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Three-Component Alkene Difunctionalization via Direct and Selective Activation of Aliphatic C-H Bonds

Sheng Xu, Herong Chen, Zhijun Zhou and Wangqing Kong*

Abstract: Catalytic alkene difunctionalization is a powerful strategy for the rapid assembly of complex molecules and has wide range of applications in synthetic chemistry. Despite significant progress, a compelling challenge that still needs to be solved is to install highly functionalized C(sp^3)-hybridized centers without requiring pre-activated substrates. We herein report that inexpensive and easy-to-synthesize decatungstate photo-HAT, in combination with nickel catalysis, provides a versatile platform for three-component alkene difunctionalization through direct and selective activation of aliphatic C-H bonds. Compared with previous studies, the significant advantages of this strategy are that the most abundant hydrocarbons are used as feedstocks, and various highly functionalized tertiary, secondary and primary C(sp^3)-hybrid centers can be easily installed. The practicability of this strategy is demonstrated in the selective late-stage functionalization of natural products and the concise synthesis of pharmaceutically relevant molecules including Piragliatin.

Introduction

Alkenes are simple and abundant bulk commodity feedstocks in organic synthesis. Catalytic difunctionalization of alkenes represents a versatile platform for rapid construction of complex multifunctional molecules through the regioselective installation of two different carbon fragments across the C-C double bond.[1] The traditional two-electron difunctionalization of alkenes relies on the use of excessive amounts of preformed organometallic reagents, which preclude the introduction of sensitive functional groups.[2] Recently, radical-based difunctionalization of alkenes by Ni-catalyzed reductive cross-coupling[3] or Ni/photoredox dual catalysis[4] has experienced a great surge of development. Representative work from the groups of Nevado,[3b,3g,3i,4g] Molander,[4c,4e,4h] Chu,[3c] Aggarwal,[4j] Martin,[4i] Koh[3j] etc. has proved the synthetic potential of this method. A very attractive aspect of this versatile transformation is that relatively stable C(sp^3)-hybridized electrophiles or nucleophiles could be incorporated to replace highly reactive organometallic reagents.[5] Despite tremendous progress has been made, there are still some considerable limitations. (1) Most approaches rely heavily on pre-activated alkyl substrates, such as alkyl halides, alkyl silicates, alkyl trifluoroborates, oxalate esters or α-silyl amines. Pre-functionalization leads to additional steps and waste generation, and lowers efficiency and atomic economy. (2) The reported examples are restricted to perfluoroalkyl or tertiary (3°) alkyl radicals, and the secondary (2°) and primary (1°) alkyl variants are very limited. (3) Super-stoichiometric metal reductants or expensive photocatalysts are usually required (Scheme 1A).

Although the use of natural carboxylic acids or alcohols as C(sp^3)-coupling partners can increase the overall efficiency of bond formation by expanding the range of potential feedstocks, the direct functionalization of the C-H bond which is the most abundant linkage in organic molecules, is clearly a more ideal and promising way for building carbon-carbon and carbon-heteroatom bonds. In pursuing methods for difunctionalization of alkenes,[3d,6] we aspired to develop a redox-neutral and auxiliary-free strategy for difunctionalization of alkene with unactivated aliphatic C-H bonds as substrates. Such method would allow the direct late-stage functionalization of natural products and medicinally relevant molecules, thereby providing an efficient means for rapid diversification of lead molecules without the need for de novo synthesis.

In this context, tetrabutylammonium decatungstate (TBADT) is a versatile, inexpensive and easy-to-synthesize hydrogen atom transfer (HAT) photocatalyst, which can generate carbon-centered radicals from strong C-H bonds by near-ultraviolet-light irradiation, and has been widely used in many useful C(sp^3)-H functionalization reactions,[7] including oxidations,[8] dehydrogenations,[9] azidation,[10] amination,[11] fluorinations,[12] and conjugate additions.[13] Very recently, a dual decatungstate-HAT and nickel catalysis enabling the direct arylation of C-H bonds had been developed by the MacMillan group.[14] Nevertheless, the majority of these catalytic processes are essentially confined to two-component cross-couplings.[15] Inspired by these precedents and our ongoing interest in nickel-catalyzed difunctionalization of alkenes,[3d,6] we sought to combine nickel catalysis with decatungstate photo-HAT, and provide a new protocol for three-component difunctionalization of alkenes. The successful implementation of this strategy is expected to complement existing approaches and offers a straightforward access to functionalized complex molecules from the most abundant hydrocarbon feedstocks. However, modulating the matching reactivity of the three involved components is extremely challenging (see below for further discussion).

