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Solid-Phase Photochemical Decarboxylative Hydroalkylation of Peptides

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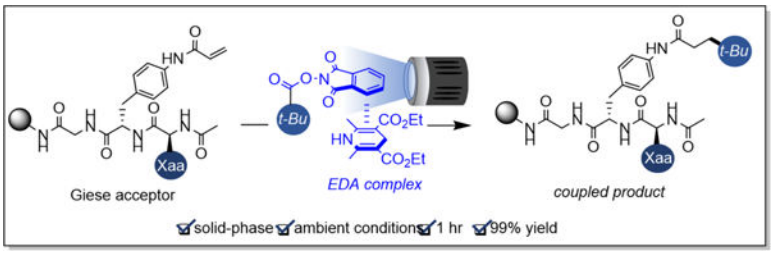
Abstract

The compatibility of photochemistry with solid-phase peptide synthesis is demonstrated via photochemical hydroalkylation to form C(sp^3)-C(sp^3) bonds between on-resin Giese acceptors and redox-active esters. Both iridium-based photocatalysts and Hantszch ester led to high yields, with final reaction conditions producing full conversions within 30 minutes under ambient conditions. The chemistry is compatible with a broad range of peptide sidechains, redox-active esters, and resin. These conditions represent the first example of photochemical peptide modifications on resin.

Graphical Abstract



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Since the advent of solid-phase peptide synthesis (SPPS) in 1963, over 60 peptide pharmaceuticals have been approved in the US, Europe, and Japan, more than 150 peptides are currently undergoing clinical development, and over 260 have been investigated in human clinical trials.[1] SPPS depends greatly on the adaptation of solution-phase reactions to solid-phase conditions. As examples, since the 1990s, C-C bond-forming transformations such as the Stille,[2] Heck,[3] Suzuki-Miyaura,[4] and Sonogashira[5] reactions have been adapted to solid-phase by both industry and academia. Additionally, in 1996, the first example of solid-phase ruthenium-catalyzed metathesis was reported, and soon after, the first solid-phase peptide ring-closing metathesis (RCM) reaction was communicated.[6,7] Since that time, RCM has been extensively used to form hydrocarbon-stapled peptides in biotherapeutics.[8] Although peptide macrocycles generated via RCM can be reduced to $C(sp^3)$-$C(sp^3)$ bonds, few direct routes to such structures exist under mild conditions.

Recently, Baran et al. reported two nickel-catalyzed decarboxylative conjugate addition procedures and demonstrated their compatibility with solid-phase conditions.[9,10] Both procedures utilize nickel-catalyzed cross-coupling mechanisms to forge $C(sp^3)$-$C(sp^3)$ bonds under inert conditions and required 8–16 h reaction times. Given the importance of solid-phase peptide $C(sp^3)$-$C(sp^3)$ bond formation, an alternate route through a complementary mechanistic pathway was deemed desirable.

Although photochemistry on peptides and proteins has been a very active field,[11,12] to our knowledge, no studies on the compatibility of photochemistry with on-resin peptides have been reported. The application of photochemistry to solid-phase peptide synthesis offers several distinct advantages over extant protocols. First, photo-chemically induced reactions involving open-shell intermediates exhibit extraordinary toleration of diverse functional groups. Additionally, light-mediated transformations typically operate at room temperature and permit the use of buffers or aqueous mixtures that offer biocompatible reaction conditions. The reliance on photon flux also allows the exclusion of light to quench reactions and control reaction progression precisely and conveniently.[13] Finally, dual photocatalytic cycles have enabled multi-component reactions, ideal for making diverse peptide macrocycles and bicycles in a single, mild synthetic step.[14]

With a goal to elaborate peptides by photoinduced Giese-type reactions on solid support, several procedures were assessed. In the seminal solution phase, photosensitized decarboxylative Giese addition reported by Okada,[15] redox-active esters (RAEs) were employed as radical precursors and coupled with Giese acceptors in the presence of 1-benzyl-1,4-dihydronicotinamide as a reductant and Ru(bpy)3Cl2 as a photocatalyst in aqueous THF.[15] Up to 69% yields were reported. However, the scope of redox-active esters was limited to three hydrocarbons. Given the structural complexity of polypeptides, reaction conditions with high functional group tolerance were imperative. Furthermore, the Okada reaction conditions utilized an aqueous reaction medium, which was expected to be challenging for nonpolar peptide substrates.

