

Nickel-Catalyzed Reductive Arylalkylation via a Migratory Insertion/ **Decarboxylative Cross-Coupling Cascade**

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ABSTRACT: Reported is a nickel-catalyzed reductive arylalkylation of unactivated alkenes tethered to aryl iodides with redox active N-hydroxyphthalimide esters as the alkyl source through successful merging of migratory insertion and decarboxylative cross-coupling in a cascade. This new method avoids the use of pregenerated organometallic reagents and thus enables the synthesis of diverse benzene-fused carbo- and heterocyclic compounds with high tolerance of a wide range of functional groups.

atalytic dicarbofunctionalization of unactivated alkenes is a powerful tool to rapidly increase the molecular complexity from simple precursors by allowing the installation of two carbon moieties across an olefinic unit. The majority of these reactions are realized by applying a redox-neutral strategy in which an organohalide and an organometallic reagent are utilized as the carbon sources.¹⁻³ Moreover, there is one example of oxidative dicarbofunctionalization of unactivated olefins, enabling the introduction of two identical aryl groups through the use of organostannes.⁴ Despite the tremendous progress in this territory, dicarbofunctionalization using reactive organometallics is plagued by two intrinsic issues, the low functional group compatibility and the additional step for pregeneration of organometallic precursors. On the contrary, reductive dicarbofunctionalization employing only electrophilic organohalides as the coupling partners with olefins is more advantageous concerning step economy and functional group compatibility.5

Arylalkylation of tethered olefin can provide an efficient access to a variety of benzene-fused cyclic compounds. For instance, Fu and Cong reported a Ni-catalyzed redox-neutral arylalkylation involving aryl borane as the nucleophilic carbon source (Scheme 1A).^{2b} Recently, our group developed a reductive strategy for two-component arylalkylation between primary alkyl bromides and aryl bromides incorporating a pendant olefinic unit (Scheme 1B).^{5j,k} However, alkyl halides, particularly iodides, are less desirable from the viewpoint of stability, toxicity, and availability. In comparison to alkyl halides, alkanoic acids are more stable, less toxic, and available from both natural and synthetic sources and, thus, are

Scheme 1. (A) Redox-Neutral Arylalkylation; (B) Reductive Arylalkylation Using Alkyl Bromides; (C) Reductive Arylalkylation Using NHP Esters



considered as superior coupling partners. Although carboxylic acids and their derivatives find wide applications as surrogate of alkyl halides in decarboxylative cross-coupling reactions,⁸ application of these compounds as a component in dicarbofunctionalization of unactivated alkenes is still elusive.¹¹

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Table 1. Variation of the Reaction Parameters for the Ni-Catalyzed Reductive Arylalkylation Reaction^a



Ligands:

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N ^{rCN} NH ₂				
L1	L2	L3	L4	L

-	LZ	LJ	L4	EJ		
entry	variation from the optimal conditions	yield of $3a^b$ (%)	yield of $3a-1^{b}$ (%)	yield of $3a-2^b$ (%)	yield of $3a-3^{b}$ (%)	yield of $3a-4^b$ (%)
1	none	71 (68) ^c	6	9	6	0
2	bromo-analogue of 1a used	0	0	0	0	0
3	L2 instead of L1	19	9	21	4	0
4	L3 instead of L1	trace	0	0	0	0
5	L4 instead of L1	16	trace	4	trace	0
6	L5 instead of L1	45	11	13	trace	0
7	NiBr ₂ instead of NiBr ₂ ·diglyme	trace	0	0	0	0
8	NiI ₂ instead of NiBr ₂ ·diglyme	trace	0	0	0	0
9	Ni(COD) ₂ instead of NiBr ₂ ·diglyme	17	trace	trace	trace	0
10	DMA instead of THF	32	8	trace	trace	30
11	NMP instead of THF	29	trace	trace	trace	45
12	1,4-dioxane instead of THF	16	7	17	2	0
13	toluene instead of THF	0	0	0	0	0
14	Mn instead of Zn	14	18	6	trace	0
15	without ZnI ₂	49	11	15	5	0
16	20 $^{\circ}\mathrm{C}$ instead of 40 $^{\circ}\mathrm{C}$	53	4	9	6	0
17	60 °C instead of 40 °C	58	6	12	7	0