Herein, we report that by merging nickel catalysis and decatungstate photo-HAT, three-component difunctionalization of alkenes can be achieved through direct activation of aliphatic C-H bonds. This strategy exhibits good selectivity and broad substrate scope, and is compatible with various functionalized tertiary (3°), secondary (2°) and primary (1°) alkyl radicals, which is unprecedented in previous reports. The utility of this strategy was demonstrated in selective late-stage functionalization of complex natural products and the concise synthesis of

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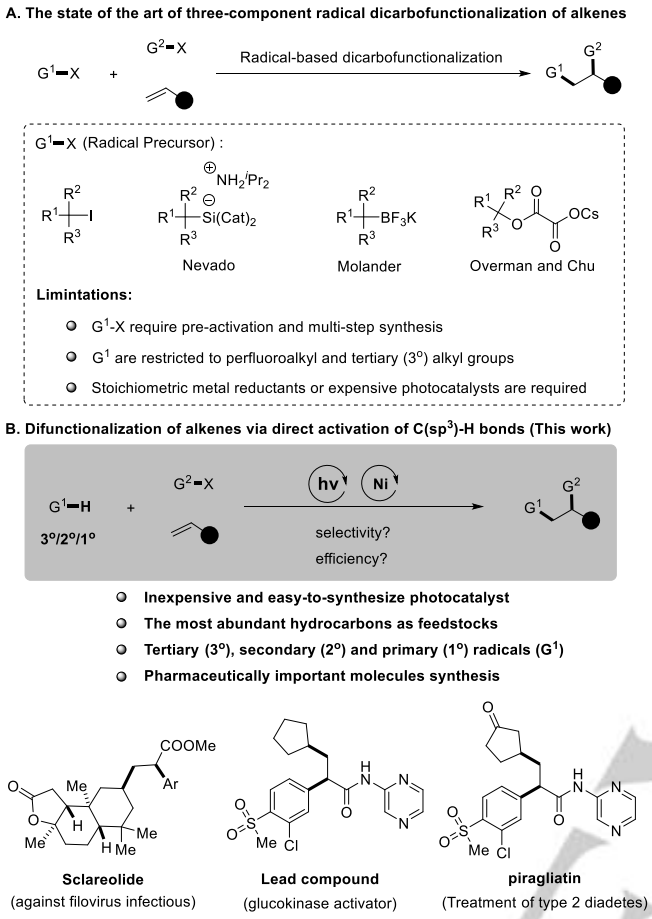
pharmaceutically relevant molecules including Piragliatin (Scheme 1B).

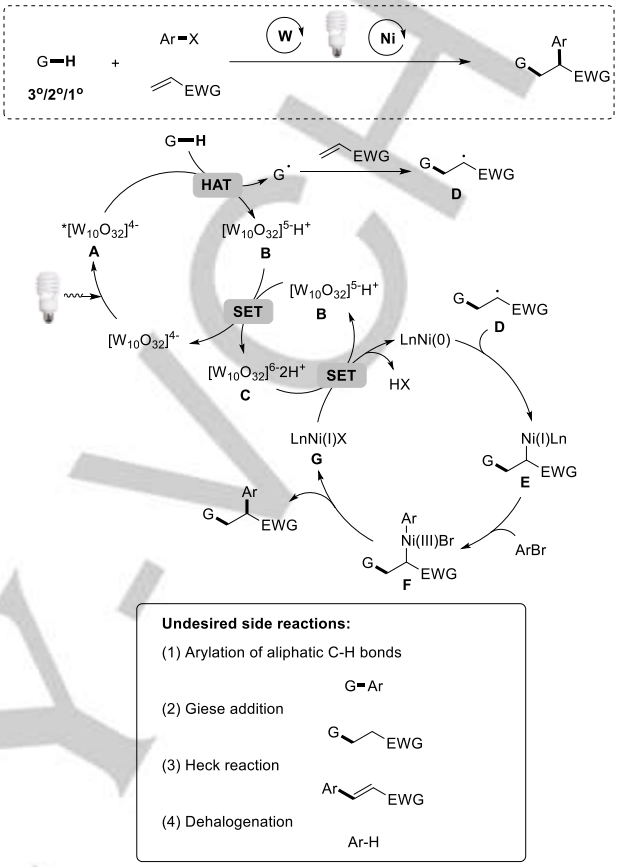


Scheme 1. Catalytic Three-Component Difunctionalization of Alkenes.

