Ni-Catalyzed Regioselective Intermolecular Dialkylation of Alkenylarenes. Generation of Two Vicinal C(sp^3)-C(sp^3) Bonds Across Alkenes

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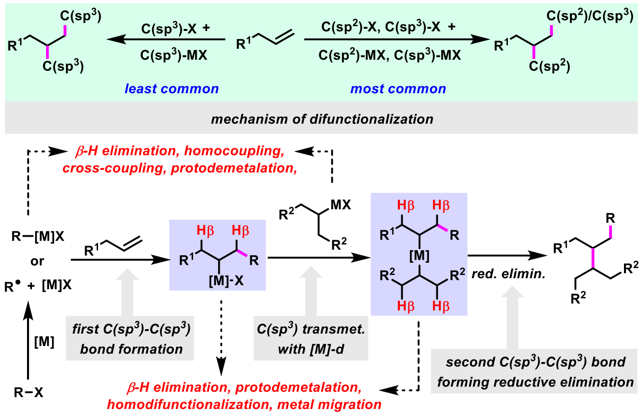
Supporting Information Placeholder

ABSTRACT: We disclose a Ni-catalyzed regioselective dialkylation reaction of alkenylarenes with α-halocarbonyls and alkylzinc reagents. The reaction produces γ-arylated alkanecarbonyl compounds with the generation of two new C(sp^3)-C(sp^3) bonds at the vicinal carbons of alkenes. This reaction is effective for the use of primary, secondary and tertiary α-halocarboxylic esters, amides and ketones in conjunction with primary and secondary alkylzinc reagents as the sources of two C(sp^3) carbons for the dialkylation of terminal and cyclic internal alkenes.

Transition metal [M]-catalyzed vicinal difunctionalization of alkenes with two carbon sources is emerging as a powerful method to build molecular complexity rapidly.[1] Recently, an astounding number of catalytic protocols have focused on the generation of two C(sp^2)-C(sp^2)[2] or a combination of one C(sp^2) and one C(sp^3) bonds[3] across alkenes. These reactions generally utilize aryl, alkenyl and alkyl halides in conjunction with aryl, alkenyl and alkynyl nucleophiles and their analogs. In sharp contrast, a simultaneous construction of two vicinal C(sp^3)-C(sp^3) bonds involving two discrete alkyl sources is a rare occurrence. In limited reports, the alkenes in vinyl-Bpin and *N*-vinyl pyrrolidinone were previously dialkylated with a combination of *t*-alkyl halide/alkylzinc halide, *t*-alkyl/*n*-alkyl bromide and difluoroalkyl bromide/alkyl$_2$Zn reagents.[4] A dual photoredox/Fe(OTf)$_2$ catalysis also enabled styrene dialkylation with cycloalkanes and active methylene compounds via dehydrogenative coupling.[5] Koh, Engle and us have disclosed imine and pyridylamide-assisted dialkylation reactions[6] of 2-alkenylbenzaldimines and alkenyl-8-aminoquinolinamides with two alkyl halides and a combination of alkyl halide and alkylzinc reagents, respectively.[7]

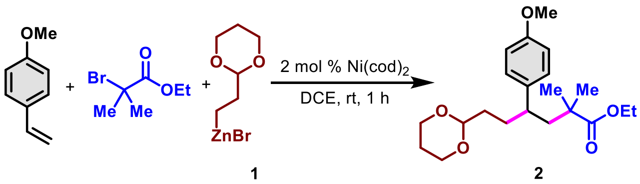
The difficulty in incorporating two alkyl, C(sp^3), fragments across an alkene resides in the directional C(sp^3)-orbitals that discount productive bonding overlap for C(sp^3)-C(sp^3) bond formation. Critically, the C(sp^3)-C(sp^3) reductive elimination from a dialkylmetal intermediate, C(sp^3)-[M]-C(sp^3), is much slower than from a C(sp^2)-[M] center when a [M]-catalyst functions as a conduit of bond formation.[8] Even prior to reductive elimination, an *in situ*-generated secondary carbon-bound *sec*-C(sp^3)-[M]X species requires navigation of a critical step of C(sp^3)-[M]-*d* orbital bond-forming transmetallation (or oxidative addition, C-radical recombination). This step is further riddled with multiple possibilities of faster β-H elimination than reductive elimination from the kinetically competent dialkylmetal species, C(sp^3)-[M]-C(sp^3), even after the formation of C(sp^3)-[M](*d*) bond is attained. Despite these challenges, we herein demonstrate that Ni(cod)$_2$ can catalyze a regioselective dialkylation of alkenylarenes with two C(sp^3) carbon sources, α-halocarbonyls and alkylzinc reagents, under mild conditions, a process that proceeds with the generation of two vicinal C(sp^3)-C(sp^3) bonds across an alkene. The dialkylation reaction can be performed with a range of 1°/2°/3° α-halocarbonyls and 1°/2° alkylzinc reagents along with terminal and cyclic internal alkenylarenes.



