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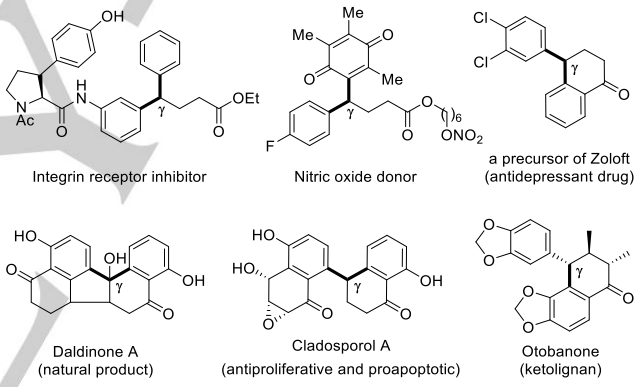
Nickel-Catalyzed α-Carbonylalkylarylation of Vinylarenes. Expedient Access to γ,γ-Diarylcarbonyl and Aryltetralone Derivatives

Shekhar KC,[†] Roshan K. Dhungana,[‡] Namrata Khanal,[†] and Ramesh Giri [‡,*]

Abstract: We report a Ni-catalyzed regioselective α-carbonylalkylarylation of vinylarenes with α-halocarbonyl compounds and arylzinc reagents. The reaction works with primary, secondary and tertiary α-halocarbonyl molecules, and electronically varied arylzinc reagents. The reaction generates γ,γ-diarylcarbonyl derivatives with α-secondary, tertiary and quaternary carbon centers. The products can be readily converted to aryltetralones, including a precursor to Zoloft, an antidepressant drug.

Three-component vicinal dicarbofunctionalization of alkenes[1] is a powerful tool to synthesize complex molecules rapidly from readily available starting materials.[2] Recently, significant progress has been made in this area by reductive coupling,[3] radical coupling,[4] photoredox catalysis[5] and cross-coupling,[6] which have been programmed to introduce two carbon entities across alkenes with high regioselectivity. The success of the reaction relies upon the ability of the carbon source to intercept *in situ*-generated alkylmetal species prior to β-H elimination,[7] a formidably challenging process that derails alkene difunctionalization to form Heck products. Strategies that stabilize alkylmetal species, such as the formation of metallacycles[8] and π-allyl/π-benzylmetal species,[9] and the generation of carbon radicals,[5] have been successful in addressing both issues of regioselectivity and β-H elimination, and executing alkene dicarbofunctionalization on various alkene substrates.[10]

Vinylarenes are important precursors in complex molecule synthesis, as they are a valuable source of both alkyl and aryl scaffolds. Vinylarenes are also excellent sources of alkenes for difunctionalization owing to the polarizability of alkenes for regiocontrol and the stabilization of alkylmetal species as π-benzylmetal intermediates. However, vinylarenes are still seriously underutilized for dicarbofunctionalization, despite recent reports on dialkylation,[4a] alkylarylation,[11] diarylation[9a, 12] and vinylarylation.[9b] Herein, we report a Ni-catalyzed regioselective α-carbonylalkylarylation of vinylarenes with primary, secondary and tertiary α-halocarbonyl compounds and arylzinc reagents. This reaction generates γ,γ-diarylcarbonyl compounds via the addition of α-carbonylalkyl radicals to alkenes. γ,γ-Diarylcarbonyl motifs are prevalent in bioactive molecules, natural products and pharmaceuticals (Scheme 1).[13] Known molecules with γ,γ-diarylcarbonyl scaffolds are integrin receptor inhibitors and nitric oxide donors.[14] These bioactive compounds display antiproliferative and proapoptotic activity and serve as a precursor of Zoloft, a marketed antidepressant drug.[15]



Scheme 1. Bioactive and Naturally Occurring γ,γ-Diaryl Esters and Aryltetralone Cores

We envisioned that vinylarenes could serve as excellent precursors to access γ,γ-diarylcarbonyl compounds and aryltetralone derivatives. In our efforts to generate such scaffolds, we examined difunctionalization of indene with ethyl α-bromoacetate and *m*-$CF_3C_6H_4ZnI$ under various conditions (Table 1). We found that $Ni(cod)_2$ was an excellent catalyst, which enabled α-carbonylalkylarylation of indene to proceed at room temperature and afforded the 1,2-difunctionalized indane **4** in 76% yield (entry 1). $NiBr_2$ and $(Ph_3P)_4Ni$ formed product **4** in lower yields (entries 2-3). Fe, Co, Pd and Cu-based catalysts were ineffective (entry 4). The reaction can also be conducted in DMA albeit with lower product yield (entry 5). Additionally, product **4** was formed in lower yield in DMF, THF, DCM and toluene (entries 6-7). Moreover, ethyl α-bromoethyl acetate can be replaced with ethyl α-chloroethyl acetate, which formed product **4** in 63% yield (entry 8).