Results and Discussion

Based on the previous studies,[14] a hypothesized catalytic cycle was proposed as shown in Scheme 2. Photoexcitation of TBADT produces its excited state **A**, which can abstract a hydrogen atom from unactivated hydrocarbon substrates, thereby providing reduced decatungstate **B** and carbon-centered radical G^1•. Addition of the resulting radical G^1• to an alkene would afford radical adduct **D**, which can be intercepted by Ni(0) species to generate alkyl-Ni(I) intermediate **E**. Oxidative addition of Ni(I) species **E** with aryl bromide affords an alkyl-Ni(III)-aryl intermediate **F**, which undergoes reductive elimination to deliver the desired difunctionalization product and Ni(I) species **G**. A final single-electron transfer between Ni(I) species **G** and decatungstate **C** regenerates the reduced decatungstate **B** and active Ni(0) catalyst, thereby closing both catalytic cycles.

Compared with tertiary (3°) alkyl radicals, secondary (2°) and primary (1°) alkyl radicals are much less stable and have much less steric hindrance. Therefore, products of competitive direct arylation of aliphatic C-H bonds are unavoidable for secondary (2°) and primary (1°) alkyl radicals.[13a] Photocatalytic scission of strong aliphatic C-H bonds generates nucleophilic alkyl radicals, which can be effectively captured by electron-deficient alkenes, leading to the corresponding Giese addition products.[14a] Another obstacle that cannot be ignored is the dehalogenation of aryl halides and the nickel-catalyzed Heck reaction of aryl bromides and alkenes (Scheme 2).



Scheme 2. Proposed Mechanism and Synthesis Challenges.

Our study commenced with the three-component coupling reaction of cyclohexane (**1**), 4-bromo-1,1'-biphenyl (**2**) and methyl acrylate (**3**). In the presence of 2 mol% of photocatalyst TBADT, 10 mol% of Ni(bpy)Br$_2$, K$_3$PO$_4$ in MeCN and exposure to near-ultraviolet light (10 W LEDs), the desired product **4** was isolated in 23% yield (entry 1, Table 1). As expected, the selective formation of **4** is challenged by many side reactions, such as the direct Csp^3-Csp^2 cross-coupling (**5**), Giese-type hydroalkylation (**6**), and debromination of aryl bromide **2**. Unlike nickel-catalyzed reductive cross-coupling reactions,[3] the electronegativity of the substituents on the ligand backbone had little effect on the selectivity and reactivity (entries 2-4), whereas phenanthroline (**L5**), bisoxazole (**L6**), and terpyridine (**L7**) completely suppressed the desired reaction (entries 5-7). The key to success lies in the discovery that the use of acetone instead of acetonitrile as a solvent could dramatically improve the selectivity of the reaction, which is favorable for product **4** rather than Giese-type hydroalkylation **6** (compare entry 8 with entry 3). The effect of the reaction concentration was further investigated (entries 11-12). To our delight, the three-component cross-coupling reaction proceeded optimally at high concentration, providing the desired product **4** in 71% yield, and only trace amounts of by-product **5** and **6** were observed (entry 12). Reducing the amount of alkene from 3 equiv. to 1.5 equiv., the yield of **4** only slightly decreased (63%, entry 13). In addition, reducing the C-H nucleophile to 5

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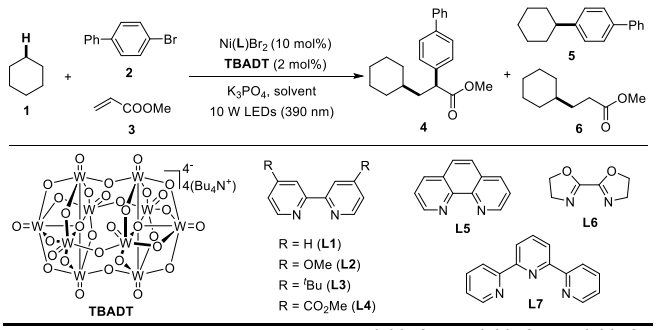
equiv. could still obtain the target product **4** in 61% yield (entry 14). Finally, control experiments confirmed that the reaction did not proceed in the absence of nickel-precatalyst, TBADT or light (entries 15-17).