Scheme 1. Challenges in regioselective alkene dialkylation via the formation of two C(sp^3)-C(sp^3) bonds

Our initial studies began by examining parameters to effect the dialkylation of 4-methoxystyrene with ethyl α-bromoisobutyrate as an electrophile and (2-(1,3-dioxan-2-yl)ethyl)zinc bromide (**1**) as a nucleophile (Table 1). Pleasingly, we found that 2 mol % Ni(cod)$_2$ was able to catalyze the reaction in 1,2-dichloroethane (DCE) at room temperature, and the dialkylated product **2** was generated in 99% yield in 1 h when two equivalents of each of the ethyl α-bromoisobutyrate and dioxanylzinc bromide **1** were used. We also found that, at the expense of time (24 h), the catalyst loading could be lowered to as little as 1000 ppm to form the desired product in 69% yield (entry 2). The reaction can be conducted in toluene, instead of DCE, without loss in product yield (entry 3). Replacing DCE with dioxane or pentane generated the product **3** in moderate yields (entry 4) while the other solvents like MeCN, DMSO, DMA, DMF, DME or NMP were less effective (entry 5). Use of other Ni-catalyst precursors, such as NiBr$_2$ and NiCl$_2$(PCy$_3$)$_2$, and decreasing the equiv of either of the coupling reagents both lowered the product yield (entries 6-8). No product was observed when Ni(cod)$_2$ was replaced with Pd(OAc)$_2$, CoCl$_2$, CuI or FeCl$_3$ as a catalyst (entry 9), suggesting the importance of the Ni(cod)$_2$ to efficiently catalyze the current dialkylation reaction.

