Ni-Catalyzed Arylbenzylation of Alkenylarenes. Kinetic Studies Reveal Autocatalysis by ZnX_2 and 3-Fold Catalytic Rate Increase

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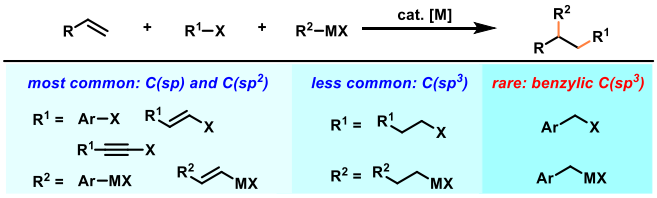
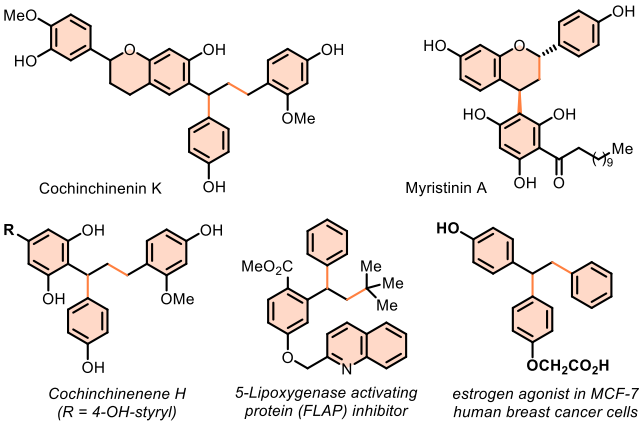
Abstract: We report a Ni-catalyzed regioselective arylbenzylation of alkenylarenes with benzyl halides and arylzinc reagents. The reaction furnishes differently substituted 1,1,3-triarylpropyl structures that are reminiscent of the cores of oligoresveratrol natural products. The reaction is also compatible for the coupling of internal alkenes, secondary benzyl halides and variously substituted arylzinc reagents. Kinetic studies reveal that the reaction proceeds with a rate-limiting single electron transfer process and is autocatalyzed by *in situ*-generated ZnX_2. The reaction rate is amplified by three-fold through autocatalysis upon addition of ZnX_2.

Metal-catalyzed alkene dicarbofunctionalization is an emerging method in organic synthesis.[1] This process is rapidly evolving with great promise to streamline the synthesis of complex molecules from readily available starting chemicals.[2] In the past few years, significant progress has been made in expanding its scope,[3] and complex molecules have been served through unifying three carbon fragments and post-synthetically modifying bioactive molecules, pharmaceuticals and natural products. Despite rapid progress, these reactions are typically conducted with both coupling partners containing sp^2- and sp-hybridized carbons exemplified by aryl, alkenyl and alkynyl groups (Scheme 1).[4] Alkene difunctionalization with one or both coupling partners comprised of sp^3-hybridized carbons is limited[5] and the majority of known reports use *tert*-alkyl[6] and 1,1-difluoroalkyl[7] reagents.[8]



Scheme 1. Common alkene dicarbofunctionalization reactions

Benzyl halides are some of the most extensively used sp^3-hybridized carbon sources in organic reactions. Despite their prevalence, their use as sp^3-carbon sources in alkene difunctionalization is exceptionally rare.[5b] Their rarity in use largely arises from their very nature of excellent reactivity with organometallic reagents toward S_N2 reactions to generate cross-coupling products, and their ability to be readily reduced to tolyl derivatives in the presence of transition metal catalysts. Development of a regioselective dicarbofunctionalization reaction on alkenylarenes that can harness benzyl halides as a sp^3-carbon source could offer a straightforward approach toward the synthesis of 1,1,3-triarylpropyl cores that are ubiquitous in a large number of bioactive molecules and natural products (Scheme 2).[9] For example, 1,1,3-triarylpropyl scaffolds constitute the cores of oligoresveratrol natural products,[10] such as cochinchinenene H,[10a]