Next, we examined the scope of the α-carbonylalkylarylation reaction with respect to arylzinc reagents (Table 2). A wide range of electron deficient, neutral and electron-rich arylzinc reagents, along with ethyl α-bromo- and α-chloroacetates, are capable of difunctionalizing indene and affording α-carbonyl- alkylarylated products in good yields. The reaction tolerates arylzinc reagents bearing halides such as F, Cl, di-Cl and Br (**8**-**12** and **15**). Arylzinc reagents bearing

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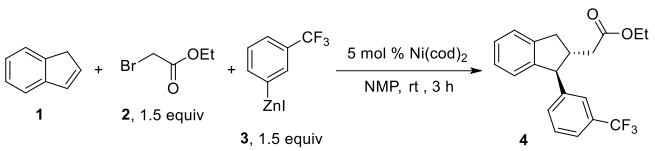
sensitive functional groups such as nitriles and esters (**13** and **14**) are also good coupling partners. The reaction also works well with *ortho*-substituted arylzinc and heteroarylzinc reagents (**7** and **15**). The α-carbonylalkylarylated products are formed as *trans*-stereoisomers with high diastereoselectivity (≥ 10:1). The structure of the major *trans*-diastereomer was confirmed by single crystal X-ray crystallography of the carboxylic acid derivative of the product **10**.

Table 1. Optimization of reaction conditions[a]

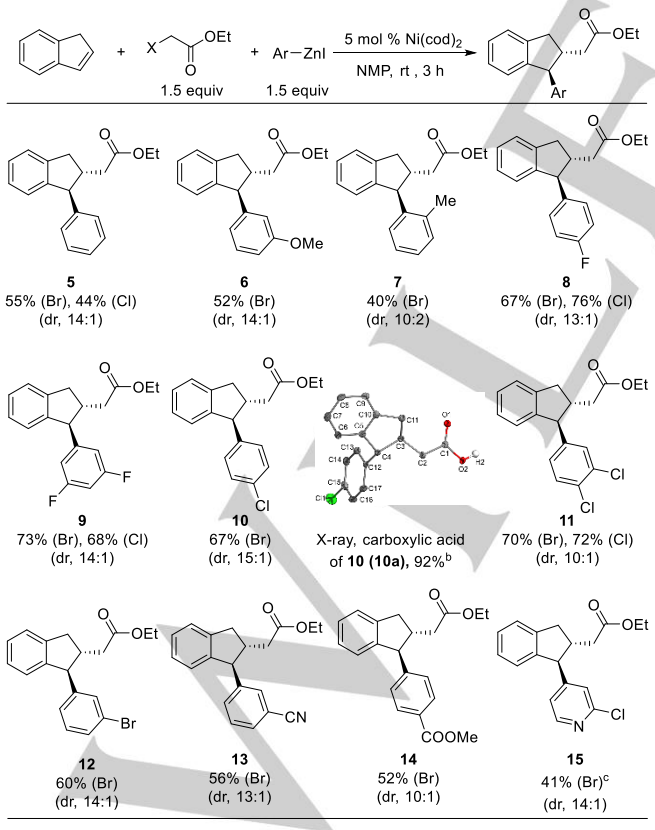


1 **2**, 1.5 equiv **3**, 1.5 equiv **4**

Entry	Modified conditions	Yield of **4** (%)
1	None	76 (72)[b]
2	$NiBr_2$ instead of $Ni(cod)_2$	61
3	$(Ph_3P)_4Ni$ instead of $Ni(cod)_2$	10
4	$Pd(OAc)_2$, $CoCl_2$, $FeCl_2$ or CuI instead of $Ni(cod)_2$	0
5	DMA instead of NMP	52
6	DMF or THF instead of NMP	10-15
7	DCM or Toluene instead of NMP	10-16
8	ethyl α-chloroacetate instead of ethyl α-bromoacetate	63

[a]0.1 mmol scale reactions. [b]Isolated yield (0.5 mmol scale) in parenthesis. dr 16:1.