Table 1. Optimization of Reaction Conditions^a

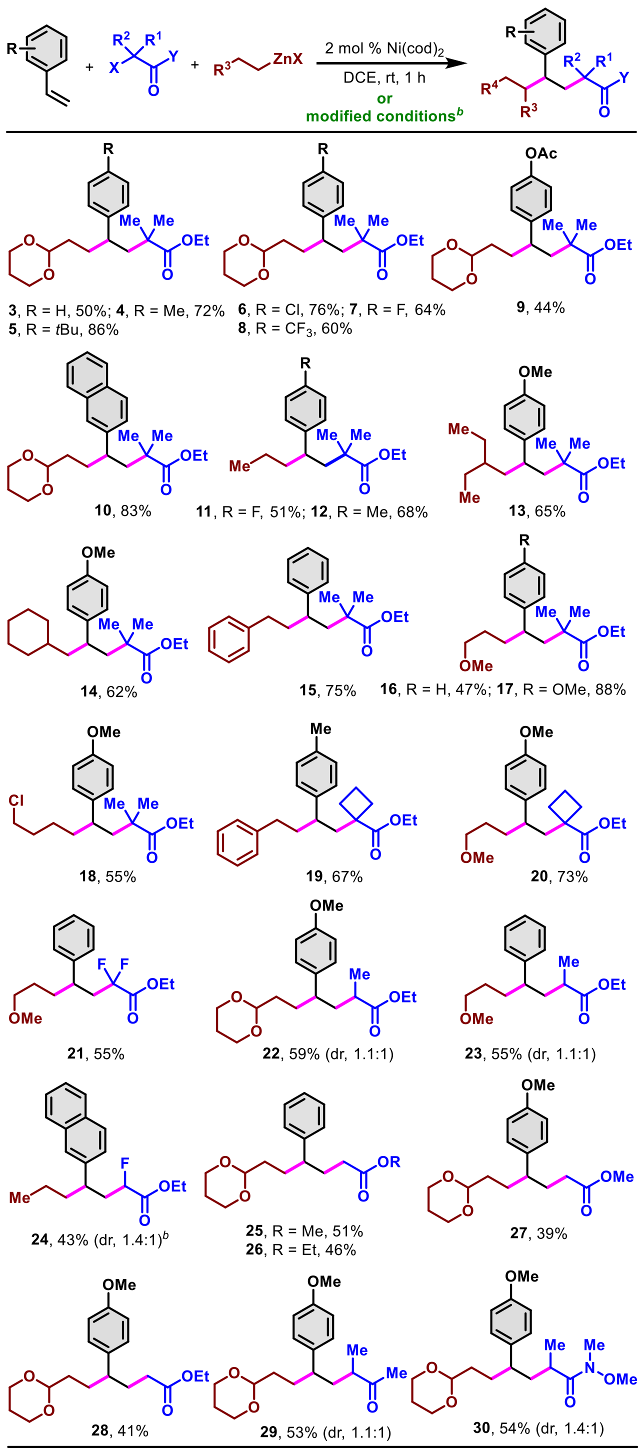


Entry	Deviation in reaction condition	Yield [%]^b
1	None	99 (93)
2	0.1 mol % catalyst, 24 h	69
3	Toluene instead of DCE	99
4	Dioxane, pentane or DCM instead of DCE	50-79
5	MeCN, DMSO, DMA, DMF, DME or NMP instead of DCE	10-22
6	NiBr$_2$ or Ni(PCy$_3$)$_2$Cl$_2$ instead of Ni(cod)$_2$	10-24
7	1 equiv. RZnX instead of 2 equiv.	55
8	1 equiv. ethyl α-bromo-isobutyrate instead of 2 equiv.	64
9	Pd(OAc)$_2$, CoCl$_2$, CuI or FeCl$_3$ instead of Ni(cod)$_2$	0

Conditions. ^{a}Reactions were run in 0.10 mmol scale in 0.5 mL solvent. ^{b}Isolated yield from a 0.5 mmol scale in parenthesis.

With the optimized reaction conditions in hand, we began to explore the scope of this reaction by varying the alkenylarenes, α-halocarbonyl, and alkylzinc halide (Table 2). The reaction tolerates both electron-rich as well as electron-poor alkenyl arenes. The reaction is compatible with arenes containing various functional groups, such as methyl, *tert*-butyl, methoxy, fluoro, chloro, trifluoromethyl and acetoxy. The reaction proceeds well with a range of primary alkylzinc reagents including unfunctionalized and those containing functional groups like dioxanyl-protected aldehydes, methoxy and chloro. Branched acyclic and cyclic alkylzinc reagents also function as good coupling partners. Likewise, the reaction demonstrates a wide scope with regard to α-bromocarboxylic esters. The reaction is amenable to primary, secondary and tertiary α-bromocarboxylic esters with reactivity trends following tertiary > secondary > primary consistent with the nucleophilic nature of α-carbon radicals (see Scheme 3). Tertiary α-bromocarboxylic esters, such as α-bromoisobutyrate, α-bromocyclobutyl carboxylate and α-bromo-α,α-difluoroacetate, and secondary α-bromocarboxylic esters, like α-bromopropionate and α-bromo-α-fluoroacetate, could be readily added to different alkenylarenes along with unfunctionalized and functionalized alkylzinc reagents. However, the reaction of α-bromo-α-fluoroacetate with 2-vinylnaphthalene and propylzinc iodide required to be conducted in toluene with the catalytic amounts of DMFU and $AgBF_4$.[3v] In alkene dicarbofunctionalization reactions, the majority of reactions are only compatible with secondary, tertiary, α-monofluorinated and α,α-difluororinated α-bromocarboxylates owing to their ability to stabilize α-carbon radicals and the developing positive charge during nucleophilic radical additions. Primary α-carbon radicals are typically not compatible. Pleasingly, current dialkylation reaction is also compatible with primary α-bromocarboxylates, which afford dialkylated products with different alkylzinc reagents in moderate yields.

