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Direct C−C Bond Formation from Alkanes Using Ni-Photoredox Catalysis

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Supporting Information

ABSTRACT: A method for direct cross coupling between unactivated $C(sp^3)$−H bonds and chloroformates has been accomplished via nickel and photoredox catalysis. A diverse range of feedstock chemicals, such as (a)cyclic alkanes and toluenes, along with late-stage intermediates, undergo intermolecular C−C bond formation to afford esters under mild conditions using only 3 equiv of the C−H partner. Site selectivity is predictable according to bond strength and polarity trends that are consistent with the intermediacy of a chlorine radical as the hydrogen atom-abstracting species.

The development of catalytic methods for functionalization of unactivated aliphatic C−H bonds represents a prominent challenge in organic synthesis.[1] A variety of useful strategies have been developed for selective $C(sp^3)$−H oxidation of hydrocarbons to give C−X bonds (e.g., X = O, N, B, F, or Cl).[2] While valuable in their own right, these products are also frequently used as precursors for $C(sp^3)$−C bond-forming reactions. Direct formation of C−C bonds from unactivated hydrocarbons would thus provide an attractive strategic alternative to this multistep sequence (Figure 1A). However, most catalytic methods that effect intermolecular C−C bond formation of unactivated alkanes require the use of substrates with a coordinating directing group or the use of a substrate in large excess to impart reactivity, which limits applications at an early and late stage in synthesis.[3] Alternatively, Rh-catalyzed $C(sp^3)$−H insertion with donor−acceptor carbenoids represents a powerful methodology for nondirected C−C bond formation with alkane as the limiting reagent.[4] Despite its attributes, the methodology is restricted to the installation of a specific type of C−C bond. The identification of alternative strategies that enable the modular installation of C−C bonds from unactivated alkanes could have a significant impact on organic synthesis. Here we report that Ni and photoredox catalysis represents one such strategy, enabling the generation of valuable carbonyl derivatives from unactivated $C(sp^3)$−H bonds via catalytic C−C bond formation with chloroformates.

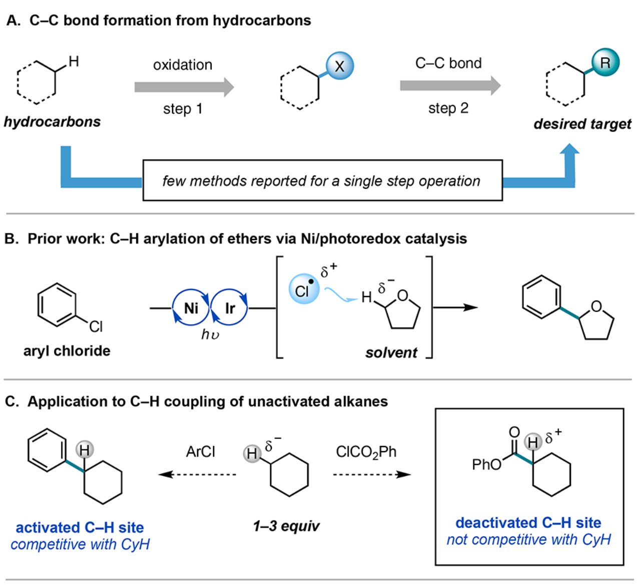

Figure 1. Direct C−C bond formation from $C(sp^3)$−H bonds.

Over the past several years, Ni and photoredox catalysis has emerged as a modular strategy for the construction of $C(sp^3)$−C bonds from $C(sp^3)$−H partners.[5,6] Under this manifold, Ni catalysts are proposed to intercept and functionalize carbon-centered radicals generated from $C(sp^3)$−H bonds via one of two distinct pathways: an oxidative single electron transfer (SET)/deprotonation process for electron-rich amines or a H-atom abstraction (HAT) step for electron-poor amines and ethers. Thus far, successful substrates in these coupling reactions have required $C(sp^3)$−H bonds proximal to functional groups. For example, we recently disclosed a strategy for the arylation of ethereal $C(sp^3)$−H bonds via the photocatalytic generation of chlorine radical from Ni (Figure 1B).[5c] Although chlorine radical is capable of abstracting C−H bonds of unactivated alkanes (HCl BDFE 97 kcal/mol; cyclohexane BDFE 91 kcal/mol),[7] we found that the cross coupling of cyclohexane with aryl chlorides was only feasible in moderate yield using a large excess of substrate (44% yield at 10 equiv).