Table 2. Scope with ArZnI[a]



5 55% (Br), 44% (Cl) (dr, 14:1)

6 52% (Br) (dr, 14:1)

7 40% (Br) (dr, 10:2)

8 67% (Br), 76% (Cl) (dr, 13:1)

9 73% (Br), 68% (Cl) (dr, 14:1)

10 67% (Br) (dr, 15:1)

X-ray, carboxylic acid of **10 (10a)**, 92%[b]

11 70% (Br), 72% (Cl) (dr, 10:1)

12 60% (Br) (dr, 14:1)

13 56% (Br) (dr, 13:1)

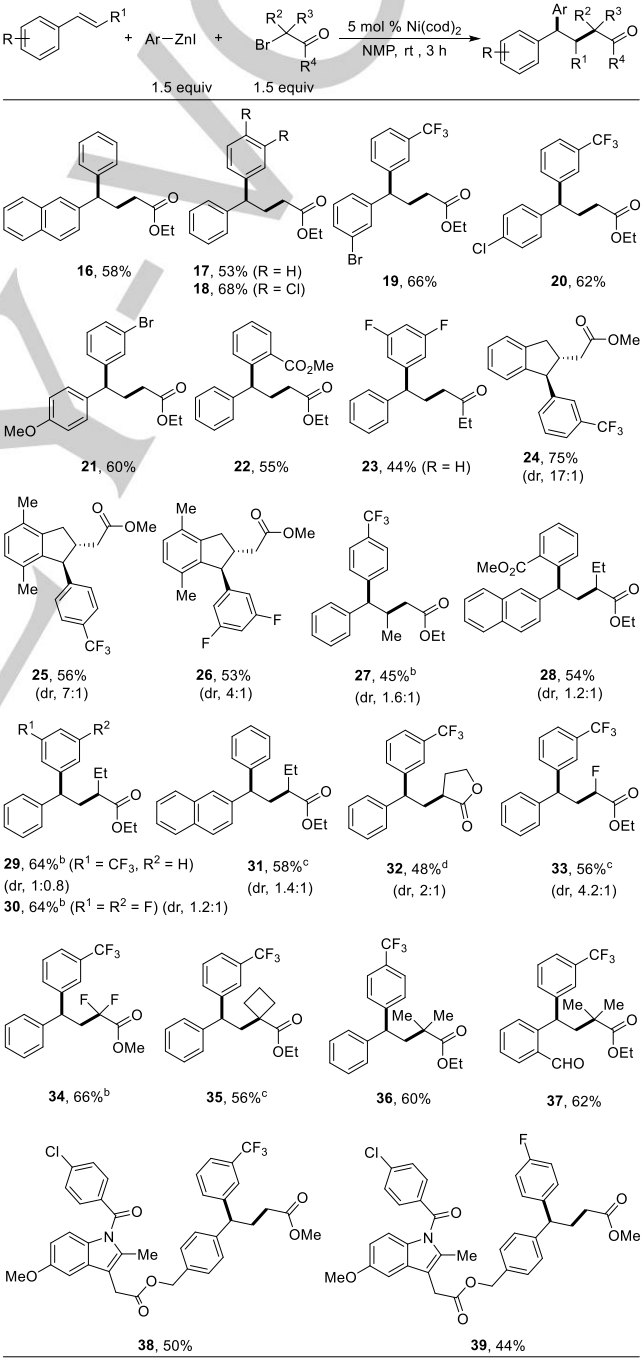
14 52% (Br) (dr, 10:1)

15 41% (Br)[c] (dr, 14:1)

[a]0.5 mmol scale reactions. Letters in parenthesis indicate X in α-haloacetate. [b]0.2 mmol scale reaction. [c]10 mol% $Ni(cod)_2$.

Various vinylarenes based on aryl, naphthyl and indenyl scaffolds bearing both electron-donating and withdrawing functional groups readily undergo the difunctionalization reaction (Table 3). Halides (Cl, Br), OMe and *ortho*-Me are tolerated on vinylarenes (**19**-**21**, **25** and **26**). β-Methylstyrene and styrenes containing an aldehyde group at the *ortho*-position are also good alkene substrates, in which the *ortho*-aldehyde remains intact after the reaction (**37**). These vinylarenes are coupled with different primary, secondary and tertiary α-bromocarboxylates along with arylzinc reagents containing various

Table 3. Scope with vinylarenes, RX and ArZnI[a]



16, 58%

17, 53% (R = H)
18, 68% (R = Cl)

19, 66%

20, 62%

21, 60%

22, 55%

23, 44% (R = H)

24, 75% (dr, 17:1)

25, 56% (dr, 7:1)

26, 53% (dr, 4:1)

27, 45%[b] (dr, 1.6:1)

28, 54% (dr, 1.2:1)

29, 64%[b] (R^1 = CF_3, R^2 = H) (dr, 1:0.8)
30, 64%[b] (R^1 = R^2 = F) (dr, 1.2:1)

