COMMUNICATION

Nickel-Catalyzed Exo-Selective Hydroacylation/Suzuki Cross-Coupling Reaction

Shao-Chi Lee, Lin Guo and Magnus Rueping*

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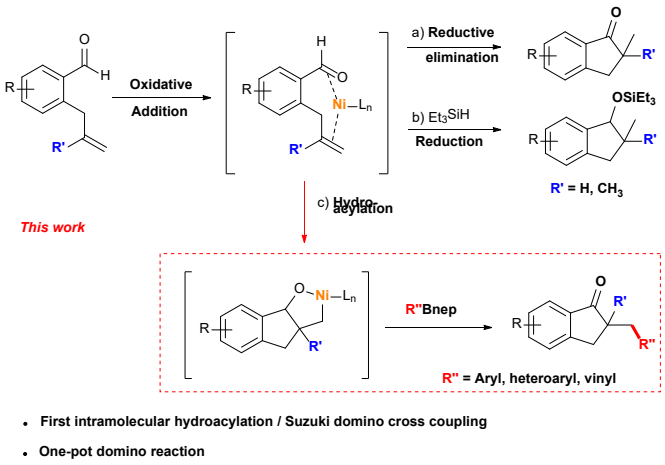
The first nickel-catalyzed intramolecular hydroacylation/Suzuki cross coupling cascade of *o*-allylbenzaldehydes with a broad range of phenylboronic acid neopentyl glycol esters has been developed. This strategy shows high regioselectivity and step economy in the construction of two C-C bonds via aldehyde C-H bond activation, affording valuable indanones with high efficiency.

Hydroacylation is an effective reaction enabling the functionalisation of formyl C-H bonds with unsaturated C-C bonds, which has attracted growing attention due to its facile and straightforward manner in synthesizing various carbonyl structures.[1] Following the initial hydroacylation,[2] protocols regarding the control of stereo-[3] and enantioselectivity,[4] the synthesis of macro-[5] and heterocycles,[6] as well as related mechanistic studies[7] have been published. Among the transition metals used, rhodium, ruthenium, cobalt and nickel were found to be effective for the inter- and intramolecular hydroacylation of alkenes and alkynes.[1] Regarding the application of nickel based catalysts in intramolecular hydroacylation reactions the cyclization of *o*-allylbenz-aldehydes has been reported and the mechanism has been supported by the isolation of key intermediates (Scheme 1a).[8] Subsequently, triethylsilane was shown to achieve silyl-protected 1-indanol products (Scheme 1b).[9] Thus, both strategies lead to the generation of products bearing methyl groups at the generated tertiary/quaternary carbon centre. The feasibility of promoting an intramolecular acylation reaction with subsequent cross coupling reaction, leading to products bearing various substituents in the α-position to the carbonyl group (Scheme 1c) has not been demonstrated yet.

We therefore aimed at developing a nickel-catalyzed intramolecular hydroacylation/Suzuki cross coupling domino reaction[10] which allows the synthesis of different substituted indanones.[11]



Scheme 1 Hydroacylation/Suzuki Domino Cross-Coupling.

Based on our recent work,[12] boronates were selected as nucleophilic coupling partners due to their stability, straightforward manipulation, and excellent functional group tolerance in transition-metal catalyzed cross coupling reactions. Moreover, in a recent publication, an in-situ generated σ-alkyl-Ni(II) species was proposed to undergo Suzuki cross coupling with organoborons.[13] Herein, we report the first nickel-catalyzed *exo*-selective intramolecular hydroacylation/Suzuki cross coupling domino reaction for the construction of a variety of substituted indanones. Notably, an additional hydride acceptor is unexpectedly not required in this protocol.

2-Allylbenzaldehyde (**1a**) and phenylboronic acid neopentyl glycol ester (**2a**) were used for evaluating the nickel-catalyzed *exo*-selective intramolecular hydroacylation/Suzuki cross-coupling domino reaction (Table 1). Our preliminary investigation was performed with $Ni(cod)_2$, 1,3-bis-(2,6-di*iso*propylphenyl) imidazolium chloride (IPr·HCl) and cesium fluoride in toluene at 130 °C, providing the desired indanone product **3a** in 25% GC yield after 16 h (entry 2). Using Cs_2CO_3 as base afforded indanone **3a** in 28% yield (entry 3). The main side product of the reaction was found to be 2-methyl-2,3-dihydro-1*H*-inden-1-one, the product from intramolecular hydroacylation with subsequent reductive elimination (*vide infra*, Scheme 3). Accordingly, we hypothesized that the yield of