Guided by this result, we set out to develop a catalytic $C(sp^3)$−H cross-coupling reaction of unactivated alkanes using substrate in stoichiometric quantities. A principal concern in the development of such a process was identifying conditions in which the unactivated alkane would undergo preferential HAT in the presence of cross-coupled product. For arylation reactions, the benzylic $C(sp^3)$−H bond of the product is considerably weaker than the starting material $C(sp^3)$−Hs (BDFE of 80 versus 90−95 kcal/mol),[7] which could lead to overfunctionalization or unproductive consumption of the

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chlorine radical. Since chlorine radical is an electrophilic hydrogen atom acceptor, we anticipated that use of an electron-deficient coupling partner such as a chloroformate would discourage competitive HAT on the basis of polar effects in free-radical chlorination (Figure 1C).[8] The application of chloroformates in a C(sp^3)−H functionalization reaction was appealing as it would deliver direct access to carbonyl derivatives, arguably the most versatile functional groups in synthesis. Moreover, chloroformates are abundant, inexpensive reagents that undergo facile oxidative addition to Ni.[9]

According to our prior mechanistic studies[5c,10a] and literature precedent,[10b−d] a hypothesized catalytic cycle for the C(sp^3)−H functionalization is displayed in Figure 2. We envisioned that (dtbbpy)Ni^0 (**1**) would undergo oxidative addition to a chloroformate derivative to generate (dtbbpy)-Ni^{II}(CO_2R)(Cl) (**2**).[9b,c,11] Concurrently, visible light irradiation of the photocatalyst Ir[dF(CF_3)ppy$]_2$(dtbbpy)PF_6 (**3**) would enable a long-lived excited species **4** that serves as a potent single electron oxidant (τ = 2.3 μs, $*E_{1/2}(Ir^{III}/Ir^{II})$ = +1.21 vs SCE in MeCN) for **2**.[12,13] Subsequent visible light irradiation of transient (dtbbpy)Ni^{III}(CO_2R)(Cl) (**5**) would affect photoelimination of chlorine radical, followed by rapid hydrogen atom abstraction of the aliphatic substrate to generate a carbon-centered radical. Addition of this radical to Ni^{II} would result in **8**, followed by reductive elimination of the ester product. Single electron transfer from the reducing Ir^{II} (**10**) to Ni^{I} (**9**) would allow for regeneration of both the Ni and photoredox catalysts.[13]

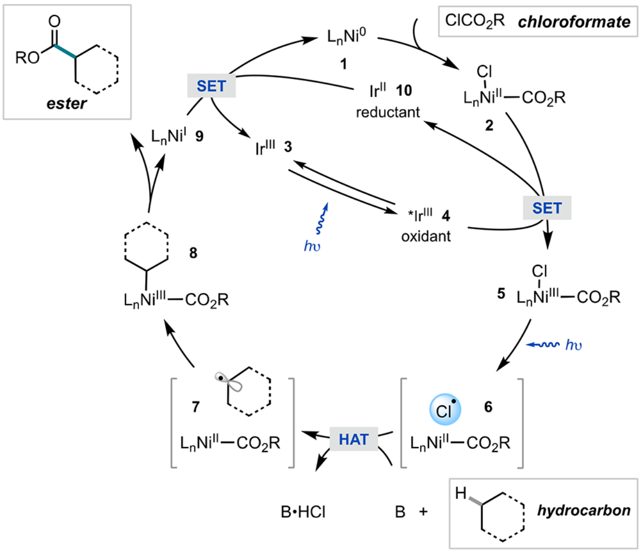
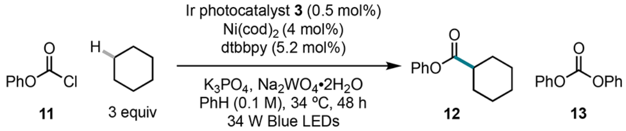


Figure 2. Proposed photoelimination mechanism for ester formation from hydrocarbons. **3** = Ir[dF(CF_3)ppy$]_2$(dtbbpy)PF_6; dF(CF_3)ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine.

Our investigation began with the reaction of phenyl chloroformate ($0.16/g)[9] with cyclohexane (Table 1). Use of this coupling partner under our previously reported conditions (10% Ni, 2% Ir, 10 equiv cyclohexane, 2 equiv K_3PO_4, in 0.04 M benzene) delivered **12** in only 14% yield (Figure S3). Upon extensive investigation, we identified conditions that delivered ester **12** in 66% yield after 48 h using only 0.5 mol % Ir photocatalyst **3** and 4 mol % Ni (entry 1).[14] Whereas 1 equiv of alkane may be used, highest yields are obtained using a ratio of 3:1 alkane:chloroformate (entry 2).