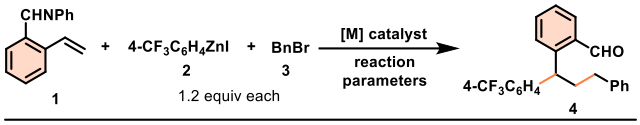


Scheme 2. Natural products bearing diarylalkyl and triarylalkyl cores

ampelopsin F[10b] and myristinin A,[10c] which display a range of bioactivity including anti-neuroinflammatory, antimalarial, and DNA polymerase β inhibition. Prior reports disclosed methods to prepare 1,1-diarylalkyl[11] and 1,1,2-triarylethyl[12] scaffolds by regioselective 1,2-alkylarylation and 1,2-diarylation of alkenylarenes, respectively. Herein, we report the first Ni-catalyzed arylbenzylation of alkenylarenes with benzyl bromides and arylzinc reagents to generate 1,1,3-triarylpropyl products. Kinetic studies reveal unprecedented autocatalysis by ZnX_2 and a three-fold amplification of catalytic rate.

Inspired by the prevalence of 1,1,3-triarylpropyl scaffolds in natural products,[10] we ventured to scrutinize various reaction parameters to difunctionalize 2-vinylbenzaldimine (**1**) with 4-trifluoromethylphenylzinc iodide (**2**) and benzyl bromide (**3**) (Table 1). We found that the reaction proceeded well with 0.5 mol% $Ni(cod)_2$ as a catalyst in 12 h in toluene and furnished the arylbenzylation product **4** in 85% yield (entry 1). The reaction could also be conducted in THF, dioxane and dichloroethane, albeit, in a slightly lower yield of the product (entries 2-4). The reaction also furnished low product yield in other solvents such as NMP, DMF, DMSO and MeCN (entry 5). Reactions conducted at either lower catalyst loadings or shorter reaction times decreased the product yield (entries 6-8). Ni(0) catalysts other than $Ni(cod)_2$, such as $Ni(PPh_3)_4$, could also catalyze the reaction but with much lower efficiency while Ni(II) catalysts like $NiBr_2$ remained completely ineffective (entries 9-10). Likewise, catalysts based on other metals, such as CuI, $Pd(OAc)_2$, $CoCl_2$ and $FeCl_2$, did not catalyze the reaction (entry 11). Benzyl bromide could be replaced with benzyl chloride, although the reaction required an elevated temperature (60 °C) to generate the arylbenzylation product **4** in a similar yield (entries 13-14). Control experiments with styrene and 2-vinylbenzaldehyde indicated that the coordination by the imine group was crucial for the reaction to proceed to generate the arylbenzylation product **4** (entries 15-16).

Table 1. Examination of reaction parameters[a]



entry	[M] catalyst	reaction parameters	yields of 4 (%)[b]
1	0.50 mol % $Ni(cod)_2$	toluene, rt, 12 h	85 (82)
2	0.50 mol % $Ni(cod)_2$	THF, rt, 12 h	40
3	0.50 mol % $Ni(cod)_2$	dioxane, rt, 12 h	76
4	0.50 mol % $Ni(cod)_2$	dichloroethane, rt, 12 h	55
5	0.50 mol % $Ni(cod)_2$	other solvents, rt, 12 h[c]	20-30
6	0.10 mol % $Ni(cod)_2$	toluene, rt, 12 h	42
7	0.50 mol % $Ni(cod)_2$	toluene, rt, 3 h	38
8	0.50 mol % $Ni(cod)_2$	toluene, rt, 6 h	64
9	0.50 mol % $Ni(PPh_3)_4$	toluene, rt, 12 h	30
10	0.50 mol % $NiBr_2$	toluene, rt, 12 h	0
11	other metals[d]	toluene, rt, 12 h	0
12	without [M] catalyst	toluene, rt, 12 h	0
13	benzyl chloride instead of 3	toluene, rt, 12 h	8
14	benzyl chloride instead of 3	toluene, 60 °C, 12 h	85
15	2-vinylbenzaldehyde instead of 1	toluene, rt, 12 h	0
16	styrene instead of 1	toluene, rt, 12 h	0

[a]Reactions run at 0.10 mmol scale in 0.5 mL solvent. ^{1}H NMR yields with pyrene as a standard. [b]The yield of isolated product from a 0.50 mmol scale reaction in 2.5 mL toluene in parenthesis. [c]NMP, DMF, DMSO or MeCN. [d]CuI, $Pd(OAc)_2$, $CoCl_2$, $FeCl_2$.