Table 2. Scope of dialkylation reaction with alkenylarenes, α-bromocarbonyl compounds, and primary alkylzinc reagents

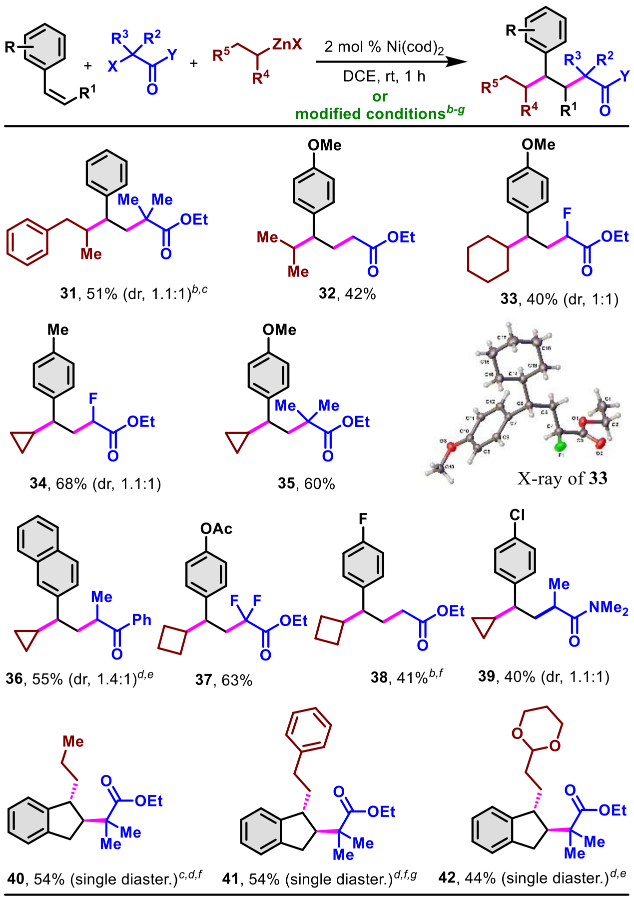


3, R = H, 50%; **4**, R = Me, 72%
5, R = *t*Bu, 86%
6, R = Cl, 76%; **7**, R = F, 64%
8, R = CF_3, 60%
9, 44%
10, 83%
11, R = F, 51%; **12**, R = Me, 68%
13, 65%
14, 62%
15, 75%
16, R = H, 47%; **17**, R = OMe, 88%
18, 55%
19, 67%
20, 73%
21, 55%
22, 59% (dr, 1.1:1)
23, 55% (dr, 1.1:1)
24, 43% (dr, 1.4:1)[b]
25, R = Me, 51%
26, R = Et, 46%
27, 39%
28, 41%
29, 53% (dr, 1.1:1)
30, 54% (dr, 1.4:1)

[a]Conditions. Reactions were run in 0.50 mmol scale in 2.5 mL solvent. Isolated yields. [b]In toluene with 5 mol% Ni(cod)$_2$, 5 mol% DMFU and 30 mol% AgBF$_4$.

