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Hydroalkylation of Alkenes Using Alkyl Iodides and Hantzsch Ester under Palladium/Light System

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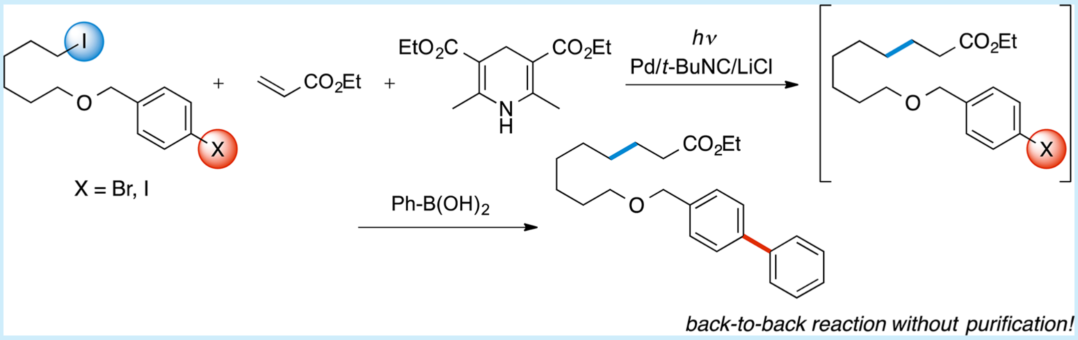
S Supporting Information



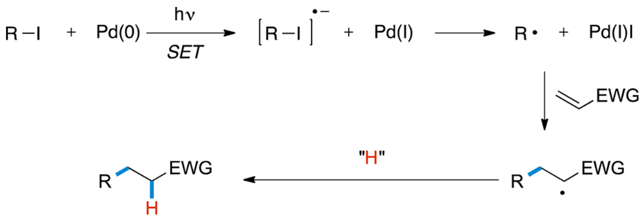
back-to-back reaction without purification!

ABSTRACT: The hydroalkylation of alkenes using alkyl iodides with Hantzsch ester as a hydrogen source occurred smoothly under a Pd/light system, in a novel, tin-free Giese reaction. A chemoselective reaction at C(sp^3)−I in the presence of a C(sp^2)−X (X = Br or I) bond was attained, which allowed for the stepwise functionalization of two types of C−X bonds in a one-pot procedure.

The addition of radicals to alkenes is among the most basic of radical reactions. The Kharasch[1] and Giese reactions[2−4] both proceed with a radical chain composed of radical addition to alkenes followed by S_H2 reaction delivering halogen and hydrogen, respectively. There has been a recent renewal of interest in palladium-assisted radical reactions using alkyl iodides[5−7] whereby a SET (single electron transfer) process from Pd(0) to alkyl iodides is typically proposed for the generation of alkyl radicals/PdI radical pair as a first event. Based on this concept, we previously developed a series of cascade carbonylation reactions using alkyl iodides, CO, and coupling reagents using a Pd/light combined system[6] in which CO trapping by alkyl radicals ultimately leads to the formation of acylpalladium intermediates.[8]

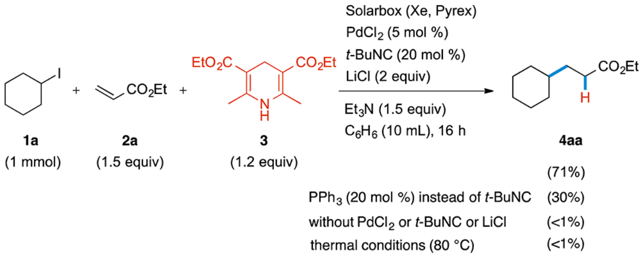
We expected that such a Pd/light combined system would be applicable even to a tin-free Giese reaction, as outlined in Scheme 1. A key issue here was deciding what reagent would work as a hydrogen source in the presence of a Pd complex. We focused on the use of Hantzsch ester, which has been used successfully in radical reductions[9] and glycosylations[10] based on photoredox catalysts such as Ir(ppy)$_3$ and [Ru(bpy)$_3$](BF$_4$)$_2$. In this paper, we report that a palladium/light system worked well to achieve the Giese-type reaction of alkyl iodides with electron-deficient alkenes by introducing Hantzsch ester as a hydrogen source.

