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Formation of C(sp^3)-C(sp^3) Bonds through Nickel-catalyzed Decarboxylative Olefin Hydroalkylation Reaction

Xi Lu,[a, b] Bin Xiao,[a] Lei Liu,[b] Yao Fu*[a]

Abstract: Olefins and carboxylic acids are among the most important feedstock compounds. They are commonly found in natural products and drug molecules. We report a new reaction of nickel-catalyzed decarboxylative olefin hydroalkylation, which provides a novel practical strategy for the construction of C(sp^3)-C(sp^3) bonds. This reaction can tolerate a variety of synthetically relevant functional groups and shows good chemo- and regio-selectivity. It enables cross-coupling of complex organic molecules containing olefin groups and carboxylic acid groups in a convergent fashion.

Carbon-carbon bond formation reactions are among the most important transformations in organic synthesis because they afford basic paradigms in the retrosynthetic analysis towards complex molecules.[1] As an increasingly popular strategy, transition metal-catalyzed C(sp^3)-C(sp^3) cross-coupling reactions enabled convergent synthesis of complex molecules.[2] For a long time, the use of alkyl organometallic reagents and alkyl halides dominates the field of C(sp^3)-C(sp^3) cross-coupling (**Figure 1A**).[3-8] New C(sp^3)-C(sp^3) cross-coupling reactions benefiting from readily available and stable starting materials, such as olefins[9] and carboxylic acids[10], present a continuing opportunity as well as challenge to modern synthetic organic chemistry (**Figure 1B**).

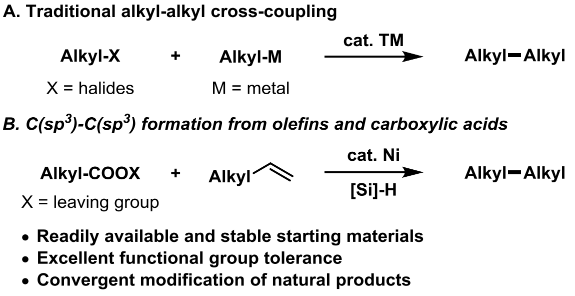

Figure 1. Strategies for alkyl-alkyl cross-coupling. TM = transition-metal.

Simple un-activated olefins are important feedstock compounds in chemical industry, but these compounds usually are poorly reactive either as nucleophiles or electrophiles.[11] Very recently, we discovered that Ni can catalyze the hydrocarbonation of un-activated olefins with alkyl halides (**Figure 2A**).[12] This surprising finding prompted us to develop practically useful processes that could use alternative reagents to complement the use of alkyl halides. We therefore aimed to find conditions that allowed the hydrocarbonation of olefins with aliphatic carboxylic acids. Recent advances have shown that decarboxylative cross-coupling of aliphatic carboxylic acids and derivatives can be accomplished by using photocatalysts.[13] Thus we tested the decarboxylative olefin hydroalkylation process using the dual catalyst system of Ni and photocatalyst (**Figure 2B**). We were delighted to observe the desired product, but to our great surprise, control experiments revealed that the Ni-only system can already catalyze decarboxylative olefin hydroalkylation (**Figure 2C**).

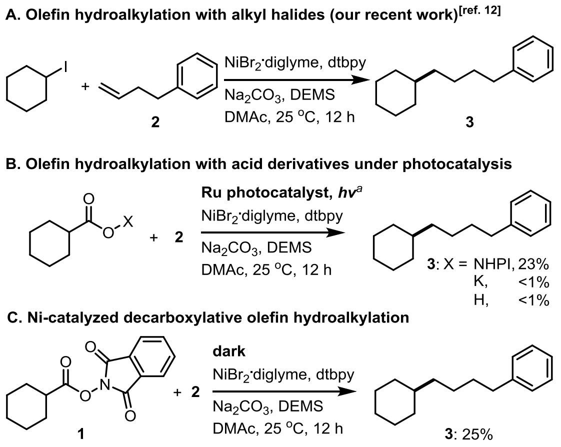

Figure 2. Olefin hydroalkylation reactions. [a] $Ru(bpy)_3(PF_6)_2$. DEMS = diethoxymethylsilane. bpy = 2,2'-bipyridine. dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine. NHPI = *N*-hydroxyphthalimide. DMAc = dimethylacetamide.