[a] *Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074, Aachen, Germany.*
[b] *KAUST Catalysis Center (KCC), King Abdullah University of Science and Technology (KAUST), Thuwal 23955-6900, Saudi Arabia*
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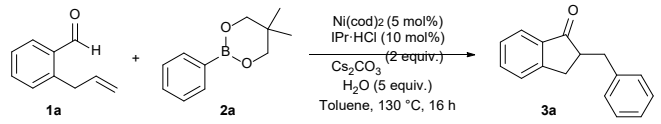
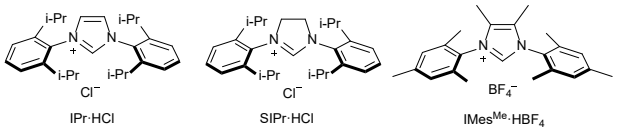
the desired reaction could be increased if the hydride from the nickel-complex **C** is transferred and the undesired reductive elimination is effectively avoided.

Table 1 Optimization of the *exo*-selective intramolecular hydroacylation / Suzuki cross-coupling domino reaction.[a]



Entry	Change from standard conditions	Yield (%)[b]
1	none	80 (75)[c]
2	CsF instead of Cs_2CO_3 and H_2O	25
3	Without H_2O	28
4	SIPr·HCl instead of IPr·HCl	68
5	$IMes^{Me}·HBF_4$ instead of IPr·HCl	28
6	Phenylboronic acid instead of **2a**	30
7	$NiCl_2$ instead of $Ni(cod)_2$	<10
8	$Pd(OAc)_2$ instead of $Ni(cod)_2$	0
9	Xylene instead of toluene	35
10	110 °C instead of 130 °C	56
11	36 h instead of 16 h	78
12	Without Cs_2CO_3	trace
13	Without $Ni(cod)_2$	trace

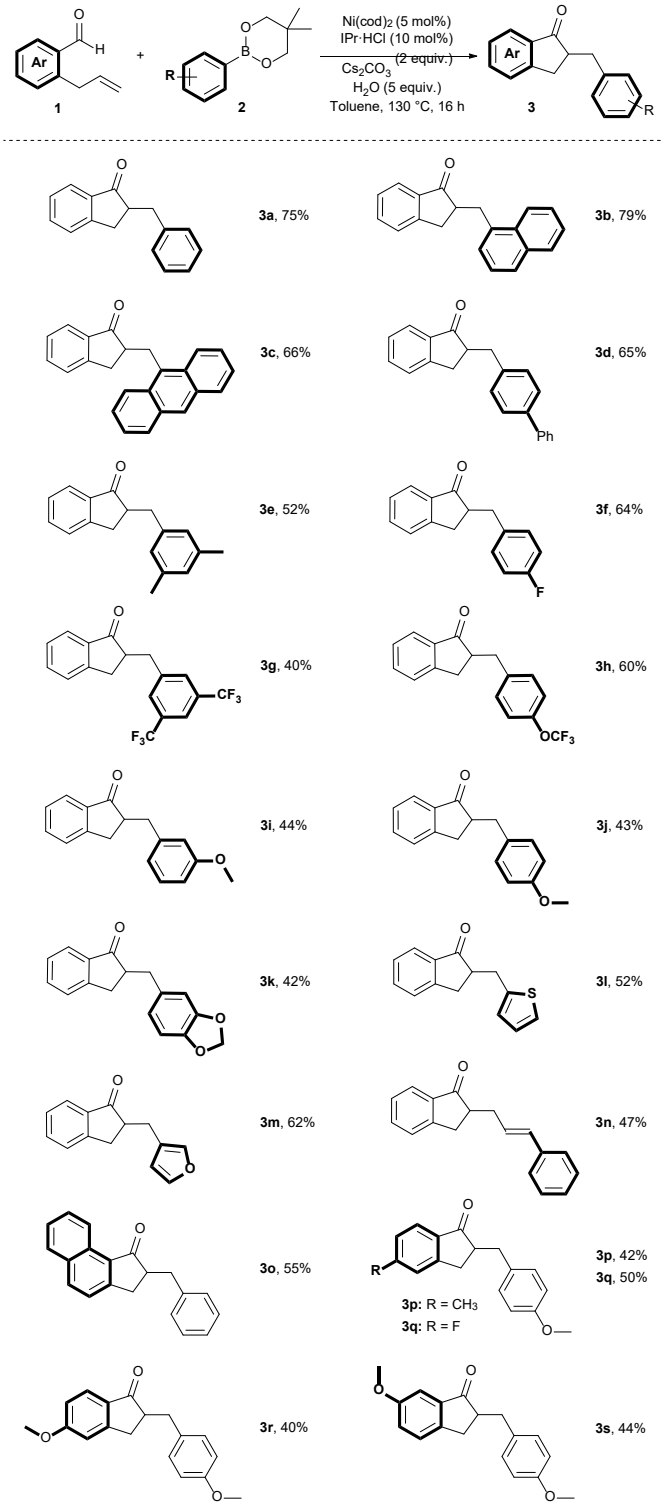
[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), [M] (5 mol%), ligand (10 mol%), base (2 equiv.), H_2O (5 equiv.), toluene (1 ml) at 130 °C, 16 h. [b] GC yields, decane as internal standard. [c] Yield after isolation.