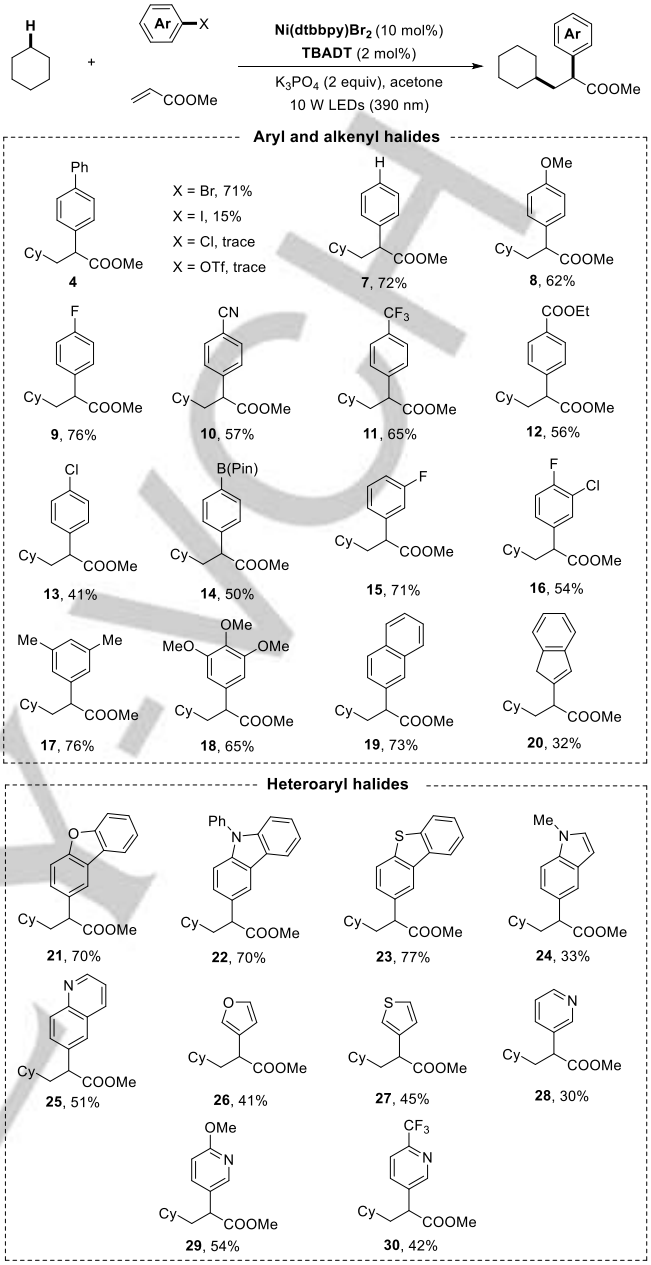
Table 1. Optimization of the reaction conditions[a]



entry	Ni(**L**)Br_2	solvent	yield of **4** (%)[b]	yield of **5** (%)[b]	yield of **6** (%)[b]
1	**L1**	MeCN	23	30	32
2	**L2**	MeCN	20	30	36
3	**L3**	MeCN	35	15	27
4	**L4**	MeCN	22	18	54
5	**L5**	MeCN		no reaction	
6	**L6**	MeCN		no reaction	
7	**L7**	MeCN		no reaction	
8	**L3**	acetone	57	13	17
9	**L3**	DCM		no reaction	
10	**L3**	DMSO		noreaction	
11[c]	**L3**	acetone	66	6	13
12[d]	**L3**	acetone	71	< 2	8
13[d,e]	**L3**	acetone	63	11	5
14[d,f]	**L3**	acetone	61	12	7
15[d]	-	acetone		no reaction	
16[d,g]	**L3**	acetone		no reaction	
17[d,h]	**L3**	acetone		no reaction	

[a] Reactions conditions: **1** (2 mmol), **2** (0.2 mmol), **3** (0.6 mmol), Ni(**L**)Br_2 (10 mol%), TBADT (2 mol%), K_3PO_4 (0.4 mmol) in solvent (2 mL) at 30 °C under irradiation of LEDs (10 W, 390 nm) for 12 hours. [b] Yields of isolated products. [c] Acetone (1 mL). [d] Acetone (0.5 mL) [e] 1.5 equivalents of alkene **3** were used. [f] 5 equivalents of cyclohexane were used. [g] Without TBADT. [h] Without light.