^{*a*}Unless otherwise specified, reactions were performed on a 0.2 mmol scale of aryl iodide 1a with 2 equiv of NHP ester 2a, 15 mol % of NiBr₂. diglyme₂, 15 mol % of ligand L1, 4 equiv of Zn as reductant and 1.5 equiv of ZnI₂ as additive in 0.5 mL THF at 40 °C for 10 h. ^{*b*}GC yields using *n*-dodecane as an internal standard. ^{*c*}Yield of the isolated product.

In this context, we report the successful use of redox-active *N*-hydroxyphthalimide (NHP) esters as the alkyl source in the Ni-catalyzed reductive arylalkylation of tethered olefins, which proceeds in a migratory insertion/decarboxylative cross-coupling cascade (Scheme 1C).

For optimization of the reaction conditions, we used the iodobenzene 1a tethering a terminal olefinic unit and the nonanoic acid NHP ester 2a as benchmark substrates (Table 1). After extensive examination of the reaction parameters, we successfully identified the optimal conditions: NiBr₂·diglyme/ L1 as catalyst, Zn as reducing agent, and ZnI₂ as additive in THF at 40 °C (entry 1). Concerning the conversion of the tethered olefin 1a, the formation of one or more of the following byproducts was observed under various conditions, which are the dimer compound 3a-1, the reductive Heck product 3a-2, the deiodination product 3a-3, and the crosscoupling product 3a-4. Remarkably, under the optimal conditions the bromo analogue of 1a remained intact (entry 2). The reactions employing other pyridine-based ligands L2-L5 proceeded with lower yields (entries 3-6). NiBr₂ and NiI₂ were not able to promote the desired reaction possibly due to their low solubility in THF (entries 7 and 8), while a low yield was achieved in the case of $Ni(COD)_2$ as the catalyst (entry 9). Conducting the reaction in DMA and NMP afforded no improved results (entries 10 and 11). Notably, in these cases the cross-coupling reaction turned out to be the main reaction. Furthermore, performing the reaction in 1,4-dioxane resulted in a lower conversion (entry 12), whereas no reaction occurred

in toluene (entry 13). Replacing Zn by Mn as reductant gave rise to a diminished yield (entry 14). The reaction still proceeded without ZnI_2 , albeit in relatively low efficiency (entry 15). Moreover, the studied reaction was also carried out at 20 °C and 60 °C, respectively, providing no better results in either case (entries 16 and 17).

With the optimal reaction conditions in hand, we commenced examining the substrate spectrum of both tethered alkenes 1 and alkyl NHP esters 2 (Scheme 2). First, an array of primary alkyl NHP esters were reacted with the aryl iodide 1a, furnishing various indanes 3a-o in moderate to good yields. Good compatibility of diverse functional moieties including indole (3i), ester (3j), ketone (3k), carbamate (3l), halides (3m and 3n), and alcohol (3o) was observed in this Nicatalyzed reaction. Notably, the reaction using the NHP ester with a primary bromide as substrate proceeded with complete chemoselectivity (3n). To our delight, secondary NHP esters were also successfully utilized as the coupling partners (3p-s), demonstrating a broader substrate spectrum than our previously reported arylalkylation using alkyl bromides.^{5j,k} However, no desired product was obtained in the case of tertiary and benzyl NHP esters as precursors.¹² Subsequently, the influence of the geometry and substitution of the olefinic unit on this Ni-catalyzed reaction was surveyed. The reaction using geminal disubstituted olefins as substrates afforded the products 3t-z in moderate to good efficiency. When 1,1,2trisubstituted alkenes with a low E/Z ratio (ca. 1:1) were employed as precursors, the corresponding products 3aa and