In 2015, Overman et al. reported a solution-phase decarboxylative Giese-type addition involving a reductive single electron transfer (SET) of redox-active esters via photoredox catalysis.[16] The contribution by Overman and coworkers involved the photochemical

coupling of various Giese acceptors and tertiary radicals generated from corresponding redox-active esters at room temperature and in dichloromethane as solvent.[16] The reaction employed Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate, HE), $Ru(bpy)_3(BF4)_2$, and *i*-Pr_2NEt, and featured a broad substrate scope for both coupling partners. A visible light-induced approach to the synthesis and chemical modification of solid-phase peptides was thus initiated based on Overman's mild photochemical hydroalkylation.

We began our studies using Chem Matrix Rink Amide resin, which features a PEG-based polymer, rather than polystyrene, to avoid potentially reactive aromatics. Aromatic Giese acceptor 1 was employed for ease of analysis by LC-MS and ^{1}H NMR. Acrylamide was chosen as the electron deficient olefin over acrylate for its ease of incorporation into peptides. Installation of the solid-phase Giese acceptor began with synthesis of Fmoc-(4-acrylamide)-Phe-OH, which was then incorporated onto resin. The Fmoc group was deprotected using non-nucleophilic DBU, and subsequently the substrate was acylated on the N-terminus. Alternatively designed as a late-stage peptide modification, Fmoc-(4-Trt-amino)-Phe-OH was incorporated onto the resin. After N-terminal deprotection and acylation, the Trt group was removed, and the aniline was reacted with acrylic acid and (1-cyano-2-ethoxy-2-oxoethylidene-aminooxy)dimethylamino-morpholino-carbenium hexafluorophos-phate (COMU). The purity of crude material in this protocol was 86% as judged by analytical HPLC (SI, S15).

Attempts to optimize the coupling of on-resin olefin (**1**) with 1-adamantyl *N*-(acyloxy)phthalimide (**2a**) rapidly generated fruitful conditions with $Ru(bpy)_3(PF_6)_2$ as photocatalyst and *i*-Pr_2NEt as reductant in DMF with blue LED irradiation at room temperature. These conditions produced the coupled product **3a** with a 30% conversion (Table 1, entry 1). Examination of photocatalysts identified $[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$ ($E^{1/2}$ M*/M- = +1.32 V)[17] as a suitable catalyst for the solid-phase photocoupling (Table 1, entries 2–5). A similar conversion was observed using the Rink amide polystyrene resin (Table 1, entry 6). Lowering the reaction time below 16 h proved detrimental to the reaction yield (SI, S7). The use of THF as a solvent, which was advantageous for the coupling of *tert*-alkyl *N*-phthalimidoyl oxalates,[18] decreased the conversion to **3a** to 89% (Table 1, entry 7). In the absence of light, no product was observed (Table 1, entry 8). Excluding the photocatalyst or *i*-Pr_2NEt resulted in product formation with substantially diminished yields (Table 1, entries 9–10), demonstrating that the superstoichiometric amine reductant was ineffective at fragmenting redox-active esters. Comparable results in the absence of the photocatalyst were observed by Okada and co-workers in the initial decarboxylative Michael addition report.[15] The addition of Hantzsch ester as a reductant generated superior yields (Table 1, entry 11) particularly for primary re-dox-active esters (SI, S8). A similar yield and conversion were produced in the absence of the photocatalyst (SI, S8).

After incorporating the Hantzsch ester, a reaction time screen revealed full conversions within 30 minutes (SI, S9). Control studies produced similar NMR yields under air and without the amine base (Table 2, entries 1–3). Conversion of 100% was also observed using Rink amide polystyrene resin (Table 2, entry 4).Comparable catalyst-free conditions were reported in the original Okada report, as well as by Overman and Shang in the solution

phase.[15,16,19] No product was formed in the absence of light or Hantzsch ester (Table 2, entries 4–5). Increasing the number of equivalents of Hantzsch ester and redox-active ester resulted in no improvements, while reducing the equivalents of these reactants led to inconsistent results (SI, S10).

