a stronger σ-donating property, allowed the C3-selective alkylation[14,15] of **1a** with vinylsilane **5** to 3-silylethylindone **6** with exclusive linear selectivity (eqn (1)). This result is consistent with our previous findings that NHC ligands are effective to promote the alkylation of $C(sp^2)$–H bonds of (hetero)arenes by nickel catalysis.[9b,14,16] Phosphine ligands did not afford any alkylation products as was the case with the previous studies. No alkylation took place in the absence of MAD, indicating the importance of the acceleration by MAD. Although we also examined other 1-alkenes such as 1-octene and styrene, these atempts afforded trace amounts of the corresponding 3-alkylindoles. Moreover, *N*-acylpyrrole (**7**) also underwent the C3 alkenylation with **2a** under the original reaction conditions to give a mixture of C3-mono- (**8**) and C3,4-dialkenylation (**9**) products in modest yield (eqn (2)).[17] Modification of the *N*-substituent from the benzoyl to adamantanoyl group was necessary to render the pyrrole substrate kinetically more stable under the reaction conditions employing the strong Lewis acid as *N*-benzoylpyrrole decomposed under these standard reaction conditions.



A plausible catalytic cycle for the C3-selective alkenylation is proposed in Scheme 1. Initially, the carbonyl moiety of the indole substrate should coordinate to MAD to form adduct **A**, while ligand exchange between $Ni(cod)_2$, ligands, and alkynes would provide nickel(0) complex **B**.[18,19] The bulkier and electron-donating ligands such as P^iPr_3 and NHC ligands would be important to generate coordinatively unsaturated mono-ligated and electron-rich intermediate **B**. η^2-Indole–nickel complex **C** and, subsequently, σ-complex **D** would be formed. **D** should then undergo ligand-to-ligand hydrogen transfer (LLHT)[19] process to construct C–C, C–H,



Scheme 1 Plausible Mechanism

and two C–Ni bonds in a concerted manner and thus generate alkenyl(indolyl)nickel complex **E**. We cannot exclude a mechanism involving stepwise formation of **E** from **D** *via* oxidative addition of the C(3)–H followed by hydronickelation across alkynes.[20] The reductive elimination of **3**–MAD adduct **F** should proceed to regenerate **B** upon coordination of an unreacted alkyne to the nickel centre. The observed regioselectivity for unsymmetrical alkynes could be explained by their coordination to the nickel centre in a way that minimises steric repulsion between the relatively bulky alkyne substituent and the ligands on the nickel centre. The coordination to the Lewis acid should decrease the electron density of the indole core to enhance the reactivity of the C(3)–H bond, while its bulkiness would cause steric repulsion with the *N*-substituent to induce the observed high C3 selectivity at the LLHT step. C3-selective alkylation of **1a** would proceed in a similar manner, in which steric repulsion between the bulky silyl substituent and the ligand on nickel accounts for the linear selectivity.

In summary, cooperative nickel/aluminium catalysis is demonstrated to achieve the C3-selective alkenylation of *N*-acylindoles with unactivated internal alkynes. In this cooperative system, a bulky Lewis acid both accelerates the desired transformation and controls the regioselectivity in collaboration with the bulky *N*-substituent of the indole substrates. Further efforts will lead to the cooperative catalysis for the regioselective C–H functionalization of otherwise unreactive (hetero)arenes.

This work was supported by the CREST program "Establishment of Molecular Technology towards the Creation of New Functions" Area from JST and by "JSPS KAKENHI Grant Number JP15H05799 in Precisely Designed Catalysts with Customized Scaffolding".

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