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Ni-Catalyzed Regioselective 1,2-Dicarbofunctionalization of Olefins by Intercepting Heck Intermediates as Imine-Stabilized Transient Metallacycles

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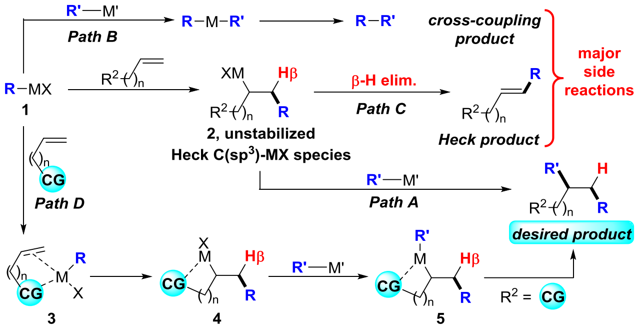
Supporting Information Placeholder

ABSTRACT: We disclose a strategy for Ni-catalyzed regioselective dicarbofunctionalization of olefins in styrene derivatives by intercepting Heck $C(sp^3)$-NiX intermediates with arylzinc reagents. This approach utilizes a readily removable imine as a coordinating group that plays a dual role of intercepting oxidative addition species derived from aryl halides and triflates to promote Heck carbometallation, and stabilizing the Heck $C(sp^3)$-NiX intermediates as transient metallacycles to suppress β-hydride elimination and facilitate transmetalation/reductive elimination steps. This method affords diversely-substituted 1,1,2-triarylethyl products that occur as structural motifs in various natural products.

Catalytic dicarbofunctionalization of olefins via interception of Heck alkyl-transition metal {$C(sp^3)$-MX} intermediates by cross-coupling could provide a powerful synthetic tool in organic synthesis.[1] This method that installs two carbon-carbon (C-C) bonds across olefins with organohalides and organometallic reagents enables to construct rapidly complex molecular architectures with new stereocenters from simple and readily available feedstock chemicals. To this end, the majority of these processes have focused on two-component reactions that generally rely upon cyclization into olefins tethered to enolates,[2] alkyl halides,[3] aryl halides[4] and organometallic reagents.[5] Some examples of oxidative dicarbofunctionalization are also known,[6] which introduce two identical aryl groups across an olefin using organometallic reagents as the aryl source.[7]

In contrast, the three-component dicarbofunctionalization of olefins with organohalides and organometallic reagents remains exceptionally rare. In this process, an oxidative addition intermediate (R-M-X) (**1**) is expected to insert an olefin to generate a new $C(sp^3)$-MX (**2**) species (Scheme 1),[8] which is subsequently intercepted by organometallic reagents (R'-M') via a transmetalation/reductive elimination sequence to form a desired product (Path A). However, the development of this kind of transformation remains formidably challenging due to two major side reactions – 1) the cross-coupling between organohalides and organometallic reagents prior to olefin insertion (Path B); and 2) the Heck reaction by β-hydride (β-H) elimination from the $C(sp^3)$-MX intermediate (**2**) after olefin insertion (Path C). Therefore, enabling 1,2-dicarbofunctionalization of olefins by cross-coupling requires careful strategies to intercept the Heck $C(sp^3)$–MX species (**2**). In this respect, Sigman and others have shown that 1,2-dicarbofunctionalization of dienes and styrenes can be effected with organometallic reagents and organohalides/tri-flates by stabilizing the Heck $C(sp^3)$-MX species by intrinsic π-allylation/π-benzylation.[9] In simple olefins where $C(sp^3)$-MX species cannot be stabilized, the reaction generally affords 1,1-difunctionalized products via a β-H elimination/M-H re-insertion cascade.[10] Similar 1,2-dicarbofunctionaliza-tion reactions have also been realized in cases where radicals are generated by transition metals,[11] such as in the addition of $BrCF_2CO_2Et$ and ArN_2BF_4-derived $•CF_2CO_2Et$/Ar• and arylboronic acids to enamides and dienes.[12]

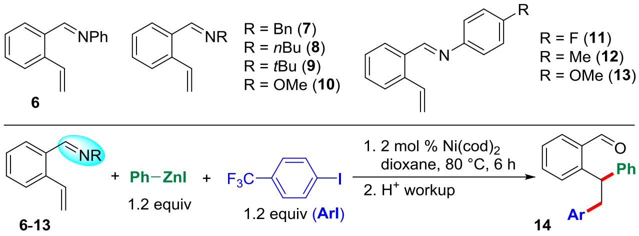


CG: coordinating group; M: transition metal; R'M': ArZnX, ArMgX, $ArBR_2$

Scheme 1: Strategy to overcome major challenges for regioselective olefin dicarbofunctionalization