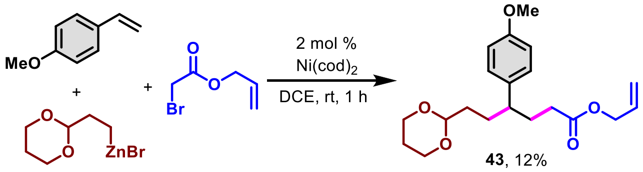
Use of secondary alkylzinc halides as nucleophilic coupling partners is typically problematic in alkene difunctionalization reactions largely because of the steric issues at transmetallation with secondary alkylmetal intermediates generated after migratory insertion. Even after transmetallation, a C-C bond-forming reductive elimination requires a bond formation between two secondary carbon centers and as such coupling with secondary alkylzinc reagents are kinetically slow and typically do not work in alkene difunctionalization reactions. Nevertheless, our current dialkylation reaction conditions can be applied toward coupling with secondary alkylzinc reagents (Table 3). Both linear acyclic and cyclic alkylzinc reagents, such as isopropyl, 1-methylphenethyl, cyclopropyl, cyclobutyl and cyclohexylzinc halides, could be added to alkenylarenes along with a range of primary, secondary, tertiary, α-monofluorinated and α,α-difluororinated α-bromocarboxylates. However, the coupling of secondary alkylzinc reagents was not straightforward and in many cases individual reaction optimization was required. In general, reactions in which either the alkylzinc reagents or alkenylarenes contained some functional groups proceeded under standard conditions. Reactions in which both alkylzinc reagents and alkenylarenes lacked functional groups required the addition of either 1.0 equiv of $ZnBr_2$ (**31** and **38**)[3j] or 5 mol% dimethyl fumarate (DMFU) and 30 mol% $AgBF_4$ (**36**, **40** and **41**)[3v] along with conducting the reactions in toluene or pentane. The structure of the dialkylation reaction with secondary alkylzinc reagents was confirmed by a single crystal X-ray structure of compound **33**.

Table 3. Scope of dialkylation reaction with secondary alkylzinc reagents



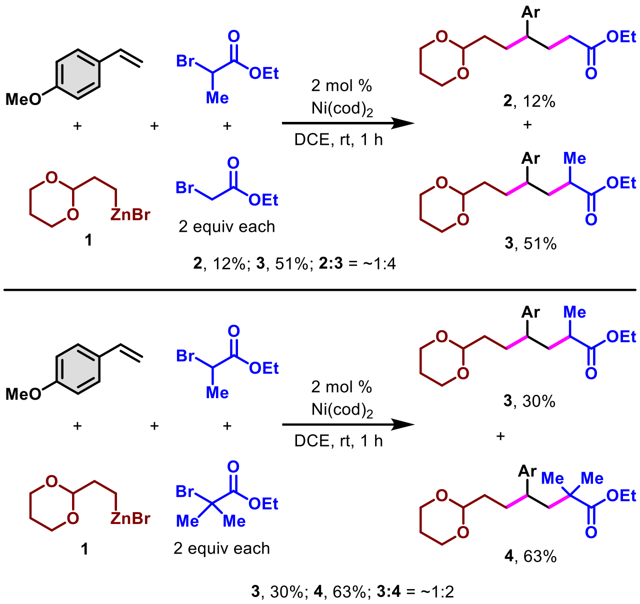
[a]Conditions. Reactions were run in 0.50 mmol scale in 2.5 mL solvent. Isolated yields. [b]1.0 equiv $ZnBr_2$. [c]In toluene. [d]5 mol% DMFU and 30 mol% $AgBF_4$. [e]In DCE. [f]5 mol% $Ni(cod)_2$. [g]In pentane.

Reactions of α-halocarbonyls are known to proceed with the generation of α-C radicals in the presence of Ni-catalysts, which generally add to alkenes prior to recombination with Ni.[9] The *trans*-stereochemical outcomes of the products from indene also indicate that the addition of α-halocarbonyls to alkenylarenes involves a radical process rather than migratory insertion. A radical clock experiment with *O*-allyl α-bromoacetate generated an uncyclized dialkylation product **43**. While cyclization would be anticipated with the tethered alkene, the outcome is also consistent with the nucleophilic nature of α-C radicals that preferentially add to the activated and electrophilic alkenes in alkenylarenes.