Although Overman proposed a photocatalytic reduction of the redox-active esters (Scheme 1A),[16,20] recent investigations have revealed that the reduction takes place largely via a light-induced charge transfer within an electron donor-acceptor (EDA) complex formed between the Hantzsch ester and the redox-active ester (Scheme1B).[21] Photoactivation of the EDA complex induces an inner sphere electron transfer from the Hantzsch ester to the redox-active ester, leading to carbon-centered radical **III** via hemolytic fragmentation and decarboxylation. The radical then adds to the electron-deficient olefin and generates intermediate **IV**, which abstracts a hydrogen atom from the oxidized Hantzsch ester to generate pyridinium salts to furnish the desired hydroalkylation product. Because of the speed, cost, and operational simplicity of the catalyst-free conditions, they were utilized to explore the scope of the process.

The performance of the hydroalkylation using a series of simple redox-active esters was first investigated (Scheme 2). The on-resin Giese acceptor coupled efficiently with primary, secondary, and tertiary alkyl RAE partners. Tertiary (**3b**) and secondary (**3f**) carboncentered radicals performed nearly identically, while their primary analogues produced diminished yields, except for α-benzyloxy radical (**3i**) and Boc-β-alanine (**3p**). Cyclic redox-active esters, including adamantyl (**3a**), 3-cyclopentenyl (**3d**), and cyclohexyl (**3e**), all converted to the desired product with excellent yields. NHPI esters featuring nitrogen- (**3h**, **3p**), oxygen- (**3n**), and sulfur-based (**3k**, **3o**) heterocyclic moieties were also compatible with the hydroalkylation protocol.

Cycloadditions between terminal alkynes and azides (“click chemistry”) are widely utilized for bioorthogonal transformations in which considerations of reaction efficiency, chemical inertness, cost, and compatibility with aqueous conditions are paramount. An alkynyl-substituted RAE was synthesized and found to deliver a 58% yield of **3j**. The moderate yield was expected because of the difficulty of generating primary radicals as well as their reduced nucleophilicities. Furthermore, reports of terminal alkynes undergoing decarbox-ylative radical addition to form alkenes suggested a loss of reactant may be partially responsible as well.[22,23] The interaction between biotin and streptavidin is one of the strongest in nature and widely utilized in biology and biochemistry (Kd = 10^{-15} M).[24] A biotinyl-substituted RAE was synthesized and found to react with the solid-phase substrate in 86% yield; high given the yields of other primary RAEs (**3o**).

We subsequently incorporated an example of a PEGylation (**3m**) featuring an α-alkoxy group that conveniently aided radical generation. Mini-PEGs are frequently used to tune the lipophilicity of bio-molecules. A coumarin moiety was also reasonably well-tolerated by the reaction protocol (**3n**). Coumarins are found in a broad range of medicinally relevant natural products, synthetic pharmaceuticals, and fluorescent labels.[25,26] The low yield of coumarin **3n** is likely a result of the low nucleophilicity of the highly stabilized radical generated (*vide infra*). Recognition of protein conformers by fluorine NMR necessitates the integration of

fluorinated moieties whose chemical shifts are responsive to slight variations in the local dielectric and magnetic shielding environment. To that end, an NHPI ester incorporating a fluorine (^{19}F) NMR tag[27,28] was evaluated, with the 3,5-bis(trifluoromethyl)phenyl moiety **3l** selected as a model fluorine probe that was successfully coupled with a reasonable yield. A single ^{19}F-NMR peak confirmed the presence of the fluorine (^{19}F) NMR tag (SI, S70).

The amenability of resonance stabilized radicals, which exhibit lower nucleophilicities than localized carbon-centered radicals, was also examined. Unfortunately, the success of substrates generating such stabilized radicals was limited. Products **3l** and **3n** derived from primary resonance stabilized radicals were obtained in 50% and 26% yields, respectively. Neither secondary nor tertiary benzylic RAE substrates produced product (**3c, 3g**), perhaps because of the combination of steric and stabilizing resonance effects.