Scheme 1. Concept: Pd/Photoirradiation System for Tin-Free Giese Reaction



As expected, under photoirradiation (SolarBox; 1500 W of xenon lamp in a box, for details see the Supporting Information) the reaction of iodocyclohexane **1a**, ethyl acrylate **2a**, and Hantzsch ester **3** in benzene in the presence of Et$_3$N and a catalytic amount of PdCl$_2$ and PPh$_3$ proceeded to give the desired Giese addition product **4aa** in a 30% yield (Scheme 2). Without Hantzsch ester **3**, the Giese product would not form.

Scheme 2. Photoinduced Reductive Radical Addition of Iodocyclohexane 1a to Ethyl Acrylate 2a



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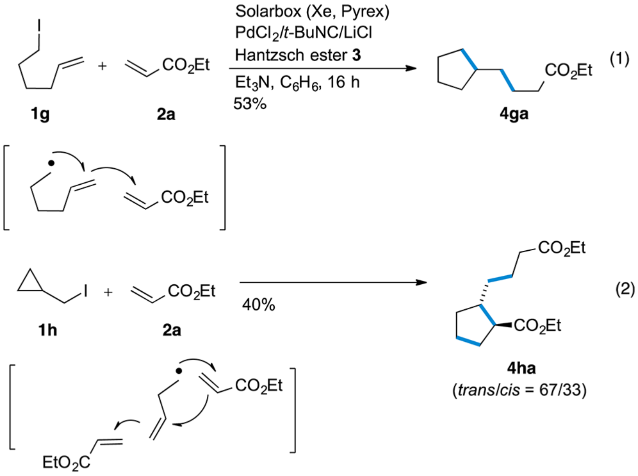
Changing the ligand from PPh_3 to *t*-BuNC[11] in benzene improved the yield of **4aa** to 71%. In the absence of a Pd catalyst, *t*-BuNC, or LiCl, only a trace amount of **4aa** was observed. No reaction took place under thermal conditions (80 °C).

Table 1 demonstrates the general nature of the present reductive alkylation of alkenes **2** by iodoalkanes **1** and Hantzsch ester **3**. A series of substituted *α*,*β*-unsaturated esters **2b**–**f** were examined (entries 2–6). The reaction of **1a** with ethyl crotonate **2b**, dimethyl maleate **2d**, and Me- and Ph-substituted ethylidene malonate **2e** and **2f** gave the corresponding addition products **4ab**–**af** in moderate to good yields. In contrast, the reaction of **1a** with methyl methacrylate **2c** gave **4ac** in a rather poor yield of 38% (entry 3). Other alkenes with an electron-deficient group, such as ethyl vinyl ketone **2g**, acrylonitrile **2h**, and phenyl vinyl sulfone **2i**, also gave the alkylation products **4ag**–**ai** in good yields (entries 7–9). The reaction of **1a** with cyclohexenone **2j** gave the desired product **4aj** in a modest yield of 48% (entry 10). Irrespective of whether the alkyl moiety of RI **1** was primary, secondary, or tertiary, the reaction worked quite well (entries 11–16).

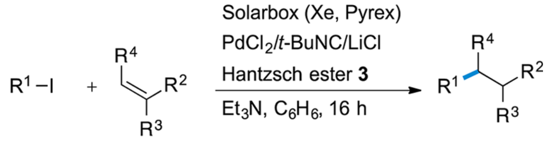
To confirm the intervention of radical species,[12] radical cascade reactions were examined (Scheme 3). The reaction of 6-iodo-1-hexene **1g** and **2a** gave ethyl 4-cyclopentylbutanoate **4ga** in 53% yield by way of 5-*exo* radical cyclization (Scheme 3, eq 1). (Iodomethyl)cyclopropane **1g** reacted with **2a** to give 1,2-disubstituted cyclopentane **4ha** in a 40% yield. In this reaction, an initially formed cyclopropylcarbinyl radical undergoes ring-opening to give a homoallyl radical,[13] which then adds to **2a** to form an *α*-carbonyl radical. The 5-*exo* cyclization and the addition of the resultant radical to the second molecule of **2a** followed by hydrogen abstraction from Hantzsch ester gives the product **4ha** (Scheme 3, eq 2). The *syn*/*anti* ratio of **4ha** was nearly the same as that of a previously established radical cyclization.[4c]