Table 1. Optimization of Reaction Conditions[a]



Entry	Deviation from standard condition	Yield **12** (%)[b]	Yield **13** (%)[c]
1	none	66	28
2	1 equiv of cyclohexane	44	33
3	no photocatalyst	0	48
4	no ligand	3	27
5	no nickel	0	17
6	no light	0	34
7	26 °C	46	17
8	40 °C	55	32
9	no $Na_2WO_4 \cdot 2H_2O$[d]	39	19
10	no $Na_2WO_4 \cdot 2H_2O$[d], 72 h	62	22
11	$Na_2SiO_3 \cdot 5H_2O$ instead of $Na_2WO_4 \cdot 2H_2O$	57	25
12	no K_3PO_4[d]	58	35
13	no K_3PO_4, no $Na_2WO_4 \cdot 2H_2O$	17	11

[a] K_3PO_4 (2 equiv); $Na_2WO_4 \cdot 2H_2O$ (1 equiv). [b] Yields determined by ^1H NMR using 4-fluoroanisole as an external standard. [c] Yield determined by GC analysis based on consumption of 2 equiv of chloroformate for production of 1 equiv of DPC. [d] 3 equiv of base used.

Control reactions demonstrated that the C(sp^3)−H functionalization process requires the presence of both Ni and Ir catalysts, as well as light, and that consistent reaction temperatures were critical to obtaining high yields (entries 3−8). Notably, the addition of sodium tungstate, and to a lesser extent, sodium silicate, provided moderate rate accelerations (entries 1 vs 9 and 11). Preliminary data suggests that sodium tungstate is acting as a base[15] rather than as a precursor to higher-order tungstates, which could function as photocatalysts and hydrogen atom acceptors.[16] For example, at 72 h, a reaction without sodium tungstate proceeds to comparable yield as a reaction in its presence (entries 1 and 10). Furthermore, use of near-UV light, which enables access to the charge-transfer excited states of higher order tungstates, leads to low reaction efficiency (Table S9). In all cases, the mass balance can be attributed to the formation of diphenyl carbonate (**13**), a byproduct primarily generated from the reaction of chloroformate with base (Table S4).

With these optimized conditions established, we set out to examine the scope of the C(sp^3)−H cross-coupling reaction (Figure 3). In exploring the chloride-containing coupling partner, we observed that both *p*-fluoro and *p*-methoxy derivatives of phenyl chloroformate are effective for C−H functionalization of cyclooctane (**15** and **16**). More notably, the use of acid chlorides in place of a chloroformate delivered aromatic and aliphatic ketones **17** and **18** in 55 and 52% yield, respectively, under identical conditions.[17,18] Additionally, 4-morpholine carbonyl chloride afforded amide **19** in 15% yield, demonstrating that this methodology could be adopted for direct amidation.

In our investigation of the C(sp^3)−H coupling partner, we first evaluated unfunctionalized alkanes. Cyclic alkyl hydrocarbons with ring sizes from 5 to 15 underwent C−C bond formation, transforming inert substrates to easily modified