In our continued efforts to dicarbofunctionalize olefins,[2a,5a] we hypothesized that the two undesired pathways (Scheme 1) could be simultaneously overcome by installing a removable coordinating group (CG) in olefin substrates that could function based on two distinct principles (Path D) – 1) CG could initially intercept the high valent, oxidative addition intermediate R-M-X (**1**) as species **3** via a bidentate coordination mode with the help of the vinyl group and promote Heck carbometallation onto the olefin faster than the direct cross-coupling through the intramolecular insertion process; 2) CG could then intercept and stabilize the Heck $C(sp^3)$-MX species as transient metallacycles (species **4** and **5**), which are expected to slow down the process of β-H elimination due to restricted bond rotations (Scheme 1).[13] We envision that this retardation will enable transmetalation/reductive elimination to proceed sufficiently faster than β-H elimination to furnish the desired products.[14] Herein we report dicarbofuntionalization of olefins in styrene derivatives with aryl halides/triflates and arylzinc reagents that relies upon the concept of intercepting the transiently stabilized oxidative addition and Heck C(sp^3)-MX intermediates.

Table 1. Optimization of reaction conditions[a]

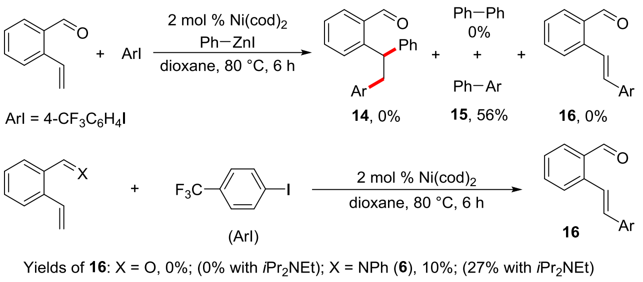


entry	reaction condition deviation	vinylimine	yield of 14 (%)[b]
1	none	**6**	85 (81)
2	without Ni(cod)$_2$	**6**	0
3	3 h	**6**	69
4	none	**7**	19
5	none	**8**, **9** or **10**	trace
6	none	**11** or **12**	34-44
7	none	**13**	78
8	Pd, Co, Fe or Cu-catalyst[c] instead of Ni(cod)$_2$	**6**	0
9	$(Ph_3P)_4Ni$ instead of Ni(cod)$_2$	**6**	9
10	$NiBr_2$ instead of Ni(cod)$_2$	**6**	42
11	NMP or THF instead of dioxane	**6**	77-78
12	DMF or DMSO instead of dioxane	**6**	48-60
13	benzene or MeCN instead of dioxane	**6**	35-49

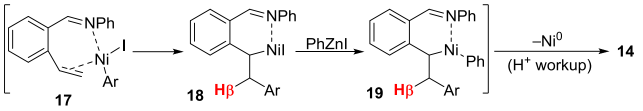
[a]0.1 mmol scale reactions in 0.5 mL solvent. [b]Yields were determined by ^1H NMR using pyrene as an internal standard. Value in parenthesis is the isolated yield from 0.5 mmol in 18 h. [c]Pd(OAc)$_2$, CoCl$_2$, FeCl$_2$ or CuI used.

In order to test the hypothesis, we chose imines as a coordinating group because of their efficacy of binding to transition metals and ease of removal by simple aqueous acidic workup. When we reacted 2-vinyl-*N*-phenylbenzylimine (**6**) with 4-iodobenzotrifluoride and PhZnI in the presence of 2 mol% Ni(cod)$_2$ in dioxane at 80 °C, we were pleased to observe the expected product **14** as a single regioisomer in 85% yield after acidic workup (Table 1, entry 1). Scaling up the reaction to 0.5 mmol required longer time for best product yield (entry 1). The reaction did not furnish any product in the absence of Ni(cod)$_2$ (entry 2). The product was formed in lower yields in shorter reaction time (entry 3). We also changed the imine group in vinylaldimine **6** to benzylimine (**7**), *n*-butylimine (**8**), *t*-butylimine (**9**) and *N*-methoxyimine (**10**), which did not afford the expected product **14** in significant amounts (entries 4-5).[15] We then electronically modified the *N*-phenyl group in vinylimine **6** with *p*-F (**11**), *p*-Me (**12**) and *p*-OMe (**13**) groups. Among these vinylaldimines, only the *N*-anisolyl-imine **13** furnished the expected product **14** in comparable yield (entries 6-7). The use of a Ni-catalyst was found to be critical for this transformation as other catalysts based on Pd, Co, Fe and Cu did not catalyze the reaction (entry 8). $(Ph_3P)_4Ni$ and $NiBr_2$ furnished the product **14** in lower yields (entries 9-10). The reaction can be conducted in NMP or THF, which furnished the product **14** in comparable yields (entry 11). Other solvents such as DMF, DMSO, benzene and MeCN afforded the product **14** in lower yields (entries 12-13).