Scheme 2. Evaluation of the Substrate Scope for the Ni-Catalyzed Arylalkylation Reaction^{*a*,*b*}

^{*a*}Unless otherwise specified, reactions were performed on a 0.2 mmol scale of aryl iodides 1 with 2 equiv of NHP esters 2, 15 mol % of NiBr₂. diglyme₂, 15 mol % of ligand L1, 4 equiv of Zn as reductant, and 1.5 equiv of ZnI₂ as additive in 0.5 mL of THF at 40 °C for 10 h. ^{*b*}Yields of the isolated products. ^{*c*}Determined by ¹³C NMR spectroscopy. ^{*d*}Reaction performed on 1 mmol scale. ^{*c*}Determined by HPLC analysis.

		Ni-Preca L1 Zn	atalyst (1 equi (1 equiv) (4 equiv)	v) H ₂ O	+	Me Me ₊	+ Me	
	1a	Additiv Me	ve (1.5 equiv) THF 40 °C		Me / /	3a-2 3a-3	Me 3a-5	
entry	condition	additive	<i>t</i> (h)	recovered $1a^b$ (%)	yield 3a-1^b (%)	yield 3a-2 ^b (%)	yield 3a-3^b (%)	yield 3a-5 ^b (%)
1 ^c	$Ni(COD)_2$		1	25	33	19	7	16
2	$Ni(COD)_2$		1	21	48	13	9	8
3	$Ni(COD)_2$	ZnI_2	1	99	trace	trace	trace	0
4	$Ni(COD)_2$	ZnI_2	10	39	6	47	7	1
5	NiBr₂∙diglyme		1	93	0	0	7	0
6	NiBr₂∙diglyme		10	0	49	31	11	9
7	NiBr ₂ ·diglyme	ZnI_2	3	0	16	67	11	6

Table 2. Stoichiometric Reactions of the Aryl Iodides 1a with Ni Precatalysts Followed by Quenching with Water^a

^{*a*}Unless otherwise specified, reactions were performed on a 0.2 mmol scale of aryl iodide 1a, 1 equiv of Ni-precatalyst, 1 equiv of ligand L1, 4 equiv of Zn as reductant, and 1.5 equiv of additive in 0.5 mL of THF at 40 °C. ^{*b*}GC yields using *n*-dodecane as an internal standard. ^{*c*}Reaction was performed without Zn.

3ab were still obtained in good yields and excellent diastereoselectivities. Unfortunately, the reactions using 1,2-disubstituted and monosubstituted alkenes failed to yield the desired products due to the high propensity to undergo β -hydride elimination.¹² Furthermore, our method is also applicable for the synthesis of benzene-fused hetereocyclic compounds including dihydrobenzofuran (**3ae-ag**), isochroman (**3ah**), indoline (**3ai** and **3aj**), and tetrahydroisoquinoline (**3ak** and **3al**), which were obtained in moderate to good yields. Notably, both the electron-withdrawing and -donating substitutions of the aryl iodides were well tolerated (**3ac**, **3ad**, **3af**, and **3ag**). In addition, we attempted to approach compounds bearing a 7- or 8-membered ring using this method. However, only direct cross-coupling products were obtained in these cases.¹²

A few control experiments were performed in order to investigate the mechanism of this annulation reaction. First, we found that Zn powder does not react with the aryl iodide **1a** under the standard reaction conditions to form the corresponding organozinc reagent, which excludes the reaction pathway initiated by transmetalation between the arylzinc and a Ni species.¹³