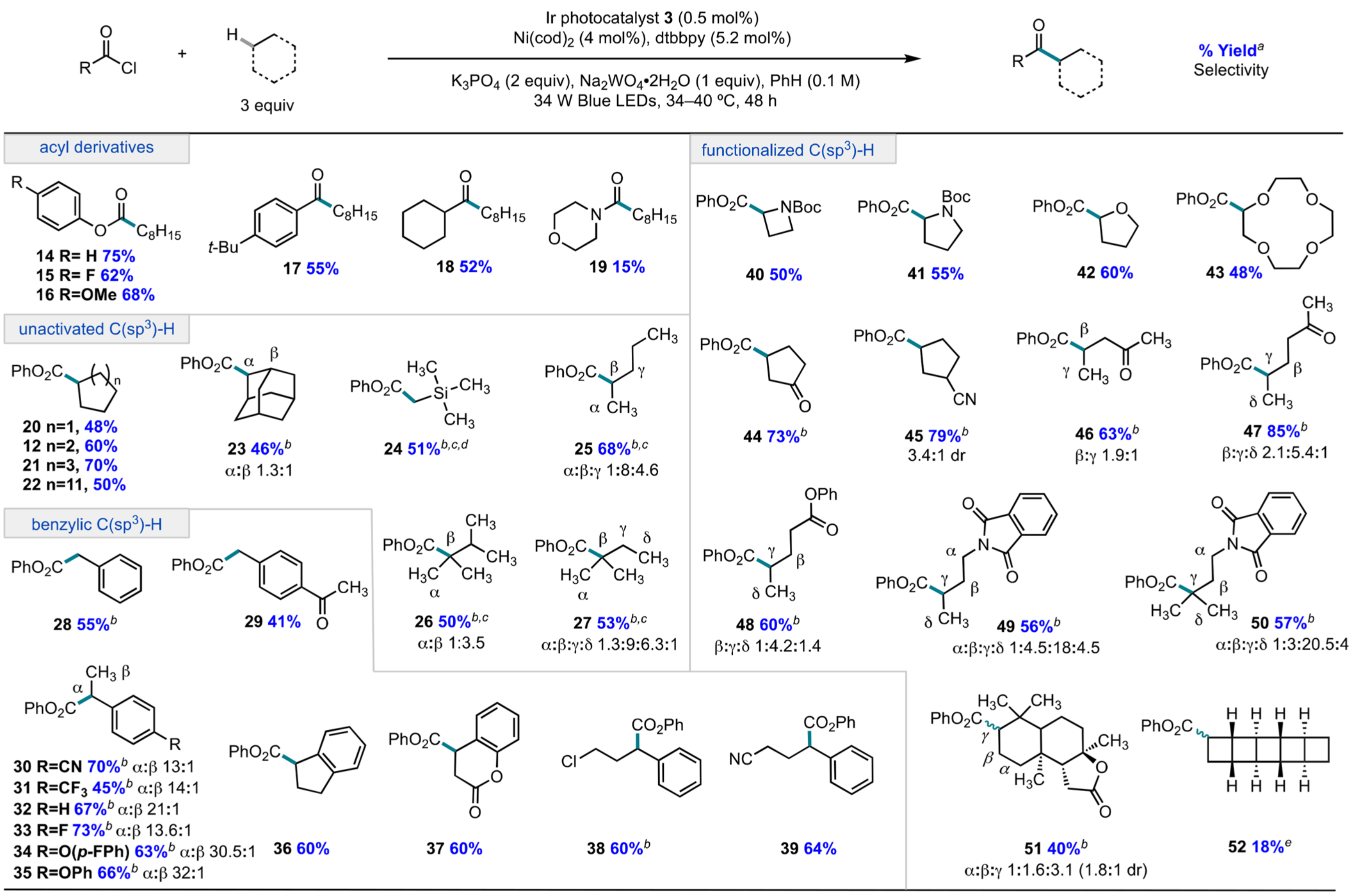


Figure 3. [a]Isolated yield of all isomers expressed as an average of two runs. Hydrocarbon substrates worked effectively at 34 °C (±5 °C), whereas hydrocarbons containing amines, ketones, or ethers, worked optimally at 40 °C (±5 °C). [b] ^{1}H NMR yield of all isomers expressed as an average of two runs using 4-fluoroanisole as an external standard. [c]6 equiv of C−H substrate used. [d]Yield reported postdesilylation. [e] ^{1}H NMR yield expressed as a single run reported on 0.08 mmol scale with 1.8 C−H equivalents of [5]-ladderane using 12 W Blue LEDs.

products in good yield (**12**, **20**−**22**). Tetramethylsilane which possesses one of the strongest C(sp^3)−H bonds (BDFE = 96 kcal/mol)[7] was functionalized in 51% yield (**24**). Examination of the functionalization of acyclic alkanes revealed a trend among various C(sp^3)−H sites consistent with the influence of BDFE on rate of C−H abstraction. Pentane was preferentially functionalized at the internal secondary positions in 68% combined yield (**25** α:β:γ 1:8:4.6). Analogously, 2-methylbutane exhibited preferential functionalization at the tertiary position in 53% combined yield (**27** α:β:γ:δ 1.3:9:6.3:1). An Evans−Polanyi plot ($E_a = \alpha\Delta G° + \beta$) for 2-methylbutane shows a linear correlation with an α value of 0.44, comparable to tabulated α values for HAT with chlorine radical ($\alpha_{Cl} = 0.45$) (Figure 4a).[8c] Thus, while the C(sp^3)−H esterification results in mixtures of regioisomeric products for these substrates, the site selectivity is predictable.