On the basis of the above finding, we now report a new reaction of Ni-catalyzed decarboxylative olefin hydroalkylation. This reaction adds an important example to the toolbox of Ni-catalyzed C(sp^3)-C(sp^3) cross-coupling reactions. As shown in Figure 1C, our model reaction involved an NHPI ester **1** and un-activated olefin **2**.[14] We used Ni^{II} salt as catalyst and dtbpy as ligand according to our previous work. A systematic screening of different bases and silanes was then carried out to optimize the reaction performance (**Table 1**). Under the optimal conditions (base = $Mg(OAc)_2\cdot 4H_2O$, silane = PMHS), the GC yield was found to be 81% (with an isolated yield of 76%).

The scope of the Ni-catalyzed decarboxylative olefin hydroalkylation is shown in **Table 2**. A variety of un-activated olefins and aliphatic acid NIHP-esters can be successfully transformed to the desired products with modest to good yields within a short time (ca. 2-3 hours). Importantly, both

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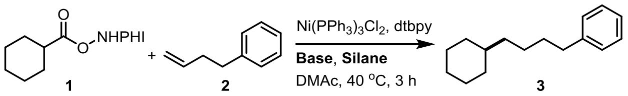
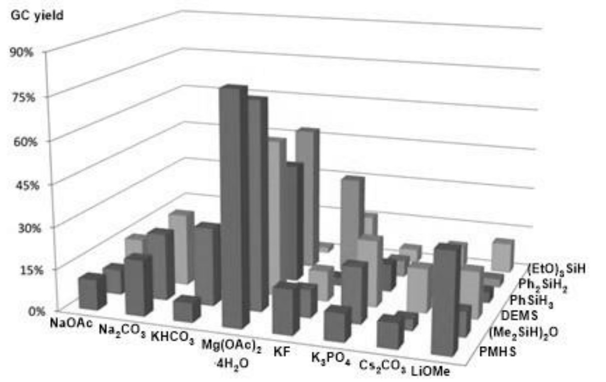
primary and secondary aliphatic acid esters can be converted. The reaction can also be applied to both cyclic (**3**) and acyclic (**4**) aliphatic acid esters. With respect to cyclic substrates, the size of the rings (**5**-**7**) posed no problem for the transformation. Due to its mild reaction conditions, the decarboxylative olefin hydroalkylation process showed excellent compatibility with a variety of synthetically relevant functional groups such as ether (**8**, **9**), sulfonamide (**8**, **9**), aryl fluoride (**8**), aryl chloride (**9**), aryl bromide (**10**), ester (**11**, **12**) and carbamate (**12**). Base-sensitive groups such as nitrile (**13**), ketone (**14**) and silicon ether (**15**) can be well tolerated. Heterocycles such as pyran (**16**), furan (**17**), thiophene (**18**), pyrrole (**19**) and pyridine (**20**) also survived in the reaction.

Table 1. Optimization of the reaction conditions. [a]



1 **2** **3**

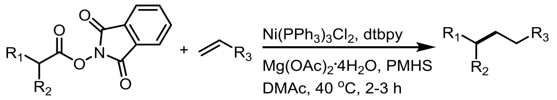


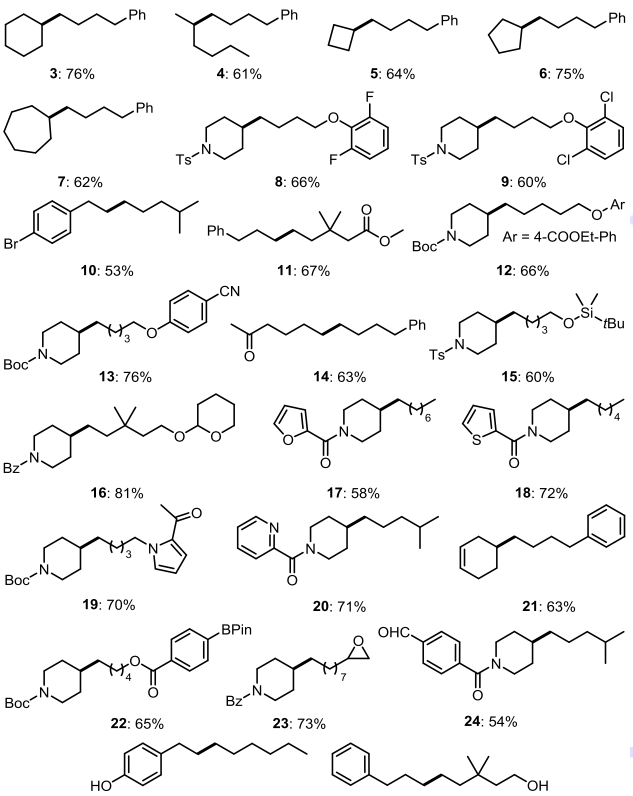
[a] The reactions were conducted in 0.2 mmol scale, GC yield. 1 eq. **1**, 2.5 eq. **2**, 10% $Ni(PPh_3)_2Cl_2$, 15% dtbpy, 3 eq. base, 200 μL (for liquid) or 200 mg (for solid) silane, 1 mL DMAc, 40 °C, 3 hours. PMHS = Poly(methylhydrosiloxane).