We conducted further studies in order to probe the role of the imine group (Scheme 2). We performed the reaction of 2-vinylbenzaldehyde with 4-iodobenzotrifluoride and PhZnI under the standard conditions. Despite Ni being a good catalyst for the Heck reaction,[16] 2-vinylbenzaldehyde did not afford any Heck or difunctionalized product. The reaction furnished only the direct cross-coupling product **15** in significant amounts. We further examined the reactions of 2-vinylbenzaldehyde and vinylaldimine **6** separately with 4-iodobenzotrifluoride under the standard conditions but in the absence of PhZnI. Only the reaction of vinylaldimine **6** produced the Heck product in 27% yield.[17] These results indicate that coordination of the imine group is indeed required for both the Heck carbometallation of ArNiI on the vinyl group of 2-vinylaldimine **6** through species **17**, and stabilizing the Heck C(sp^3)-NiX intermediates **18** and **19** for further transmetallation with ArZnI to ultimately deliver the 1,2-diarylated product **14** (Scheme 3).



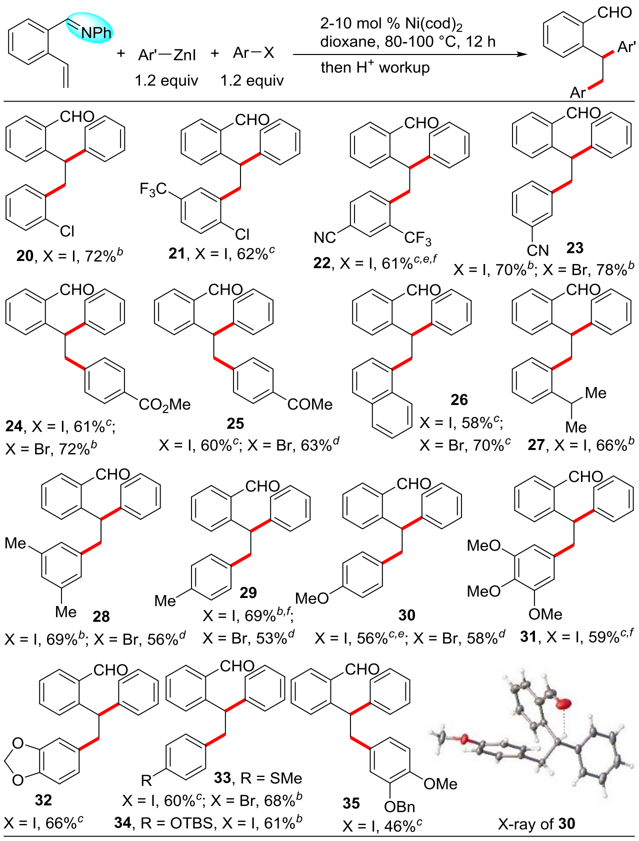
Scheme 2. Control experiments for establishing the role of the imine group



Scheme 3. Proposed mechanistic pathway for regioselective 1,2-dicarbofunctionalization