To our surprise, an improved GC yield of 80% (75% yield, entry 1) was obtained in the absence of any hydride acceptor but presence of water in the reaction system. Since ligands typically play a decisive role in catalytic reactions, we further monitored the effect of ligand. IPr·HCl was replaced by 1,3-bis(2,6-di*iso*propylphenyl)-imidazolidinium chloride (SIPr· HCl) and 1,3-bis(2,4,6-trimethylphenyl)-4,5-dimethyl-imidazolium tetrafluoborate ($IMes^{Me}· HBF_4$), yet they afforded unsatisfying results (entries 4 and 5). Next, another boron source, phenylboronic acid, was examined, however, a lower yield was detected (entry 6). With nickel (II) chloride and palladium (II) acetate as alternative catalysts only poor yield or no desired product was obtained (entries 7 and 8). Changing the solvent to xylene provided an unsatisfactory yield (entry 9). In addition, neither decreasing the temperature (entry 10), nor extending the reaction time (entry 11) offered beneficial results. Finally, control experiments revealed that the desired product formation was not achieved without base or nickel catalyst (entries 12 and 13).

With the optimal reaction conditions in hand, we next evaluated the scope of this newly developed *exo*-selective intramolecular hydroacylation/Suzuki cross-coupling domino reaction with respect to various arylboronic acid neopentyl glycol esters.

Table 2 Substrate scope of arylboronic acid neopentyl glycol esters and benzaldehydes.[a]



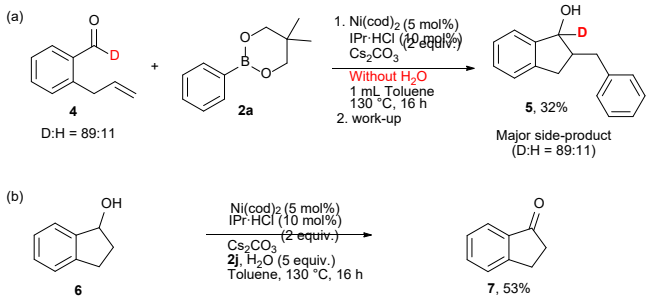
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $Ni(cod)_2$ (5 mol%), IPr·HCl (10 mol%), Cs_2CO_3 (2 equiv.), H_2O (5 equiv.), toluene (1 ml) at 130 °C, 16 h. Yields after isolation.

As shown in Table 2, a wide range of boronic esters could be converted into the appropriate products in moderate to high yields. Hydroacylation of **1a** with model phenyl boronic ester as well as π-extended derivatives generated indanone derivatives **3a-d** in moderate to high yields. Additionally, arylboronic esters bearing substituted aryl rests could also undergo this nickel catalyzed procedure smoothly. Fluoride-substituted arylboronic esters, including fluoro (**2f**), trifluoromethyl (**2g**), and trifluoromethoxy derivatives (**2h**), were applicable in our transformation and were converted into the corresponding products **3f-h** in good yields. Furthermore, substrates bearing methoxy groups were tolerated without cleavage of the C-OMe bond.[14] In addition, heterocyclic derivatives **2k-m** were also compatible with this methodology. Noteworthy, styryl boronic acid neopentyl glycol ester provided the corresponding product **3n**.