The abundance of structurally diverse, commercially available amino acids makes them a particularly appealing radical feedstock for peptide modification. They are also attractive building blocks because the amine functional group promotes radical addition and provides a site for further functionalization and peptide elongation. The scope of the coupling using α-amino alkyl radical precursors was therefore evaluated. Couplings employing Boc-, CBz-, Alloc-, and Fmoc-protected prolines all produced excellent yields (**3q-3u**). Fmoc protection is seldom used in photochemistry, but it is used abundantly with SPPS. Fmoc-proline was well-tolerated, albeit with a slightly diminished yield of 72%.

Toleration of the transformation to structural and functional complexity was further evaluated using a series of tripeptides (Scheme 3). The Giese acceptor was incorporated as a late-stage modification to prevent attack of the N-terminus on the Giese acceptor during peptide elongation. His, Trp, Cys, Met, and Tyr moieties have all participated in photochemistry under various solution-phase conditions,[12] but their behavior under similar conditions protected on solid phase has not been tested. In the event, tripeptides incorporating these amino acid derivatives exhibited high conversions and yields.

The amenability of aliphatic Giese acceptors was then demon-strated by on-resin acrylation of lysine **6** and subsequent reaction with CBz-Pro-NHPI (Scheme 4). A 98% yield was observed. Next, 15-mer collagen-model peptide **7** was synthesized and acylated on the N-terminus. A reaction with CBz-Pro-NHPI led to full conversion by HPLC (SI, S112).

In summary, the development of the photochemical hydroalkylation of electron-deficient olefins has been reported in the solid phase. These conditions offer mild, expeditious, and operationally simple routes for introducing C(sp^3)-C(sp^3) bonds to peptides on resin. They also represent the first example of a light-mediated peptide modification in the solid-phase and demonstrate the potential for further elaboration of polypeptides on solid support.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