31, 58%[c] (dr, 1.4:1)

32, 48%[d] (dr, 2:1)

33, 56%[c] (dr, 4.2:1)

34, 66%[b]

35, 56%[c]

36, 60%

37, 62%

38, 50%

39, 44%

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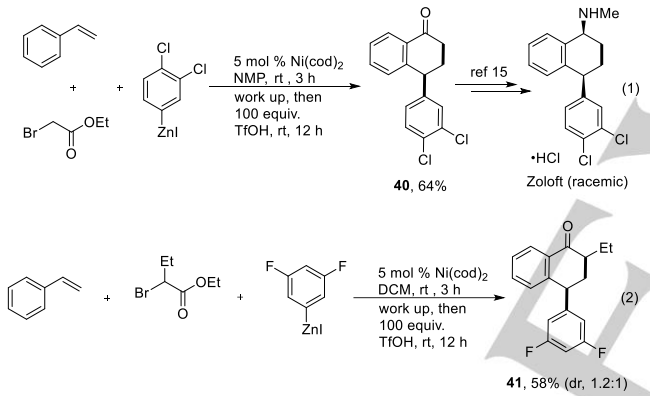
[a]0.5 mmol scale reactions. [b]5 mol% $Ni(cod)_2$ in DCM. [c]10 mol% $Ni(acac)_2$ in toluene. [d]10 mol% $Ni(acac)_2$ in DCE.

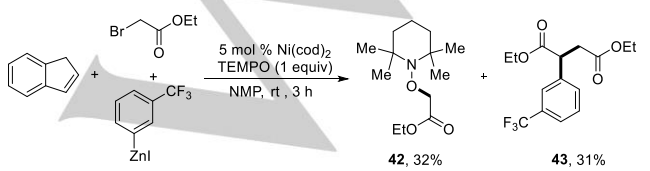
functional groups (F, di-F, Br, CF_3 and *ortho*-CO_2Me). The reaction also works well with α-bromolactones (**32**), and other secondary and tertiary α-bromocarboxylates (**33**-**35**), which generate products with α-tertiary and α-quaternary carbon centers.[16] An α-bromoketone can also be used instead of α-bromocarboxylate, which generates a γ,γ-diarylketone product (**23**). An application of the current method is also demonstrated by difunctionalizing vinylarene scaffolds attached to a commercial drug, indomethacin (**38** and **39**).

The α-carbonylalkylarylation reaction can be applied for the rapid synthesis of aryltetralone derivatives (Scheme 2). We have demonstrated a one-pot two-step synthesis of the dichlorophenyltetralone **40**, a known precursor to a commercial antidepressant drug sertraline•HCl (Zoloft)[15] (eq. 1). In this synthesis, styrene was difunctionalized with ethyl α-bromoacetate and 3,4-dichlorophenylzinc iodide to furnish ethyl γ-(3,4-dichlorophenyl)-γ-phenylbutyrate (**18**), which was then cyclized without purification to the Zoloft precursor **40** by intramolecular Friedel-Crafts acylation. We also synthesized a difluoroaryltetralone derivative **41** from the reaction of styrene with ethyl α-bromobutyrate and 3,5-difluorophenylzinc iodide followed by intramolecular Friedel-Crafts acylation without purification (Scheme 2, eq. 2).

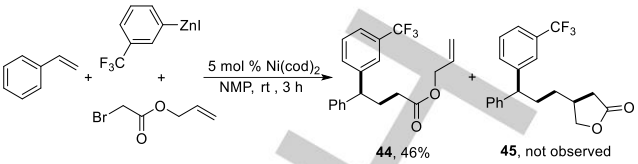


Scheme 2. Synthesis of aryltetralone derivatives

Moreover, we performed preliminary mechanistic studies utilizing radical trap and radical clock experiments. Addition of 1 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) radical to the reaction of indene with ethyl α-bromoacetate and 3-(trifluoromethyl)phenylzinc iodide generated the TEMPO adduct **42** in 32% yield, along with the diester **43**,[17] by trapping an α-ethoxycarbonylmethyl radical (Scheme 3). We then employed allyl α-bromoacetate as a radical clock, which was reacted with styrene and 3-(trifluoromethyl)phenylzinc iodide. The reaction produced the uncyclized α-carbonylalkylarylated product **44** in 46% yield (Scheme 4). The product **45**, which would be generated via radical cyclization on the tethered alkene, was not observed.[18] The results from these two experiments are consistent with the generation of a stable α-carbonylalkyl radical,[19] which undergoes radical addition to the moderately activated alkene in styrene faster than the unactivated tethered alkene.