Regarding to *chemo*-selectivity, a terminal olefin **21** afforded the desired product without any reaction at the internal alkene group. An arylboronate ester **22** selectively underwent the Ni-catalyzed C(sp^3)-C(sp^3) cross-coupling reaction with its carbon-boron bond intact affording further functionalization possibility.[15] Furthermore, the tolerance of epoxide[16] (**23**) and aldehyde (**24**) groups demonstrated that, this reaction offers important advantages over the previous transition metal-catalyzed C(sp^3)-C(sp^3) cross-coupling reactions using alkyl organometallic reagents. Finally, the decarboxylative olefin hydroalkylation reaction can be successfully conducted in the presence of unprotected phenol (**25**) or alcohol (**26**) groups.

In a scale-up reaction of the NIPH ester of dehydrocholic acid (**27**) containing three base-sensitive ketone groups, we obtained the olefin hydroalkylation product **29** successfully with a satisfactory yield of 55% (**Scheme 1**). This gram-scale reaction highlights the practicality of the new Ni-catalyzed C(sp^3)-C(sp^3) cross-coupling reaction.

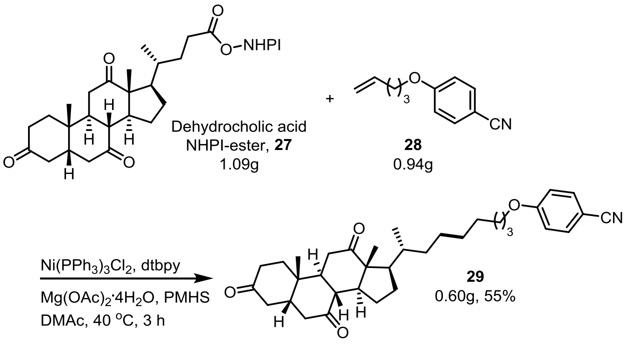
Table 2. Substrate scope of the cross-coupling of *N*-hydroxyphthalimide esters with alkenes. [a]





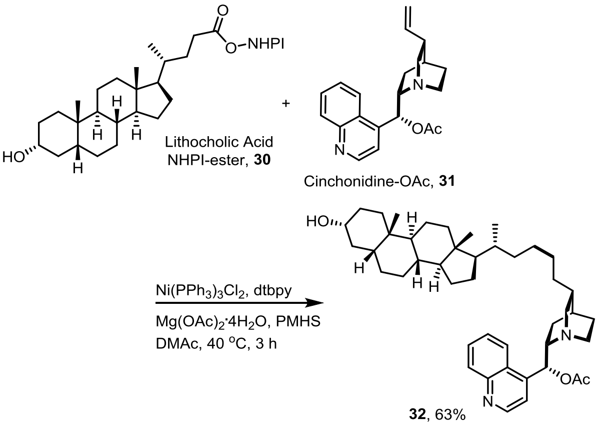
3: 76% **4**: 61% **5**: 64% **6**: 75%
7: 62% **8**: 66% **9**: 60%
10: 53% **11**: 67% **12**: 66%
13: 76% **14**: 63% **15**: 60%
16: 81% **17**: 58% **18**: 72%
19: 70% **20**: 71% **21**: 63%
22: 65% **23**: 73% **24**: 54%
25: 53% **26**: 84%

[a] The reactions were conducted in 0.2 mmol scale, isolated yield. 1 eq. NHPI-ester, 2.5 eq. alkene, 10% $Ni(PPh_3)_2Cl_2$, 15% dtbpy, 3 eq. $Mg(OAc)_2·4H_2O$, 200 uL PMHS, 1 mL DMAc, 40 °C, 2-3 hours. Ts = tosyl. Boc = *t*-butyloxycarbonyl. BPin = pinacol boronate ester. Bz = benzoyl.