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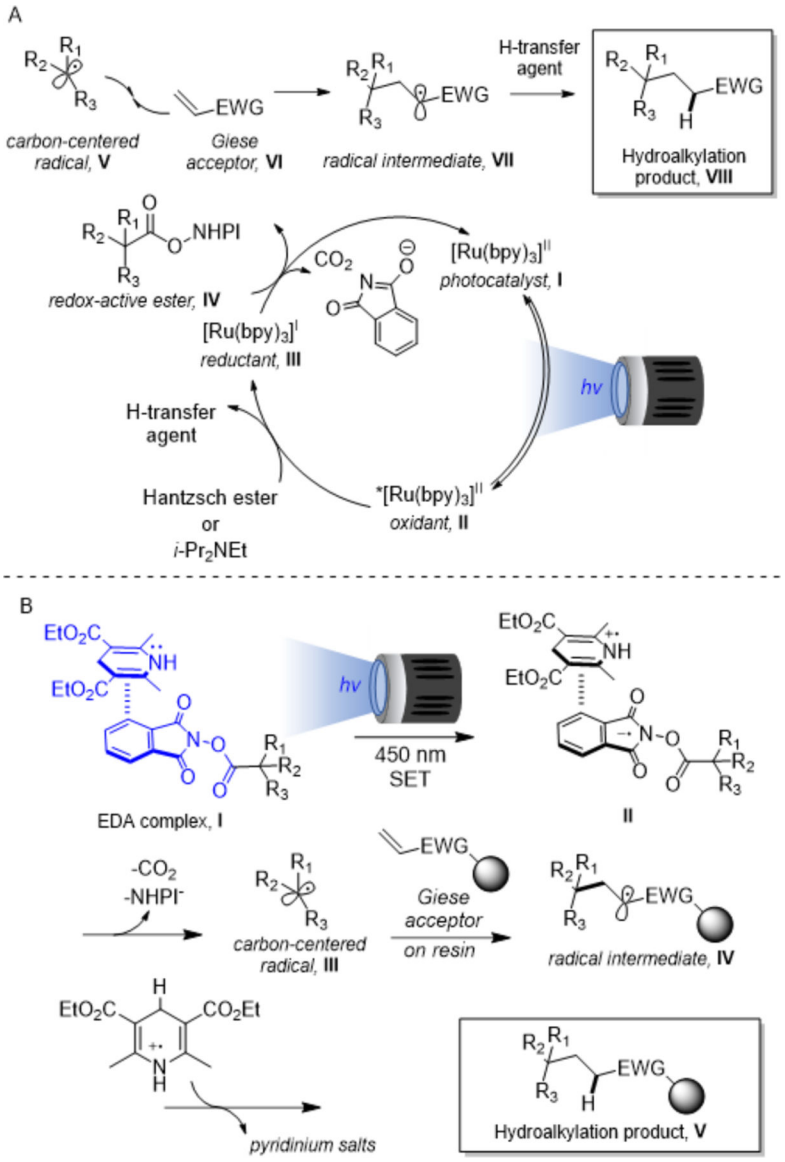
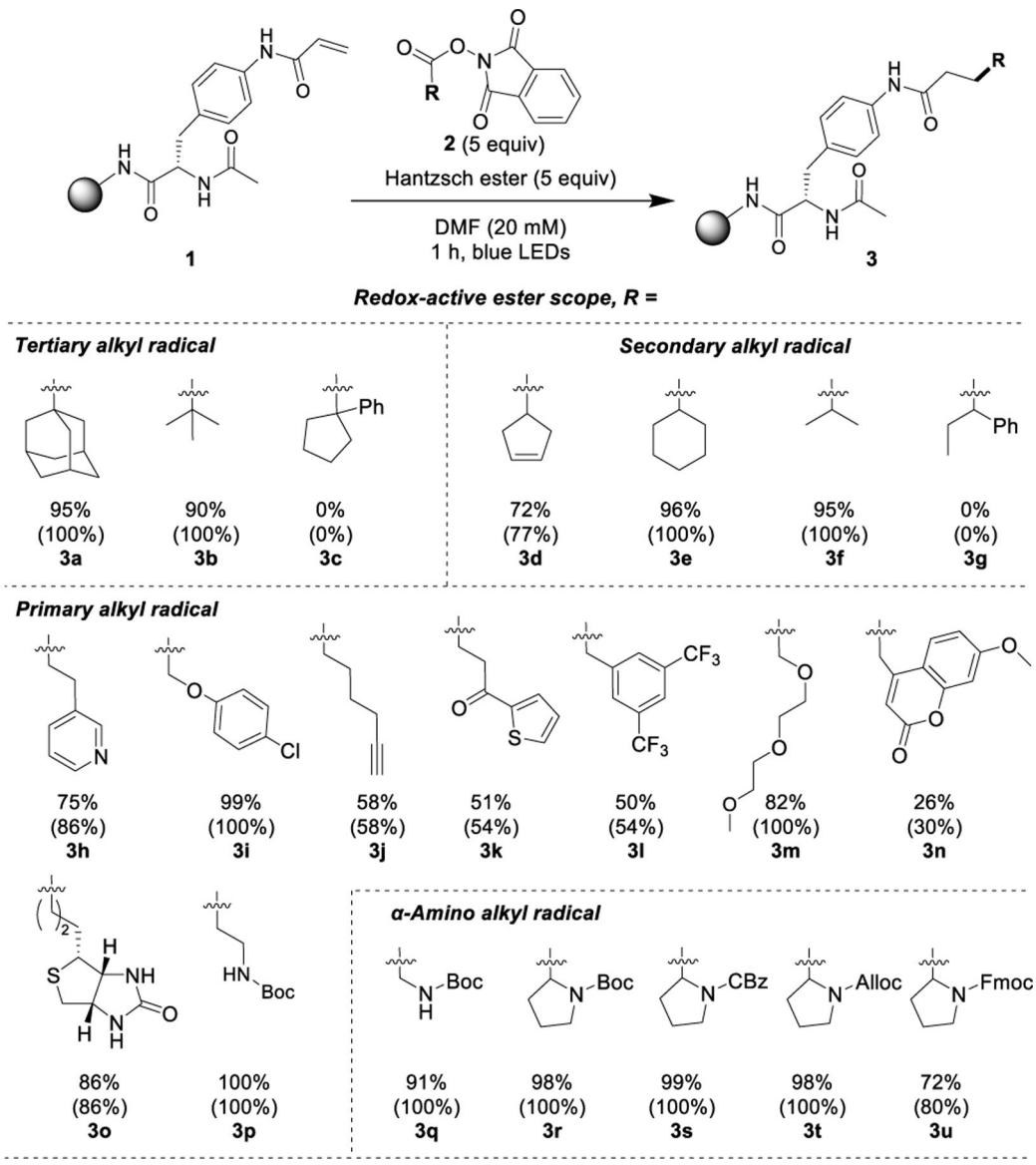