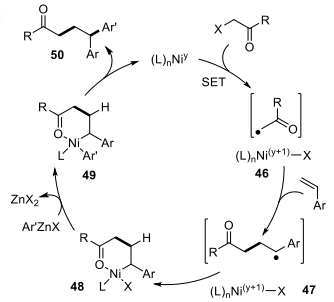


Scheme 3. Reaction with TEMPO



Scheme 4. Radical clock experiment

We also propose a catalytic cycle for the α-carbonylalkylarylation reaction (Scheme 5). The reaction is initiated by the reduction of alkyl α-bromocarboxylates via single electron transfer (SET) by the Ni(y)-catalyst (y = 0 or I), which generates α-carbonylalkyl radicals, ROC(=O)-R• (**46**), stabilized by resonance within the solvent cage with $Ni^{(y+1)}X$ bound either to cyclooctadiene (cod), vinylarene or NMP. The α-carbonylalkyl radicals then add to vinylarenes followed by radical recombination with $Ni^{(y+1)}X$ to form benzylnickel(II) intermediate (**48**). The generation of the benzylic radical, which also supports our hypothesis of $1e^-$ reduction of α-bromoester by Ni(y), is consistent with the observation of *trans*-products derived from indenes. A $2e^-$ reduction of α-bromoester by Ni(0), i.e. by oxidative addition, which is generally proposed for reduction of alkyl halides by Ni(0), would furnish *cis*-stereochemistry by migratory insertion of the cyclic alkenes – an outcome inconsistent with our observation.[20] The intermediate **48** then transmetallates with arylzinc reagents and subsequently reductively eliminates to form the difunctionalized product **50** and regenerate the Ni(y)-catalyst.



Scheme 5: Proposed catalytic cycle

In summary, we have developed a Ni-catalyzed regioselective α-carbonylalkylarylation of vinylarenes with α-halocarbonyl compounds and arylzinc reagents to generate γ,γ-diarylcarbonyl and aryltetralone derivatives. The reaction works well for the reaction of various vinylarenes with primary, secondary and tertiary α-halocarboxylates, and a variety of arylzinc reagents, which forms products with α-secondary, tertiary and quaternary carbon centers.

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Keywords: Aryltetralone • diarylcarbonyl • dicarbofunctionalization • nickel-catalyzed • vinylarenes

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[16] The acyclic substituted vinylarenes afforded products with lower dr than indenes potentially because of less steric influence of the homobenzylic substituent or 1,3-substitution on the benzylic radical during radical recombination with Ni(I) species (see the catalytic cycle) due to free carbon-carbon bond rotation.

[17] The product **43** is likely to form from the coupling of an α-acetate radical with the arylzinc reagent followed by an S_N2 reaction of the resultant arylacetate with ethyl α-bromoacetate.

[18] Allyl α-bromoacetate did not cyclize in the absence of styrene. The 1,2-addition reaction also does not proceed without the Ni-catalyst and ArZnI.

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[20] Alkyl halides are typically reduced by Ni(I) by $1e^-$ process. For detailed discussions, see: a) H. Yin, G. C. Fu, *J. Am. Chem. Soc.* **2019**, *141*, 15433-15440; b) Q. Lin, T. Diao, *J. Am. Chem. Soc.* **2019**, *141*, 17937-17948.

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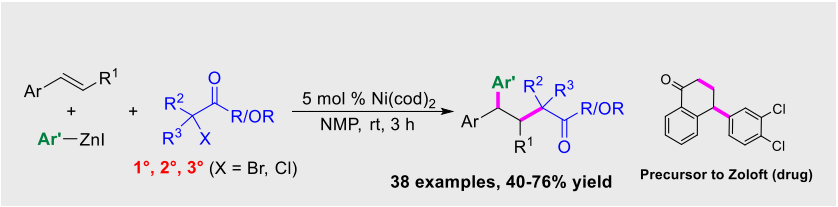

A nickel-catalyzed regioselective α-carbonylalkylarylation of vinylarenes with primary, secondary and tertiary α-halocarbonyl compounds and arylzinc reagents is reported. The γ,γ-diarylcarbonyl products can be readily converted to aryltetralones, including a precursor to Zoloft, an antidepressant drug. Mechanistic studies indicate that the reaction proceeds via additions of stable α-carbonylalkyl radicals to alkenes.

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Nickel-Catalyzed α-Carbonylalkylarylation of Vinylarenes. Expedient Access to γ,γ-Diarylcarbonyl and Aryltetralone Derivatives