Upon optimization of reaction parameters, we examined the scope of the current alkene arylbenzylation with regard to terminal alkenes, primary benzyl halides and arylzinc reagents (Table 2A). The reaction tolerated both electron-rich and electron-deficient aryl groups in alkenylarenes, such as those derived from 5-fluoro-2-vinylbenzaldehyde, 5-chloro-2-vinylbenzaldehyde, 5-methoxy-2-vinylbenzaldehyde, 5,6-dimethoxy-2-vinylbenzaldehyde and 6-vinylbenzo[d][1,3]dioxole-5-carbaldehyde, and was compatible with functional groups such as Me, OMe, dioxolyl, Cl and F (**5**-**12**, **14**). A wide range of electronically varied benzyl bromides bearing functional groups like Me, OMe, OCF_3, CF_3, ketone and ester could be used as $C(sp^3)$ coupling partners (**9**, **11**, **12**, **14**, **17**-**20**). Benzyl bromides substituted at the *ortho*-position with Br, Me and fused aryl groups were also well tolerated in the reaction (**9**, **10**, **13**). Benzyl bromides could also be replaced with benzyl chlorides, which afforded the arylbenzylated products in similar yields, albeit the reaction required a slightly elevated temperature (60 °C) (**7**, **8**, **13**, **15**, **16**). Likewise, arylzinc reagents containing both electron-withdrawing groups, such as Ar, CF_3 and di-Cl (**10**, **14**-**17**) and electron-donating groups, like Me and OMe (**11**, **12**, **19**) could be implemented as $C(sp^2)$ coupling partners. The reaction also demonstrated an excellent tolerance of neopentyl and pinacol boronate esters located at both the *ortho*- and *para*-positions of benzyl bromides, which could provide synthetic handles for further reactions (**21**, **22**). In addition, benzyl bromide bearing a bulky phenylsulfonylmethyl group at the *ortho*-position afforded a product in good yield upon tolerating an active methylene group (**23**). The reaction could also be conducted with polyaromatic hydrocarbon-based arylmethyl bromides and arylzinc reagents (**24**).

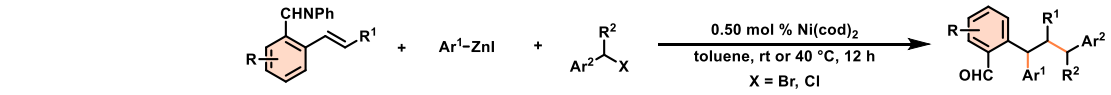
Uses of internal alkenes and secondary $C(sp^3)$ coupling partners are some of the most difficult tasks in alkene dicarbofunctionalization reactions. The difficulty spurs largely from increased steric interactions at the metal during a transition state for carbon-carbon bond formation. The current arylbenzylation reaction is compatible with both coupling of secondary benzyl bromides and difunctionalizing internal alkenes (Table 2B). For example, α-methyl benzyl bromide and even sterically congested α-isoproyl benzyl bromides could be used in the reaction to furnish arylbenzylated products in good yields (**25**-**27**). The skipped stereocenters at 1,3-positions were generated in moderate disastereoselectivity. In addition, substrates containing int ernal alkenes, such as those derived from (*E*)-2-(1-propenyl)benzaldehyde and (*E*)-2-(3-(benzyloxy)-1-propenyl)benzaldehyde, were also difunctionalized with benzyl bromide, 4-thiomethylbenzyl bromide and arylzinc reagents (**28**-**30**). The reactions with internal alkenes proceeded with very good stereocontrol of the vicinal stereocenters and afforded products with good diastereoselectivity. Determination of the relative stereochemistry of the major isomer of **28** by ^{1}H NMR confirmed that the internal alkenes underwent predominantly *syn*-additions of both the benzyl bromides and arylzinc reagents.