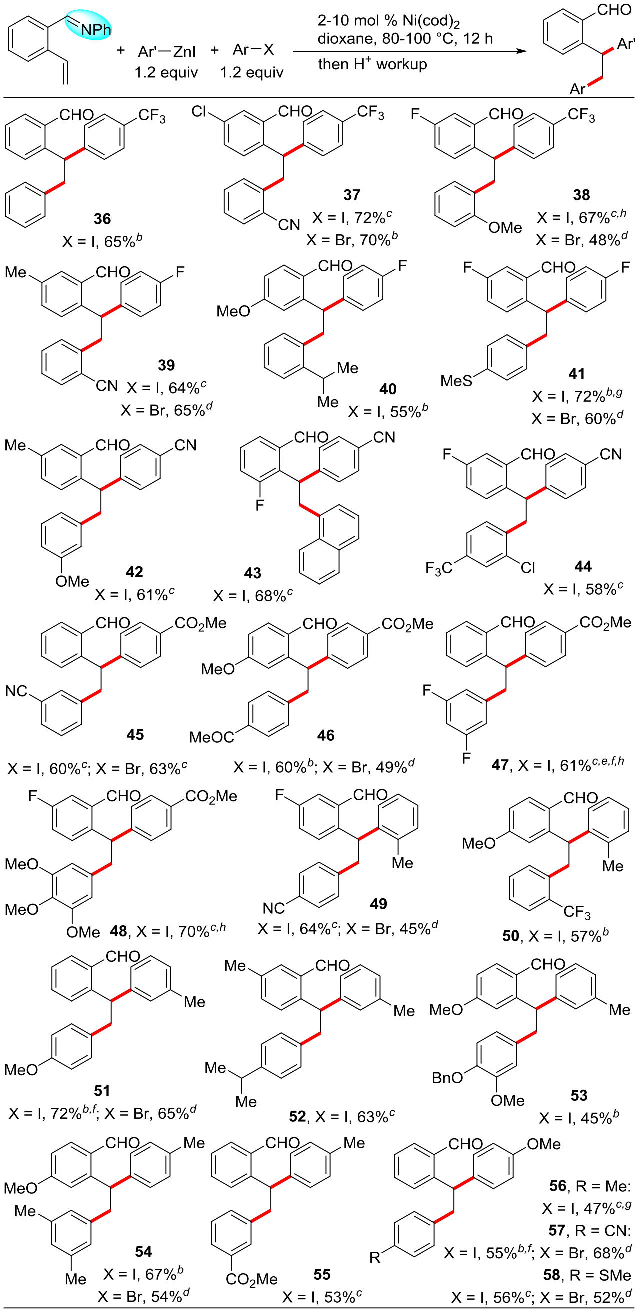
After optimizing the reaction conditions and establishing the role of the imine group, we examined the scope of the current reaction (Table 2). A wide range of electron-rich, neutral and deficient aryl

Table 2. Scope with aryl iodides and bromides[a]



[a] Isolated from 0.5 mmol. 80 °C for ArI and 100 °C for ArBr unless stated otherwise. [b] 2 mol % $Ni(cod)_2$. [c] 5 mol % $Ni(cod)_2$. [d] 10 mol % $Ni(cod)_2$. [e] $NiBr_2$. [f] 18 h.

Table 3. Scope with vinylaldimines and arylzinc reagents[a]



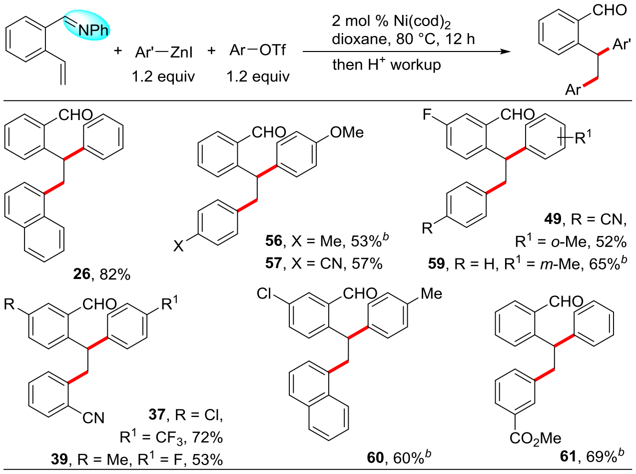
[a] Isolated from 0.5 mmol. 80 °C for ArI and 100 °C for ArBr unless stated otherwise. [b] 2 mol % $Ni(cod)_2$. [c] 5 mol % $Ni(cod)_2$. [d] 10 mol % $Ni(cod)_2$. [e] $NiBr_2$. [f] 18 h. [g] 24 h. [h] 100 °C.

halides (I, Br) and arylzinc reagents can be utilized as coupling partners with the vinylaldimine **6**, which affords the 1,2-diarylated products **20-35** as the only regioisomers in good to excellent yields. The regioselectivity of the reaction was confirmed by the single crystal X-ray structure of product **30**, and ^1H-^1H COSY experiment of compound **26**. The reaction of aryl iodides required lower catalyst loadings (2-5 mol%) than with that of aryl bromides (5-10 mol%) but the latter generally provided products in better yields (**23-26**). Similarly, aryl bromides also required higher temperature than aryl iodides (80 °C) and typically proceeded at 100 °C to afford the best product yield. The reaction tolerates chloride (**20-21**), and other sensitive functional groups such as nitrile (**22-23**), ester (**24**), ketone (**25**), dioxolyl (**32**), thioether (**33**), silyl ether (**34**) and benzyl ether (**35**). The reaction also works well with electron-rich aryl iodides containing multiple electron-donating groups as indicated by the use of 3,5-dimethyliodobenzene (**28**), 3,4,5-trimethoxyiodo-benzene (**31**), 5-iodobenzo[*d*][1,3]dioxole (**32**) and 2-(benzyl-oxy)-4-iodo-1-methoxybenzene (**35**). The reaction can also be utilized with aryl halides containing functional groups such as Cl, CF_3 and sterically bulky *i*-Pr at the *ortho*-position (**20-22**, **26**, **27**), which furnishes products in good yields.