With the optimized reaction conditions in hand, the diversity of aryl halide coupling partners was firstly evaluated (Scheme 3). The reaction with aryl iodide gave **4** in 15% yield, while aryl chloride and aryl triflate were inactive. Aryl bromides containing various synthetic valuable functional groups, such as ether (**8**, **18**), fluoride (**9**, **15** and **16**), cyano (**10**), trifluoromethyl (**11**) and ester (**12**), were all tolerated in the Ni/photo-HAT process. Notably, the presence of chlorine (**13** and **16**) or borate (**14**) on the aromatic ring did not interfere with the reaction efficiency, thus providing a wealth of new opportunity for further functionalizations. Naphthyl bromide was perfectly accommodated to furnish **19** in 73% yield. Interestingly, alkenyl bromide was also found to be applicable to this reaction, albeit in lower yield (**20**). Various heterocyclic bromides were examined. Dibenzofuran (**21**), carbazole (**22**), dibenzothiophene (**23**), indole (**24**), quinoline (**25**), furan (**26**) and thiophene (**27**) were successfully incorporated into the corresponding products in satisfactory yields. Moreover, both electron-rich and electron-deficient bromopyridines were efficiently transformed into the corresponding products **28**-**30** in useful efficiency.



Scheme 3. Scope of Aryl and Heteroaryl Halides.

The scope with respect to the aliphatic C-H coupling partners was assessed next (Scheme 4). A wide range of hydrocarbons proved to be competent coupling partners for the three-component cross-coupling reaction. Cycloalkanes with five to eight carbon atoms proceeded smoothly to provide the corresponding products **31**, **4** and **32** in 60-73% yields. For linear alkane, *n*-pentane and 1-bromobutane were likewise successful, and preferentially functionalized of the less sterically demanding 2-position (**33**-**34**, 40% and 57% yield, respectively). Due to the high BDEs of the primary C-H bonds, 2,3-dimethylbutane was selectively functionalized on the secondary C-H bonds (**35**, 62% yield). Bridged bicyclic alkanes were also suitable substrates. Norbornane was exclusively functionalized on the ethylene bridge (**36**, 78% yield), while the sterically hindered tertiary C-H bonds were almost no reactivity despite their relatively low BDEs. On the contrary, the functionalization of adamantane occurred

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predominantly on the sterically hindered tertiary C-H bonds of the bridgehead (**37**).

Importantly, this protocol is not limited to electronically neutral, unactivated hydrocarbons. Various α-heteroatom C-H bonds can also be functionalized with excellent regioselectivity. Ethers were functionalized at the α-oxy position in moderate to good yields with excellent regioselectivity (**38**-**41**). Notably, alkyl bromide was compatible with this dual catalytic system, thus opening avenues for further derivatizations (**39**, 65% yield). *Tert*-butyl methyl ether was also effective substrate (**41**). As *O-tert*-butyl can be easily removed,[16] it constitutes a route to α-aryl, γ-hydroxybutyrates. In addition to oxygen-containing nucleophiles, Boc-protected pyrrolidine, piperidine and piperidin-4-one were also competent substrates and selectively functionalized on the α-amino position in good efficiencies (**42**-**44**, 66-82% yield). Primary α-amino C-H nucleophiles, *N*-methyl-*N*-phenylaniline and *N*-Boc dimethylamine were also transformed into the desired products in moderate yields (**45** and **46**, 51% and 54% yield, respectively). As *N*-Boc is easily deprotected, it constitutes a route to *N*-unprotected α-aryl, γ-amino acid derivatives, which are unique structural motifs in pharmaceutical compounds.[17] This strategy can serve as a powerful supplement, since the previously reported method failed to obtain target product.[18] Strikingly, ketone was also found to be effective substrate for this transformation, providing product that was selectively functionalized at the distal to the electron-withdrawing carbonyl moiety (**47** and **48**, 54% and 58% yield, respectively). TMS_3SiH, which is prone to form a silyl radical, underwent three-component coupling reaction to obtain the desired organosilicon compound **49** in moderate yield with only 3 equiv. of TMS_3SiH.

Subsequently, the applicability of alkenes was also explored. Acrylates with different substituents were studied (**50**-**51**). Remarkably, a complex acrylate derivative of estrone was readily difunctionalized (**52**, 55% yield), thus demonstrating the potential of this methodology in late-stage functionalization of complex molecules. In addition to methyl acrylate, other electron-deficient olefins have also been investigated. Acrylonitriles are compatible with this dual catalytic system and provided the desired products in moderate yields (**53** and **54**, 58% and 54% yield, respectively). Notably, the resulting α-aryl-γ-amino-substituted nitrile can be easily converted into highly valuable 1,4-diamines. The more challenging α, β-unsaturated ketones are also tolerated with this three-component coupling reaction, thereby providing the corresponding products **55** and **56** in 51% and 50% yield, respectively. Interestingly, the less electron-deficient 1,1-disubstituted acrylamide afforded the oxindole **57** bearing a quaternary carbon center in 28% yield. However, vinyl boronic ester and vinyl sulfone could not delivery any desired products (**58** and **59**).