Next, we carried out the stoichiometric reactions between the aryl iodide 1a and Ni precatalysts under various conditions to explore the possible reaction pathway, which starts with oxidative addition (Table 2). The reaction of 1a with $Ni(COD)_2$ in the absence of Zn provided the reductive Heck product 3a-2 after quenching with water in a moderate yield, indicating the feasibility of a cascade consisting of the oxidative addition of aryl iodide to a Ni(0) species and the following intramolecular Ni(II)-mediated migratory insertion (entry 1). The other products in this case include the dimer 3a-1, the deiodination product 3a-3, and the 6-endo cyclization product 3a-5, which was not observed in the catalytic reactions. The 6-endo cyclization might be mediated by an aryl radical, which is formed via disproportionation of the aryl Ni(II) species formed via oxidative addition.¹⁴ Conducting this stoichiometric reaction in the presence of Zn gave a similar product profile in which the formation of 3a-5 was slightly disfavored (entry 2). Surprisingly, adding ZnI₂ to the reaction mixture slowed the reaction between the aryl iodide 1a and Ni(0) significantly (entries 3 and 4). More importantly, inhibition of the formation of 3a-1 and 3a-5 was observed in this case (entry 4). On the contrary, the stoichiometric reaction using NiBr₂·diglyme proceeded very sluggishly in the absence of ZnI₂ and the full conversion required extended reaction time (entries 5 and 6), while an increase of the reaction rate was observed by employing ZnI₂ as additive (entry 7). In comparison to the reactions using $Ni(COD)_2$, the formation of 5-exo ring-closing product 3a-2 was apparently favored in this case. The results aforementioned can be explained through the postulation that the Ni(II) species generated through oxidative addition is first reduced to a Ni(I)species prior to the migratory insertion favoring the 5-exo cyclization. The reduction of Ni(II) to Ni(I) might be accelerated by the bridging of polarized iodide anion between Ni and Zn species in the electron-transfer process.¹

Subsequently, upon full conversion of 1a in the stoichiometric reaction with $NiBr_2$ ·diglyme we added the NHP ester 2j instead of water to the reaction mixture, affording the arylalkylation product 3j in a 20% yield (Scheme 3). The result of this sequential reaction confirmed the viability of a cascade consisting of a migratory insertion and the following decarboxylative coupling.

Scheme 3. Sequential Stoichiometric Reaction of Iodide 1a and NHP Ester 2j



Furthermore, the reaction between the active NHP ester **2h** and (3-methylbut-3-en-1-yl)benzene was conducted under the standard reaction conditions (Scheme 4). In this case, the

Scheme 4. Reaction between NHP Ester 2h and (3-Methylbut-3-en-1-yl)benzene



decarboxylative product was afforded in 31% yield, while the hydroalkylation reaction did not occur. This result argues against a possible reaction pathway for the Ni-catalyzed arylalkylation reaction, which is initiated by a radical addition of an alkyl radical generated through decarboxylation to the olefinic unit of tethered aryl iodides.¹⁶

We have also studied the asymmetric version of this Nicatalyzed arylalkylation reaction involving decarboxylative coupling, and the preliminary investigations demonstrated that a high enantiomeric excess could be achieved by employing the chiral BOX L6 as ligand (Scheme 5).





In summary, we described a Ni-catalyzed reductive dicarbofunctionalization of unactivated alkenes tethered to aryl iodides with a series of primary and secondary redox active NHP esters, providing access to prepare diverse benzeneannulated cyclic compounds, such as indanes, tetrahydroisoquinolines, indolines, dihydrobenzofurans, and isochromans containing a quaternary carbon center. A good tolerance of a broad range of functional moieties was achieved in this method through avoidance of the use of pregenerated organometallic reagents. Relying on the results of a series of control experiments, we proposed a plausible reaction mechanism involving a Ni(I)-mediated migratory insertion and a decarboxylative cross-coupling as two key elementary steps.

ASSOCIATED CONTENT

G Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.9b02870.

Representative experimental procedures and necessary characterization data for all new compounds (PDF)

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The authors declare no competing financial interest.

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