The synthetic application of the current reaction can be expanded by subsequent conversion of the products to other valuable derivatives. For example, the arylbenzylation products could be reduced *in situ* with $NaBH_4$ in the presence of *p*-toluensulfonic acid to generate complex arylbenzylamines (Table 3, **31**-**33**). In addition, the arylbenzylated derivatives could be converted *in situ* to *ortho*-phenol products by the Dakin oxidation (Table 4, **34**-**36**). In the absence of a base under the Dakin conditions, a formate-protected phenol **37** could also be isolated in 58% yield. The resultant 1,1,3-tri-polyphenols represent the structural cores of many oligoresveratrol natural products (Scheme 2).[10a-c]

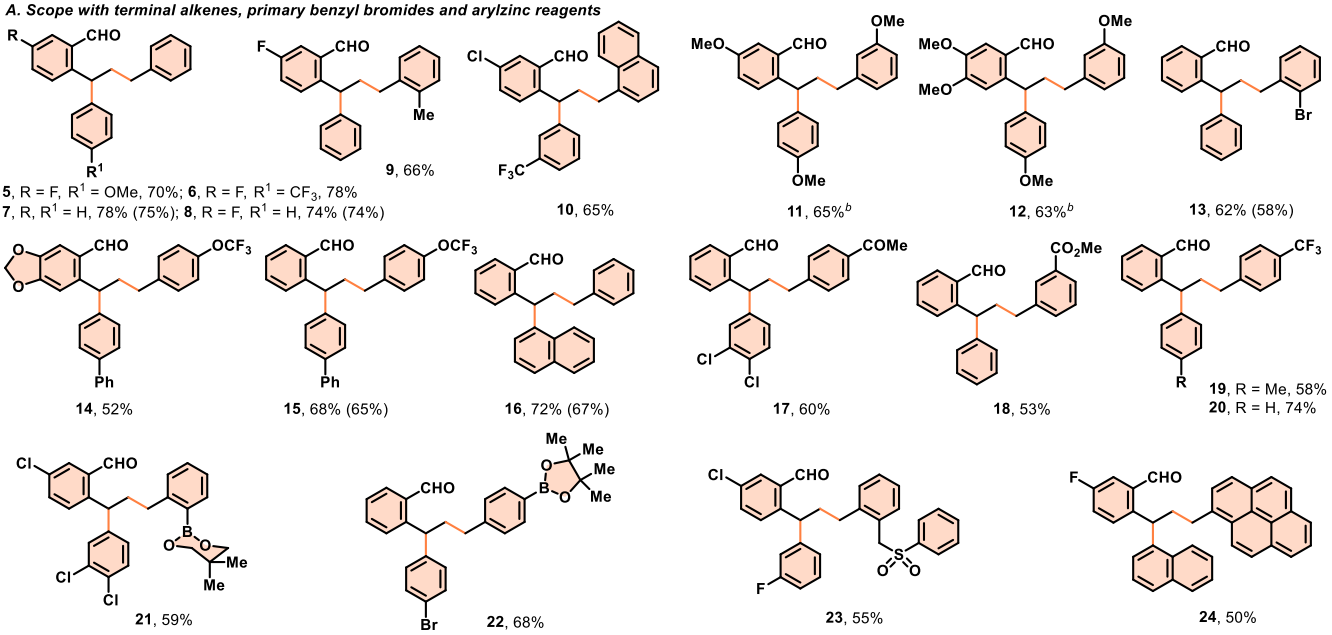
We also studied the mechanism of the arylbenzylation reaction by kinetic and competition studies, which enabled us to propose a catalytic cycle (Scheme 3).[13] Monitoring of the reaction progress by *in-situ* ^{19}F NMR spectroscopy (Scheme 4) revealed that the reaction profile followed a linear curve (Fig. 1a). Further kinetic studies diclosed that $ZnBr_2$, which was generated as a side product during transmetallation, autocatalyzed the reaction. Addition of exogenous $ZnBr_2$ into the reaction caused a three-fold increase in the catalytic rate and formed the product in near-quantitative yield without side products (Fig. 1b, blue and green). Addition of LiCl, which can readily bind to ZnX_2 to generate $[ZnX_3]^-$ to the catalytic reaction decreased the reaction rate, further supporting the role of neutral ZnX_2 in autocatalysis (Fig. 1b, brown).