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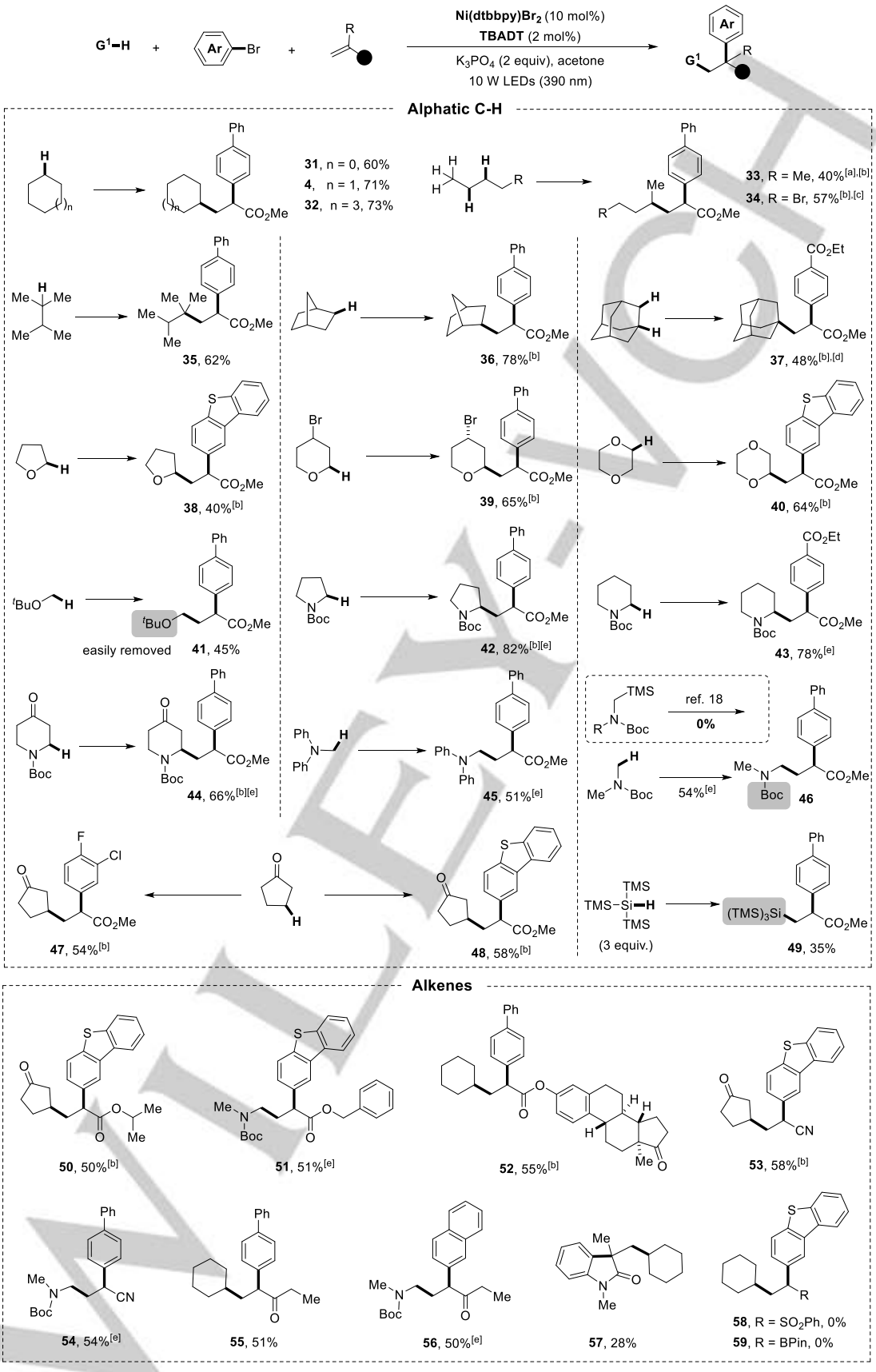

Scheme 4. Substrate Scope of Unactivated C-H Bonds and Alkenes. 10 equivalents of aliphatic C-H coupling partners were used for products **31**~**37**, and 5 equivalents for products **38**~**48**. Blue bonds denote sites where the corresponding regioisomer are observed. All yields are isolated yields. d.r., diastereomeric ratio; r.r., regioisomeric ratio. [a] 1.4:1 r.r. [b] 1:1 d.r. [c] 20:1 r.r. [d] 1.2:1 r.r. [e] **L2** was used as ligand.