Scheme 3. Radical Cascade Reactions Using 6-Iodo-1-hexene 1g and (Iodomethyl)cyclopropane 1h

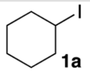
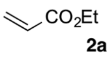
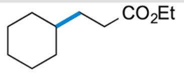
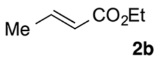
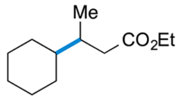
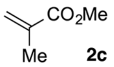
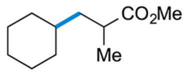
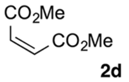
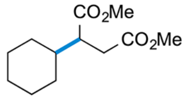
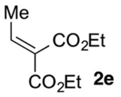
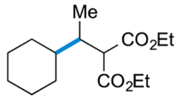
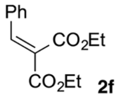
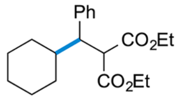
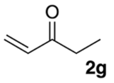
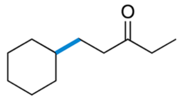
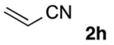
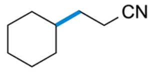
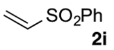
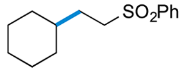
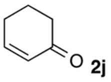
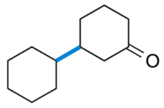
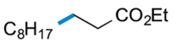
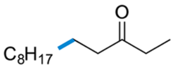
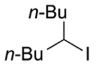
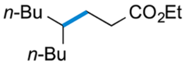
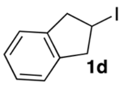
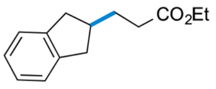
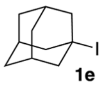
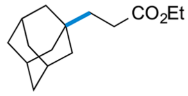
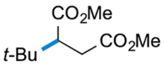


We then examined the chemoselectivity of the reaction using alkyl iodides **1i** and **1j** with a haloaryl moiety (Scheme 4). The alkylation reactions of **1i** or **1j** with **2a** proceeded chemoselectively at the $C(sp^3)$–I bond, leaving $C(sp^2)$–X bonds for the next functionalization (Scheme 4, eq 3). The crude products **4ia** and **4ja** were exposed to the standard conditions of Suzuki–Miyaura raection without additional Pd, which gave the

Table 1. Reaction of Alkyl Iodides 1 and Alkenes 2 under the Pd/*hν* System

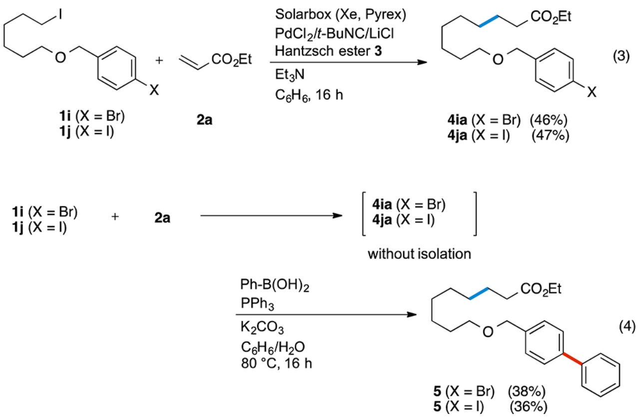


1 2 4

entry	1	2	4	yield (%)
1	 **1a**	 **2a**		**4aa** 71%
2	**1a**	 **2b**		**4ab** 55%
3	**1a**	 **2c**		**4ac** 38%
4	**1a**	 **2d**		**4ad** 72%
5	**1a**	 **2e**		**4ae** 73%
6	**1a**	 **2f**		**4af** 64%
7	**1a**	 **2g**		**4ag** 75%
8	**1a**	 **2h**		**4ah** 77%
9	**1a**	 **2i**		**4ai** 88%
10	**1a**	 **2j**		**4aj** 48%
11	C_8H_{17}–I **1b**	**2a**		**4ba** 67%
12	**1b**	**2g**		**4bg** 61%
13	 **1c**	**2a**		**4ca** 60%
14	 **1d**	**2a**		**4da** 62%
15	 **1e**	**2a**		**4ea** 68%
16	*t*-Bu–I **1f**	**2d**		**4fd** 66%

[a]Reaction conditions **1** (1 mmol), **2** (1.5 equiv), **3** (1.2 eqiuv), $PdCl_2$ (5 mol %), *t*-BuNC (20 mol %), LiCl (20 mol %), Et_3N (1.5 equiv), C_6H_6 (10 mL), 16 h, *hν* (SolarBox (Xe, 1000 W/m^2), Pyrex).