We also studied the reaction rate dependence on the coupling partners and the catalyst in order to gain insight into reasons for autocatalysis by $ZnBr_2$ and to determine the rate-limiting step. Our study on reaction rates with varying concentrations of PhZnI showed that the rate remained unchanged, suggesting a zero order rate dependence on [PhZnI] (Fig. 1c). Further studies on the effects of electronic changes on ArZnI with strongly electron-donating (*p*-OMe) and strongly electron-withdrawing (*p*-CF_3) substituents also displayed no change in the reaction rate, resulting into a zero-slope Hammett plot (Fig. 1d). These two kinetic studies evidently indicated that neither of the transmetallation and the reductive elimination steps were rate-limiting. We then measured the reaction rates upon changing the concentrations of benzyl bromide and $Ni(cod)_2$ independently. Both

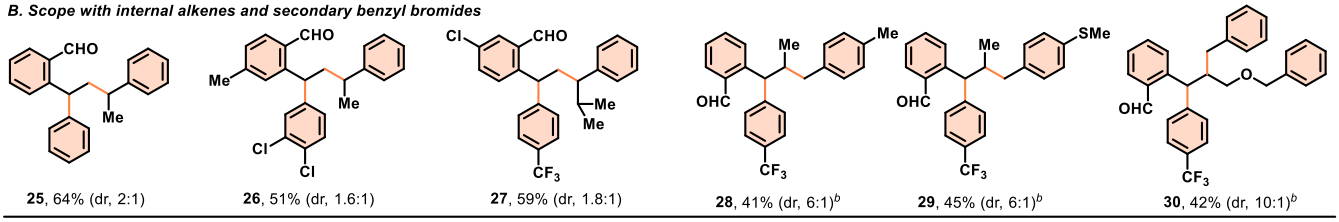
Table 2. Scope with alkenes, benzyl bromides and arylzinc reagents[a]



A. Scope with terminal alkenes, primary benzyl bromides and arylzinc reagents

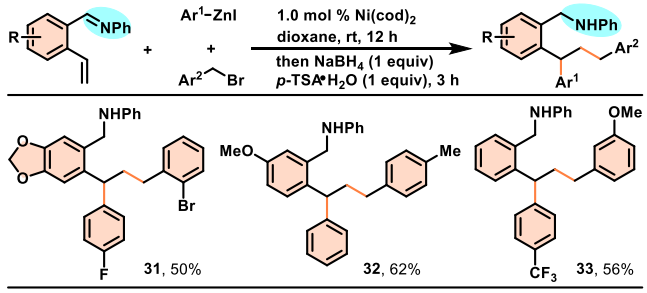


B. Scope with internal alkenes and secondary benzyl bromides



[a]Reactions were run in 0.50 mmol scale at rt (terminal alkenes, 1° BnBr) or 40 °C (internal alkenes, 2° BnBr). Yields are for isolated products. Reactions with BnCl were run at 60 °C for 12 h in toluene and yields are reported in parenthesis. **26** and **27** are derived from a 20:1 *E*/*Z* alkene. [b]2 mol % $Ni(cod)_2$.

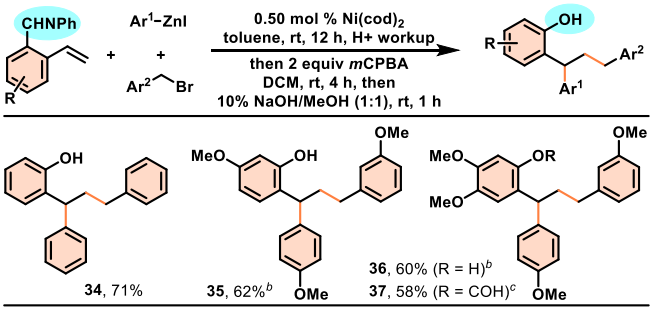
Table 3. Conversion of products to complex arylbenzylamines[a]



[a]Reactions were run in 0.50 mmol scale. Yields are for isolated products.