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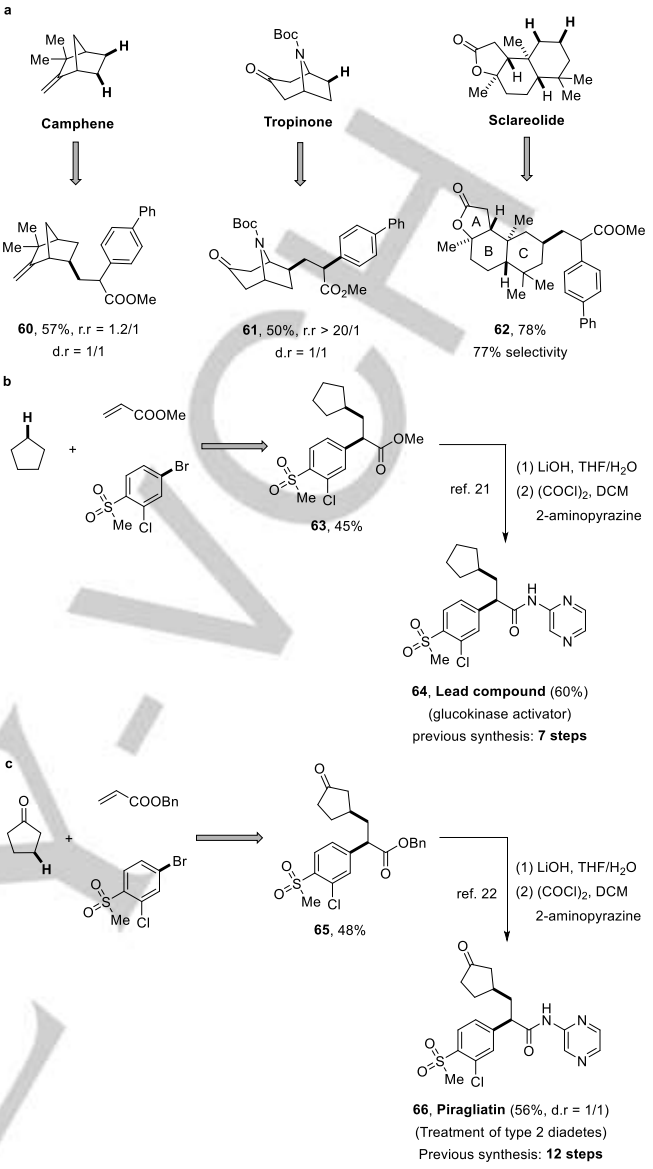
We next investigated the feasibility of this protocol for the late-stage functionalization of complex molecules. As shown in Scheme 5a, under our reaction conditions, a number of naturally occurring complex stereo-defined scaffolds were successfully functionalized at carbon sites where lack adaptive functional handles. Camphene, a terminal-alkene-containing nature product was found to be an effective substrate, and preferentially functionalized of the less sterically hindered secondly C-H bonds (**60**). Tropinone, an interesting scaffold found in a variety of natural products and drugs,[19] was also readily used in this protocol, providing the desired product **61** in moderate yield with excellent site selectivity. The sesquiterpene lactone Sclareolide contains two tertiary C-H bonds and six methylene sites, and could also be functionalized on the C ring to furnish product **62** in 78% yield.

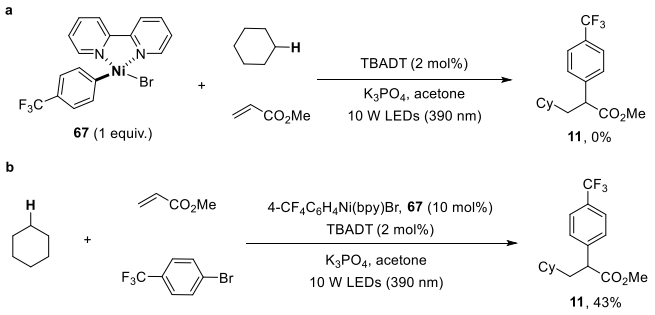
To further demonstrate the practicability of this protocol in the field of medicinal chemistry, application of this approach to the concise synthesis of pharmaceutically relevant molecules was performed. Our first target is to synthesize the lead compound **64**, an archetypal glucokinase activator (GKA), which can improve glycemic control administered a single oral dose.[20] The previous method used to synthesize the lead compound **64** requires seven steps, involving the preparation of arylpropionic acid or ester, followed by alkylation with cyclopentylmethyl iodide, hydrolysis and amidation with the corresponding aminoheterocycle.[21] Our synthesis strategy started from commercially available cyclopentane, methyl acrylate and 4-bromo-2-chloro-1-(methylsulfonyl)benzene. The three-component cross-coupling protocol proceeded smoothly, producing the precursor **63** in 45% yield. Hydrolysis of methyl ester followed by amidation with 2-aminopyrazine provided the desired GKA lead compound **64** (Scheme 5b).