We further examined the scope of the reaction with functionalized vinylaldimines and arylzinc reagents (Table 3). Vinylaldimines containing both electron-withdrawing and donating groups such as Cl, F, Me and OMe could be used as a substrate with a variety of electron-rich and deficient aryl halides and arylzinc reagents (**36-58**).[18] Arylzinc reagents containing F, CF_3, CN, CO_2Me, Me and OMe can be utilized in the reaction, which furnishes products in good to excellent yields. The reaction also tolerates *ortho*-substituted vinylaldimines (**43**) and arylzinc reagents (**49-50**).

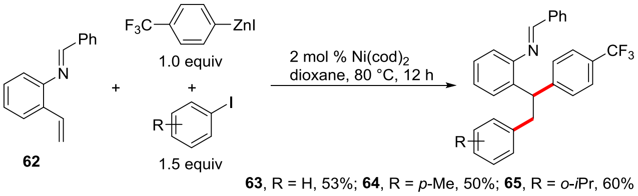
The reaction protocol can be extended to the use of aryl triflates instead of aryl halides along with a variety of arylzinc reagents and substituted vinylaldimines, which affords products in good yields (Table 4). The reaction generally works well with moderately electron-rich, neutral and deficient aryl triflates. The reactivity of these aryl triflates is similar to that of aryl iodides that was generally observed at 80 °C requiring 2-5 mol% of catalyst loading.

Table 4. Scope with aryl triflates[a]



[a] Isolated from 0.5 mmol. [b] 5 mol % $Ni(cod)_2$, 100 °C.

We also examined the scope of the current transformation with vinylimines derived from 2-vinylanilines and benzaldehyde (Scheme 4). The reaction of vinylimine **62** and (4-(trifluoromethyl)phenyl)zinc iodide with iodobenzene, 4-iodotoluene and 2-isopropyliodobenze furnished the corresponding diarylated imine products **63-65** in good yields.[19]



Scheme 4. Scope with vinylimines derived from 2-vinylanilines

In summary, we have developed a Ni-catalyzed regioselective dicarbofunctionalization of olefins in styrene derivatives with aryl halides/triflates and arylzinc reagents, the success of which arise from the stabilization of Heck C(sp^3)-NiX intermediates as transient metallacycles by imine coordination. The reaction shows high functional group and steric tolerance, and furnishes products in good to excellent yields. The current reaction affords an expedient route to differently-substituted 1,1,2-triarylethyl products that widely occur as structural scaffolds in a variety of natural products and bioactive molecules.[20]

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data for all compounds, and crystallographic data (CIF). 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 interests.

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(19) Unlike the products of vinylimines derived from 2-vinylbenzaldehydes, these products were surprisingly resistant to acidic hydrolysis and the product **63** hydrolyzed in <20% GC yield in dioxane:4N H_2SO_4 in 15 h at 120 °C.

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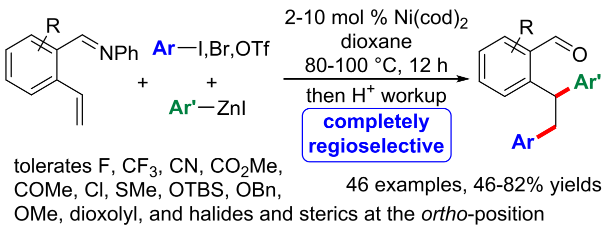
R
NPh
Ar—I,Br,OTf
+
+
Ar'—ZnI
2-10 mol % $Ni(cod)_2$
dioxane
80-100 °C, 12 h
then H^+ workup
completely regioselective
R
O
Ar'
Ar
tolerates F, CF_3, CN, CO_2Me, COMe, Cl, SMe, OTBS, OBn, OMe, dioxolyl, and halides and sterics at the *ortho*-position
46 examples, 46-82% yields