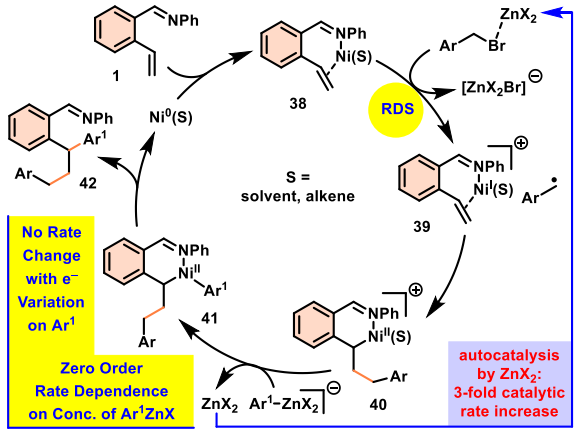
kinetic experiments showed first order rate dependence on the concentrations of BnBr and $Ni(cod)_2$ (Fig. 1e and 1f). Collectively, all the kinetic studies indicate that the single electron transfer (SET) from $Ni(cod)_2$ to benzyl bromide is rate-limiting.[5b] Since exogenous $ZnBr_2$, which autocatalyzes the reaction, also increases the rate of the reaction, we believe that $ZnBr_2$ activates BnBr through a Lewis acid-base interaction, and facilitates the abstraction of the halide anion through C-Br bond polarization. We also conducted a competition experiment between primary and secondary benzyl bromides (Scheme 5). Reactions with rate-limiting halogen atom abstraction (HAT) upon SET proceed with faster kinetics for secondary than primary alkyl halides.[11a, 14] Our competition experiment indicated that the secondary benzyl bromide reacted faster than the primary benzyl bromide. This result is consistent with the rate-limiting C-Br bond breakage, which is facilitated by $ZnBr_2$ coordination.

Table 4. Conversion to 1,1,3-tri-polyphenolic compounds[a]

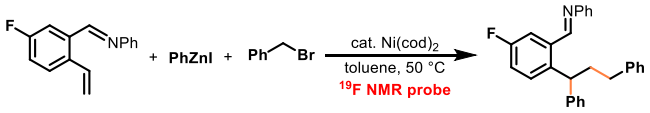


[a]Reactions were run in 0.50 mmol scale. Yields are for isolated products. [b]2.0 mol % $Ni(cod)_2$. [c]Isolated prior to treatment with NaOH.

Therefore, we propose that the catalytic cycle of the arylbenzylation reaction is initiated by a SET from $Ni(cod)_2$ to BnBr in a rate-limiting step and, facilitated by $ZnBr_2$, the bromide anion is lost to form benzylic radicals and Ni(I) (Scheme 3). The benzylic radicals then add to the alkene to produce new benzylic radicals, which recombine with Ni(I) to generate Ni(II) metallacycles. The nickellacycles subsequently undergo transmetallation followed by reductive elimination to furnish the final products.