Another important goal is to synthesize Piragliatin **66**, which is a clinically advanced drug candidate for the treatment of type 2 diabetes (T2D).[22] Excitingly, starting with commercially available cyclopentenone, benzyl acrylate and 4-bromo-2-chloro-1-fluorobenzene, the three-component cross-coupling reaction could react smoothly to obtain the key precursor **65** in 48% yield (d.r = 1/1). Note that the prior synthesis of Pilagliptin and its diastereomer required 12 steps and the overall yield was low.[22] Compound **65** can be converted into Piragliaptin in two steps (hydrolysis and amidation); Thus, the synthesis of Piragliatin **66** can now be accomplished in only 3 steps and in good overall yield (Scheme 5c). To the best of our knowledge, this is the shortest synthesis of Piragliatin in the multitude of reported procedures to date.



Scheme 5. Functionalization of Natural Products and Application to Concise Synthesis of Piragliatin.

A variety of mechanistic experiments were designed to shed light on the reaction mechanism (more details see the Supporting Information). The three-component coupling reaction was strongly inhibited in the presence of TEMPO or BHT (Supplementary Fig. 4), which points towards a radical mechanism. We further synthesized the 4-$CF_3C_6H_4$Ni(II) complex **67** and studied the catalytic efficiency of the complex. No detectable amount of **11** was observed in the stoichiometric reaction of complex **67** with cyclohexane and methyl acrylate (Scheme 6a). One possible reason is the instability of complex **67** in the absence of aryl bromide and its strong absorption in the visible light region.[23] However, using 10 mol% of Ar-Ni(II) complex **67** instead of Ni(dtbbpy)Br_2 as the catalyst, the desired product **11** could be obtained in 43% yield (Scheme 6b). Taken together, these results indicate that the Ar-Ni(II) complex may not be a reactive species in the catalytic cycle, and the generated α-carbonyl radical **D** in Scheme 2 was recombined with Ni(0) species rather than Ar-Ni(II) complex.



Scheme 6. Mechanistic Study.

Conclusion

In conclusion, a three-compoent difunctionalization of alkenes enabled by dual decatungstate photo-HAT/nickel catalysis has been realized. The advantage of this strategy is that unactivated hydrocarbons can be used as alkylating agents without requiring the use of pre-activated radical precursors. This protocol is further characterized by the unprecedented tolerance of highly functionalized tertiary, secondary and primary alkyl radicals, which was reluctant to cooperate in previous reports. Moreover, the utility of this strategy is demonstrated in the selective late-stage functionalization of complex natural products and the concise synthesis of pharmaceutically relevant molecules including Piragliatin.

Acknowledgements

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Keywords: nickel-catalysis • three-component reactions • alkene difunctionalization • aliphatic C-H bonds • dual catalysis

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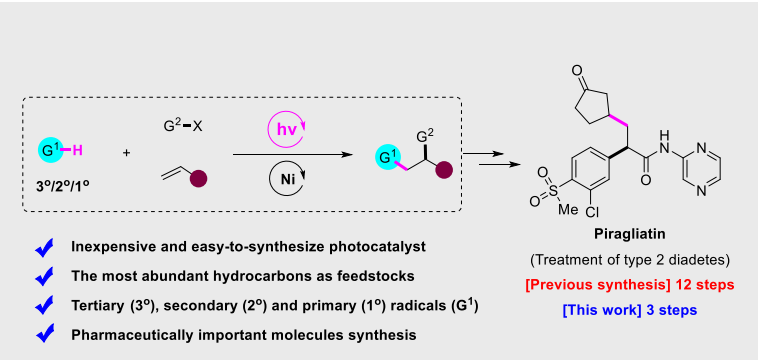

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Page No. – Page No.

Three-Component Alkene Difunctionalization via Direct and Selective Activation of Aliphatic C-H Bonds

A photocatalytic three-component alkene difunctionalization method for the direct and selective activation of aliphatic C-H bonds is developed. The significant advantages of this strategy are that the most abundant hydrocarbons are used as feedstocks, and various highly functionalized tertiary, secondary and primary C(sp3)-hybrid centers can be easily installed. The practicability of this strategy is demonstrated in the selective late-stage functionalization of natural products and the concise synthesis of pharmaceutically relevant molecules including Piragliatin.