Scheme 4. Chemoselective Reaction of 1i and 1j with Alkyl–I and Aryl–X Moieties (X = Br, I)



arylated products **5ia** and **5ja**, respectively (Scheme 4, eq 4). Although the chemoselective reaction was achieved, moderate yields of **4ia** and **4ja**, which are due to the side reactions of key alkyl radicals to add to two molecules of ethyl acrylate and H-abstraction from α-position to ether oygen, requires further optimization of the reaction conditions. On the other hand, it should be noted that GC–MS analysis of the crude reaction mixture indicated that the reduction of the yields of **5** is partly because of Pd-catalyzed aromatic reduction of **4ia** and **4ja** with Hantzch ester remaining in the one-pot procedure.

Whereas an appreciable byproduct of the reaction of **1b** with **2a** (Table 1, entry 11) was diester **7** (>10%), which incorporated two molecules of ethyl acrylate **2a**, octane **6**, a simple reduction product, was detected in only a trace amount (Figure 1). This suggests that while a reduction of the adduct α-carbonyl radical by Hantzsch ester is sluggish, that of the parent octyl radical is far more sluggish.[10a]

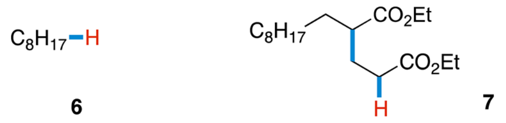
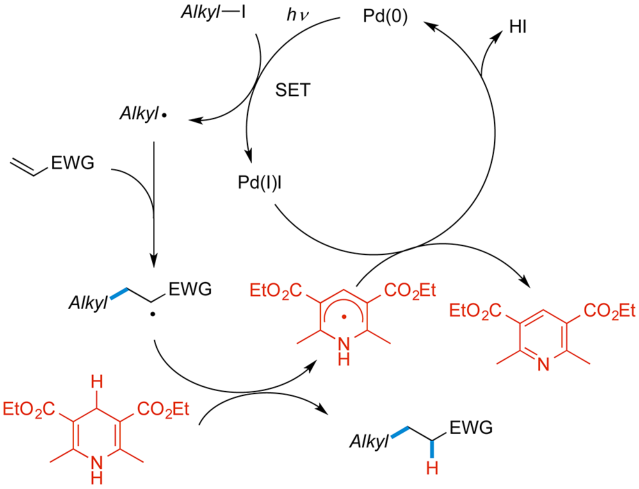


Figure 1. Byproducts.

A plausible reaction mechanism is illustrated in Scheme 5. First, alkyl radicals are generated by the reaction of alkyl iodides and Pd(0) under photoirradiation via a SET process, which is then added to olefins. The resultant radicals abstract hydrogen at the 4-position of Hantzsch ester to give the products and a dienyl radical, which reacts with the Pd(I) species to give Pd(0), HI, and a pyridine derivative.

In summary, we have demonstrated a new protocol for the Giese-type reductive alkylation of alkenes by alkyl iodides, which uses Hantzsch ester as a hydrogen source and a Pd/photoirradiation system to promote radical generation. The reaction can be applied to cascade reactions involving 5-*exo* cyclization and the ring opening of a cyclopropylcarbinyl radical. Unlike the original tin hydride conditions reported by Giese, a chemoselective reaction is possible in spite of the $C(sp^2)$–X (X = Br, I) bonds. Further synthetic applications of this new combination of a Pd/light system with Hantzsch ester are currently underway in this laboratory.

Scheme 5. Proposed Reaction Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03238.

Typical experimental procedure and characterization for all products (PDF)

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Notes

The authors declare no competing financial interest.

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