Scheme 3. Proposed catalytic cycle



Scheme 4. Model reaction for kinetic experiments

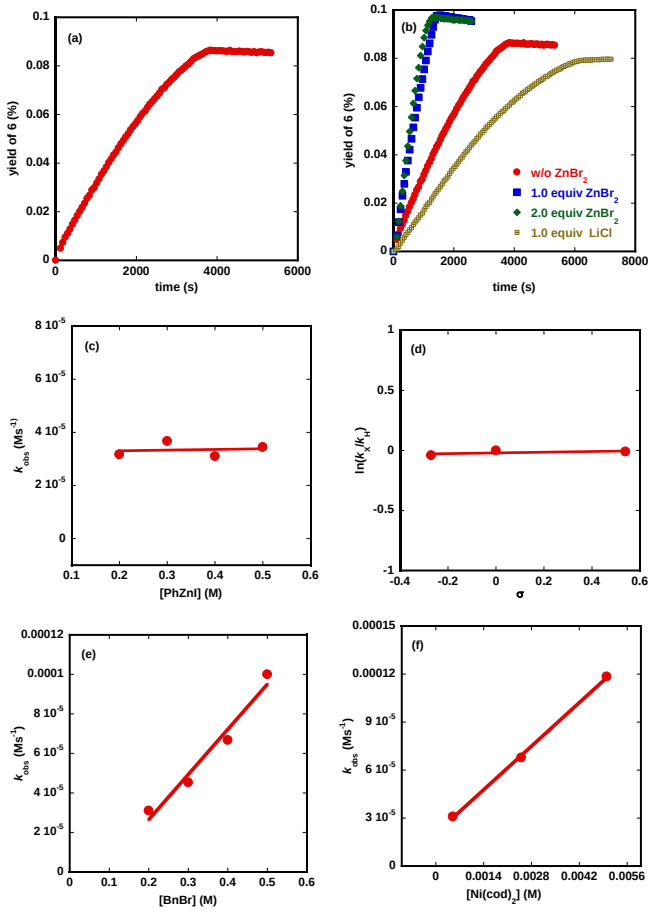
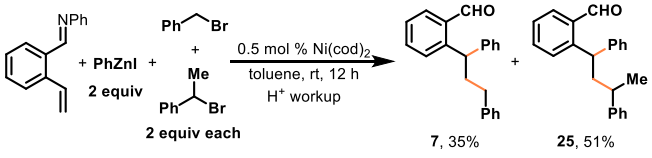


Fig. 1. (a) Reaction kinetic profile. (b) Autocatalysis by $ZnBr_2$ and the effect of LiCl. (c) Rate dependence on [PhZnI]. (d) Substituent (*p*-CF_3 and *p*-OMe) effect on reaction rate (the Hammett plot). (e) Rate dependence on [BnBr]. (f) Rate dependence on [$Ni(cod)_2$]



Scheme 5. Competition experiment

In summary, we report a Ni-catalyzed arylbenzylation of alkenylarenes with benzyl halides and arylzinc reagents. The reaction tolerates a variety of functional groups and *ortho*-substituents on all three coupling reagents, and produces 1,1,3-triarylpropyl structures. The reaction is compatible for functionalizing internal alkenes and can also implement secondary benzyl halides as coupling partners. The arylbenzylated products can be further elaborated to 1,1,3-tri-polyphenol derivatives, which are the structural cores of several oligoresveratrol natural products. Kinetic analysis of the reaction disclosed an unprecedented autocatalysis by $ZnBr_2$, which increased the catalytic rate by three-fold. Further rate measurements revealed that the reaction proceeded by a rate-limiting SET from $Ni(cod)_2$ to BnBr, which was facilitated by the Lewis acid-base activation of BnBr by the autocatalyst $ZnBr_2$.

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Author Contribution

†Authors contributed equally.

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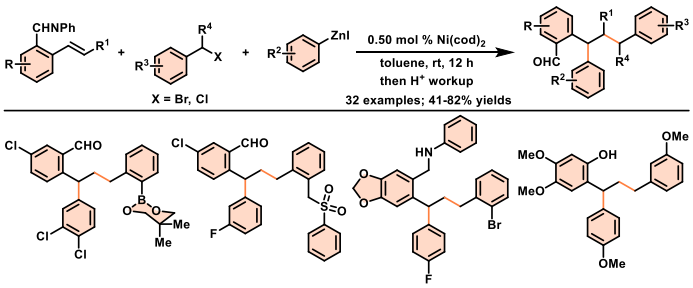
TOC


CHNPh
R
R1
R3
R4
X
X = Br, Cl
R2
ZnI
0.50 mol % Ni(cod)2
toluene, rt, 12 h
then H+ workup
32 examples; 41-82% yields
OHC

Cl
CHO
B
O
Me
Cl
F
S
HN
Br
MeO
OH
OMe