Scheme 1. Mechanistic View of the Light-Mediated Decarboxylative Hydroalkylation

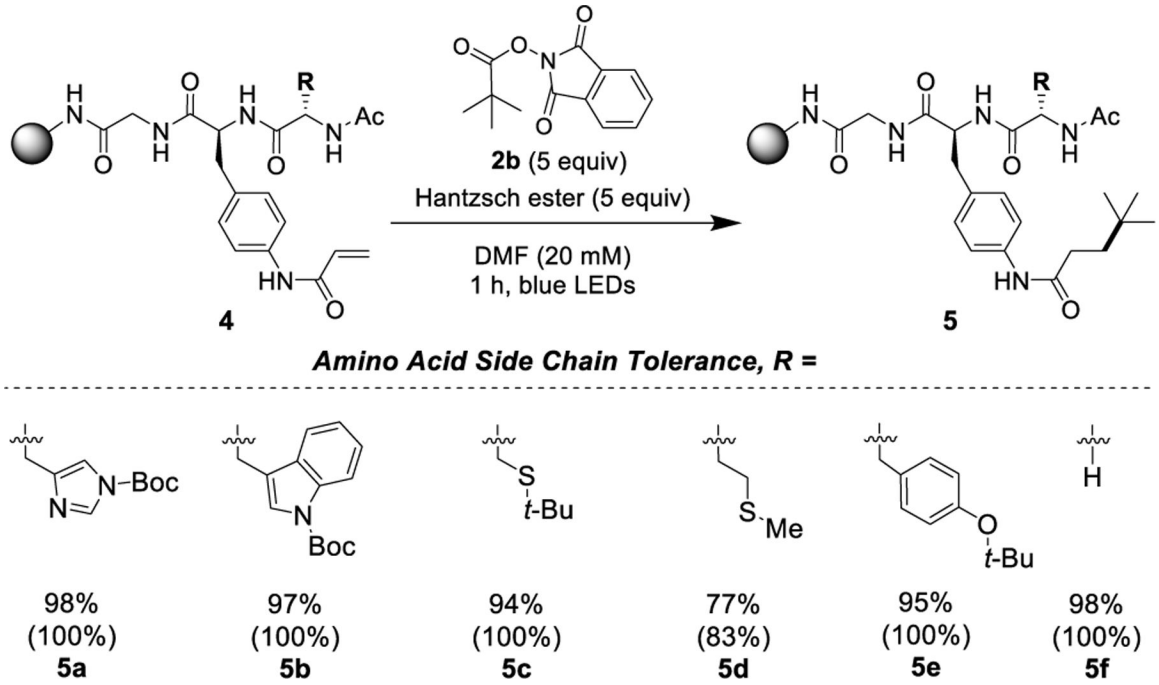
(A) Envisioned mechanism for the photocatalytic decarboxylative hydroalkylation.

(B)Mechanistic view of the catalyst-free photochemical decarboxylative hydroalkylation.