Because toluene and alkyl benzenes are abundant and inexpensive commodity chemicals, we also examined their use as substrates for the esterification reaction (**28**−**39**). Notably, the Stahl and Liu groups have recently reported Cu-catalyzed arylation reactions of alkyl benzenes with boronic acid derivatives that provide efficient access to diarylalkanes, albeit requiring a large excess of substrate or alkyl benzenes with extended aromatic systems.[19] For the esterification reaction, we were pleased to find that toluene and its acyclic as well as cyclic derivatives underwent C−C bond formation in good yields. The influence of the polar effect is evidenced in the site selectivity of these reactions. For a series of *p*-substituted ethylbenzenes, the ratio of benzylic to methyl functionalization decreases with electron-withdrawing substituents (**30**−**35**). Furthermore, a Hammett-Brown analysis of the relative rate of benzylic functionalization across this series (determined by competition experiments, see SI Section III.H) reveals that electron-rich substrates undergo C−C bond formation faster than electron-poor substrates (Figure 4B). Indeed, the small ρ value is consistent with a highly exothermic abstraction step and reports on free-radical chlorination of toluenes (ρ values

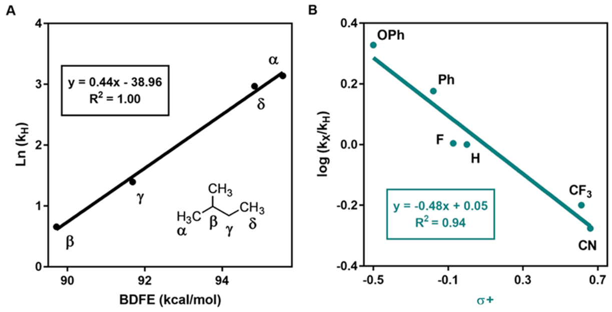


Figure 4. C(sp^3)−H abstraction selectivity profile. (a) Evans−Polanyi relationship for **27**; (b) Hammett Plot for ethylbenzene derivatives.

ranging from −0.5 to −1.0).[20] These results explain the high regioselectivity in esterification for products **29**, **37**−**39**.

When functionalized cyclic and acyclic substrates were submitted to the reaction conditions, selectivity trends reflected an interplay of polarity effects and radical stability. Cyclic amides and ethers, from a 4-membered azetidine to a 12-membered crown ether were successfully converted to α-amino and α-oxy esters **40** and **43** under the dual catalytic conditions.[17d,e] Cyclic hydrocarbons with electron-withdrawing functionality, like cyclopentanone and cyclopentylcarbonitrile, underwent C−C bond formation with predictable and high levels of selectivity, furnishing the β-functionalized product **44** and γ-functionalized product **45** in 73 and 79% yields. For an acyclic ketone, selectivity for γ functionalization increased when that site changed from a primary to a secondary position (**46** vs **47**: 22% vs 54% yield). Similarly, a preference for the γ position increased between **49** and **50** when that site was changed from a secondary position to a tertiary position. Synthetically, these examples offer complementarity to arylations of similar substrates under Pd catalysis, where regioselectivity is ligand/or directing group-dependent.[21] Likewise, the Martin laboratory recently described a method for Ni-catalyzed carboxylation of halogenated aliphatic hydrocarbons that affords C−C bond formation at two completely distinct positions of an aliphatic chain to that favored in this methodology.[22]

Application of this method to late-stage functionalization was also evaluated. Sclareolide, a model system for selective $C(sp^3)$−H oxidations, led to **51** in 40% combined yield at the most electron-rich and sterically accessible methylene sites, which is orthogonal to reactivity exhibited by most transition metal-based catalysts.[23] Additionally, a ladderane core, the derivatives of which are notoriously challenging to access, gave **52** in a modest 18% yield at 1.8 equiv of substrate. The closest reaction analog, a Mn(TMP)Cl catalyst system, delivered 40% of the chlorinated species and requires additional steps to access a C−C bond.[24]

In summary, this reaction provides a general strategy to access carbonyl derivatives directly from unactivated $C(sp^3)$−H bonds that is amenable both to early and late stage synthesis. Site selectivity is predictable, arising from hydrogen atom abstraction by chlorine radical, and affords a synthetic complement to alternative approaches for achieving C−C bond formation from alkanes. Our future efforts will be directed at elucidating the mechanism of this process and developing strategies to control the site-selectivity of $C(sp^3)$−H functionalization.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b09191.

> Experimental procedures, computational data, and characterization and spectral data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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