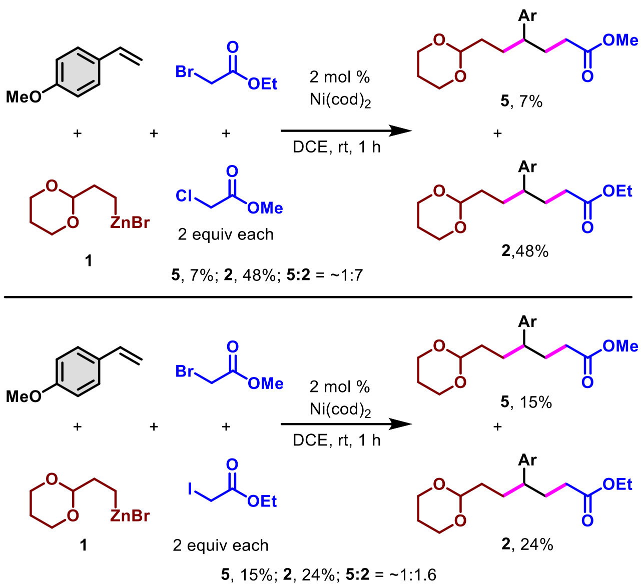
Scheme 2. Radical Clock Experiment

In order to provide further evidence for radical nature of the reaction, we conducted a series of competition experiments with α-bromo carboxylates. Competition reactions of 4-methoxystyrene and dioxanylzinc bromide **1** with α-bromoacetate as 1° and α-bromopropionate as 2° α-bromocarboxylates, and with α-bromopropionate as 2° and α-bromoisobutyrate as 3° α-bromocarboxylates revealed that 3° α-bromocarboxylate reacted faster than 2° α-bromocarboxylate, and 2° α-bromocarboxylate reacted faster than 1° α-bromocarboxylate (3° RX > 2° RX > 1° RX) (Scheme 3). Similar competition reactions conducted with primary α-iodo and α-bromo carboxylates, and with α-bromo and α-chloro carboxylates indicated that α-iodo carboxylate reacted faster than α-bromo carboxylate, and α-bromo carboxylate reacted faster than α-chloro carboxylate (RI > RBr > RCl) (Scheme 4). These results are consistent with the reaction of a nucleophilic radical in which direct halogen atom abstraction from α-bromocarboxylate happens at the rate-limiting step via an inner sphere electron transfer from a Ni-catalyst.[10]

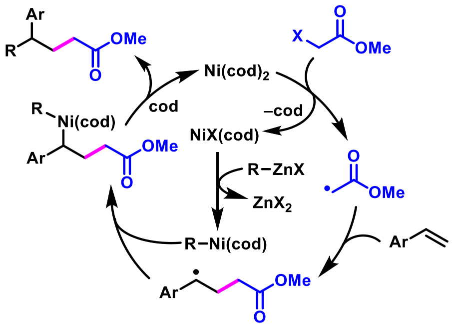


Scheme 3. Competition Experiments with 1°, 2°, and 3° R-X

Based on the literature reports[9] and our experimental results, we propose a catalytic cycle (Scheme 5) wherein the reaction proceeds via a SET from Ni(0) to the α-bromocarboxylate, generating an α-C radical which adds to an alkenylarene forming a secondary C-radical. This C-radical then recombines with (cod)Ni-R, generated after transmetalation with alkylzinc halides, prior to reductive elimination to make the final product.



Scheme 4. Competition Experiments with RI, RBr, and RCl



Scheme 5. Proposed catalytic cycle

In summary, we have developed a Ni-catalyzed dialkylation reaction of alkenylarenes with α-bromocarbonyl compounds and alkylzinc reagents to generate a wide range of γ-aryl alkyl carbonyl compounds. The dialkylation reaction works with α-bromo carboxylates, ketones and amides. The reaction can utilize primary and secondary alkylzinc reagents as nucleophiles and primary, secondary and tertiary α-bromo carbonyls electrophiles for addition across the alkenes in alkenylarenes. In addition, the method is also applicable to cyclic internal alkenes in which the dialkylation proceeds with *trans*-addition of the two alkyl groups. The relative stereochemistry of dialkylation across internal alkenes, and preliminary mechanistic studies with a radical probe and a series of competition studies indicate that the current reaction proceeds via the addition of nucleophilic α-C radicals, generated by SET from Ni(0) to α-bromo carbonyls, to alkenes followed by radical recombination with alkylnickel(I) and reductive elimination.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all compounds. 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.

ACKNOWLEDGMENT

We gratefully acknowledge the NIH NIGMS (R35GM133438) and The Pennsylvania State University (PSU) for support of this work. We thank Dr. Christy George at the PSU NMR facility for help with stereochemistry determination of product **41**.

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