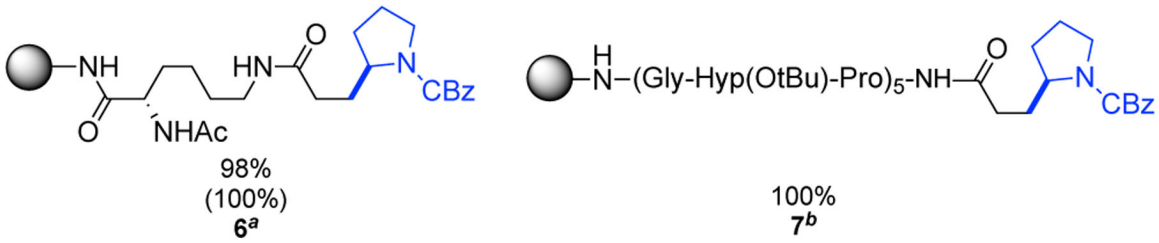
Scheme 2. Scope of Solid-Phase Photochemical Hydroalkylation[a]

[a]Yields determined by quantitative ^{1}H NMR; conversions determined by quantitative ^{1}H NMR and reported in parentheses.



Scheme 3. Tolerance of Various Amino Acid Side Chains[a]

[a]Yields determined by quantitative ^{1}H NMR; conversions determined by quantitative ^{1}H NMR and reported in parenthesis.

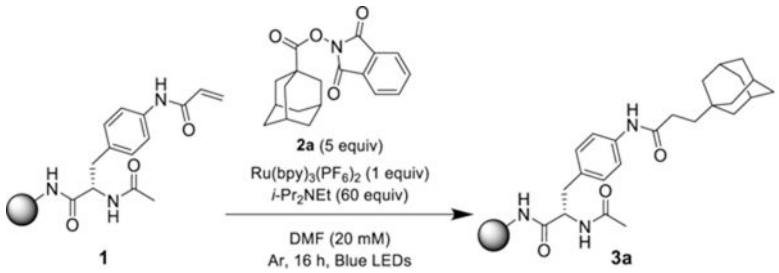


Scheme 4. Tolerance of Aliphatic Giese Acceptors

[a]Yield determined by quantitative ^{1}H NMR; conversions determined by quantitative ^{1}H NMR and reported in parenthesis. [b]Conversion determined by HPLC.

Table 1.

Optimization of Solid-Phase Photocatalytic Hydroalkylation Conditions



entry	deviation from initial conditions	3 (P/IS[a])	3 (conv, %[b])
1	none	0.26	30
2	$[Ir\{dF(CF_3)ppy\}_2(bpy)]PF_6$	0.38	100
3	$[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$	0.31	88
4	4CzIPN[c]	0.14	59
5	Cl-4CzIPN[d]	0.10	31
6	entry 2 with polystyrene resin	0.38	100
7	THF	0.24	89
8	no light	0.00	0
9	no *i*-Pr_2NEt	0.03	7
10	no photocatalyst	0.09	14
11	5 equiv Hantzsch ester	0.40	100

[a]Product-to-internal standard ratio as determined by LC/MS.

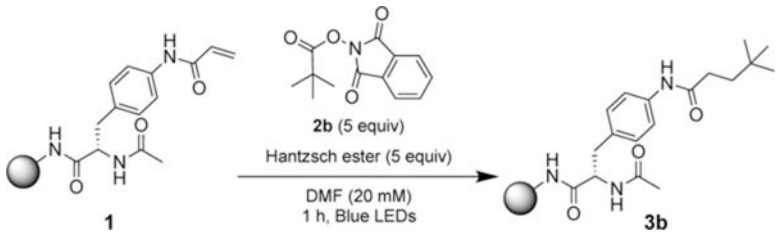
[b]Conversion to 3a as determined by LC/MS. PC = photocatalyst.

[c]1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene.

[d]2,4,5,6-Tetrakis-(3,6-dichloro-9H-carbazol-9-yl)isophthalonitrile

Table 2.

Development of Solid-Phase, Metal-Free Photochemical Hydroalkylation Conditions



entry	deviation from initial conditions	3b (conv[a])	3b (% yield[a])
1	none	100	90
2	under argon	100	88
3	under argon with DIPEA	100	90
4	Rink amide polystyrene resin	100	90
5	no Hantzsch ester	0	0
6	no light	0	0
7	>5 equiv HE and RAE	no improvement	no improvement
8	<5 equiv HE and RAE	inconsistent conv	inconsistent yield

[a]Product yield and conversion determined by crude NMR.