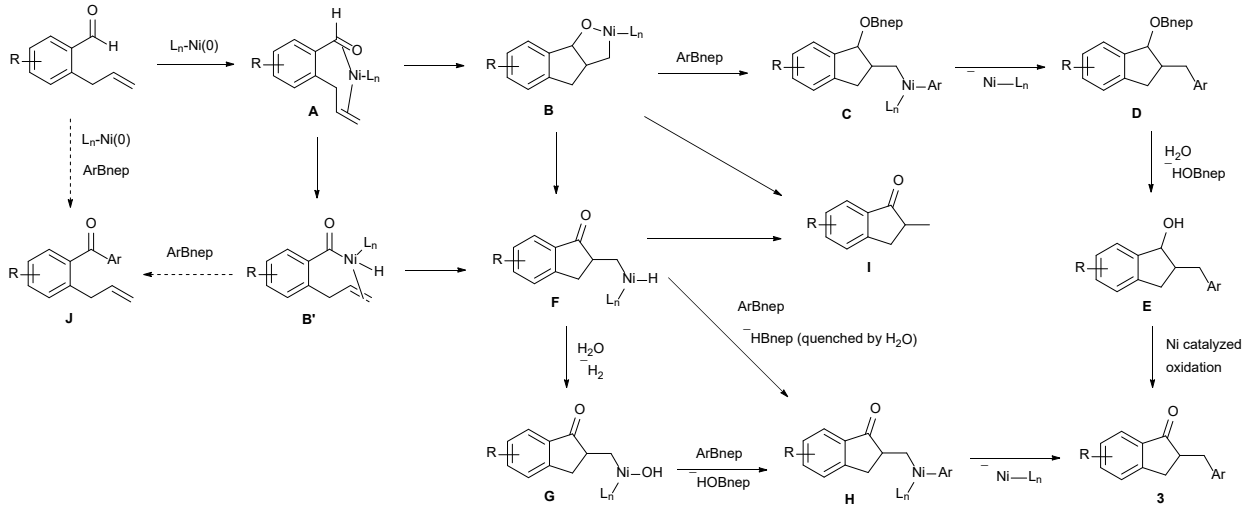
Encouraged by our satisfactory results, we next focused our attention on the domino reaction between various substituted o-allylbenzaldehydes and phenylboronic esters (Table 2). Hydroacylation of different functionalised benzaldehydes with phenylboronic esters **2a** and **2k** was investigated. 1-Napthaldehyde derivative provided the appropriate product **3o** smoothly. As anticipated, both methyl and fluoro substituted benzaldehydes successfully provided the desired products **3p** and **3q**. Furthermore, allylbenzaldehydes bearing an electron-donating methoxy group in the para- and meta- position, underwent this newly developed methodology as well.

Next, we had a closer look at our intramolecular hydroacylation/Suzuki cross-coupling domino reaction. In order to gain a better understanding of the catalysis we examined two additional reactions (Scheme 2). When deuterated aldehyde **4** was reacted with boronic acid neopentylglycol ester **2a** in the absence of water, the deuterated product **5** was isolated (Scheme 2a). In addition, subjecting indenol **6** to our standard reaction conditions led to the corresponding oxidized product **7** in 53% yield (Scheme 2b). These results, while preliminary, suggest more than one possible reaction pathway for the intramolecular hydroacylation/Suzuki cross-coupling reaction.

Scheme 2 Investigation of the reaction mechanism.



Based on our observations and our previous studies,[15] we propose the following mechanism for this *exo*-selective intramolecular hydroacylation/Suzuki cross-coupling domino reaction (Scheme 3): oxidative addition to the coordinative IPr-Ni(0) complex **A** gives oxanickelacycle intermediate **B**, which is supported by earlier studies from Ogoshi.[7d,e,8,9] Transmetallation with boronic acid neopentylglycol ester leads to **C** and subsequent reductive elimination forms boryl-protected 1-indanol **D**. Hydrolysis affords indenol **E**, which can be further oxidized to form the desired product **3**.[16] Alternatively, β-hydride elimination from **B** would lead to nickel hydride intermediate **F**.[7d-f] Direct transmetalation of **F** with boronic acid neopentylglycol ester or hydrolysis with subsequent transmetalation would yield Ni intermediate **H**. Subsequent reductive elimination leads to the desired product **3**. On the other hand, acyl nickel(II) intermediate **B'** is also feasible, hydroacylation of **B'** leading to nickel hydride intermediate **F** which can lead to the desired product **3** as described above.



Scheme 2 Proposed mechanism for the intramolecular hydroacylation / Suzuki cross-coupling domino reaction.

In summary, we have developed a nickel-catalyzed exo-selective intramolecular hydroacylation/Suzuki cross-coupling domino reaction. Various o-allylbenzaldehydes and a wide range of phenylboronic acid neopentyl glycol esters are tolerated in this process which afford indanone derivatives in a straightforward fashion. Notably, the substrate scope tolerates also heterocyclic and Csp2-boronic esters, providing the corresponding indanone products. In addition, this protocol shows an unexpected ability of the boronates to act as both Suzuki reagents and hydride transfer reagents in this domino reaction which is supported by the mechanistic studies. Further synthetic applications are currently underway in our laboratories.

Conflicts of interest

There are no conflicts to declare.

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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