Scheme 1. Gram scale reaction. 10% $Ni(PPh_3)_2Cl_2$, 15% dtbpy, 3 eq. $Mg(OAc)_2·4H_2O$, 2 mL PMHS, 10 mL DMAc, 40 °C, 3 hours.

To further demonstrate the synthetic utility of the new decarboxylative olefin hydroalkylation reaction, we explored its application as an efficient tool for the modification of complex molecules in a convergent fashion (**Scheme 2**). The coupling of the NIPH-ester of lithocholic acid (**30**) with a cinchonidine derivative (**31**) resulted in the formation of **32** with high *chemo*-selectivity and good yield 63%. In this transformation, the toleration of a basic amine, quinoline, and a free alcohol group highlights the excellent functional group compatibility.



Scheme 2. Modification of complex molecules in a convergent fashion. 20% $Ni(PPh_3)_2Cl_2$, 30% dtbpy, 3 eq. $Mg(OAc)_2 \cdot 4H_2O$, 200 uL PMHS, 2 mL DMAc, 40 ^{o}C, 3 hours.

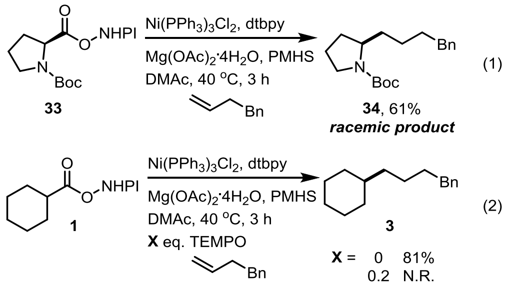


Figure 3. Mechanism experiments.

An optically pure secondary alkyl ester (**33**) was used to study the stereochemistry of the decarboxylative olefin hydroalkylation reaction (eq. 1, **Figure 3**). This reaction led to racemic products in a 61% isolated yield. In a separete reaction (eq. 2, **Figure 3**), we added TEMPO (2,2,6,6-tetramethylpiperidinooxy) as a radical trap. This reaction was completely shut down when 0.2 equiv. TEMPO was added. Collectively the above results indicated a radical type reaction mechanism for the Ni-catalyzed decarboxylative olefin hydroalkylation process.[17]

To summarize, we developed a novel user-friendly strategy for the construction of C(sp^3)-C(sp^3) bonds through decarboxylative olefin hydroalkylation of *N*-hydroxyphthalimide esters with un-activated alkenes. This reaction adds an important new example for both decarboxylative cross-coupling reactions and Ni-catalyzed C(sp^3)-C(sp^3) cross-coupling reactions. The present reaction exhibits excellent functional group tolerance regarding both of the coupling partners. Furthermore, this reaction provides efficient access for the convergent modification of complex organic molecules containing olefin groups and carboxylic acid groups. Our next challenge was the extension of the reaction to tertiary carboxylic acid derivatives and internal olefins.

Acknowledgements

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Keywords: Nickel • C-C bond formation • olefin hydroalkylation • decarboxylative cross-coupling

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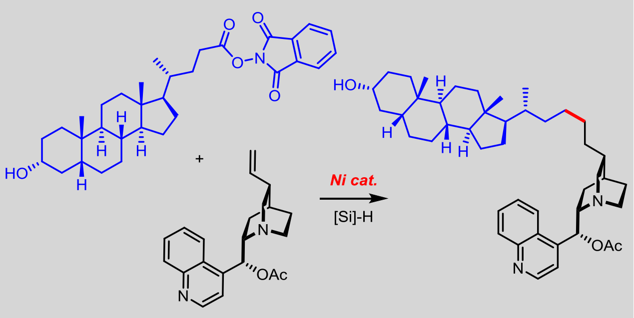
COMMUNICATION

We report a novel Nickel-catalyzed decarboxylative olefin hydroalkylation for the construction of C(sp^3)-C(sp^3) bonds.



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