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Intermolecular Photocatalyzed Heck-like Coupling of Unactivated Alkyl Bromides by a Dinuclear Gold Complex

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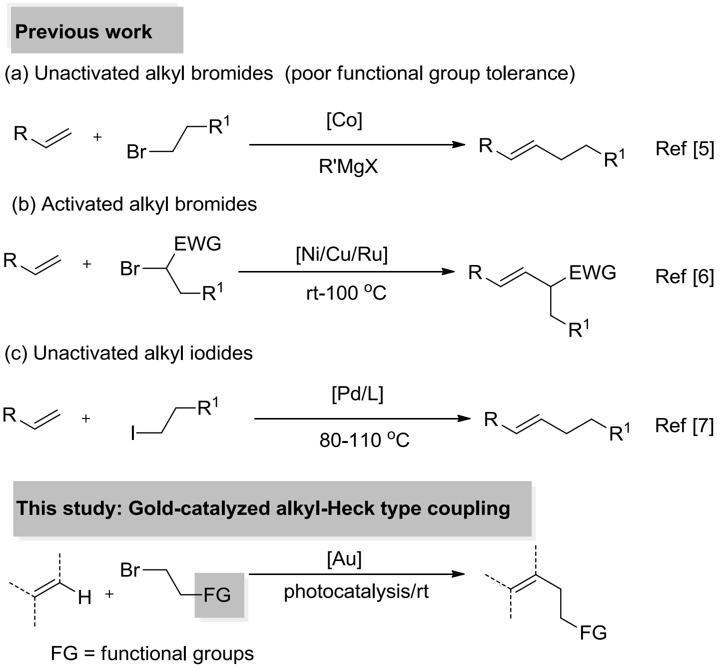
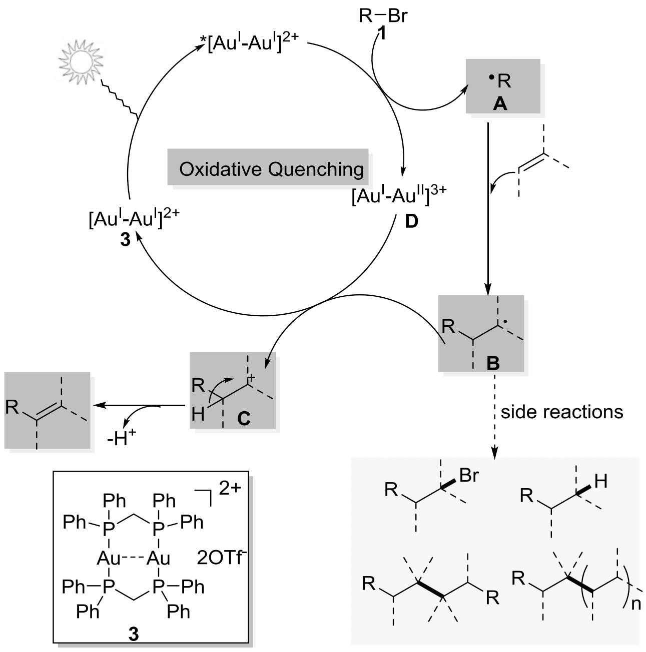
Abstract: A practical protocol for a photocatalyzed alkyl-Heck-like reaction of unactivated alkyl bromides and different alkenes by dinuclear gold photoredox catalysis in the presence of an inorganic base is reported. Primary, secondary and tertiary unactivated alkyl bromides with β-hydrogen can be applied. Esters, aldehydes, ketones, nitriles, alcohols, heterocycles, alkynes, alkenes, ethers and halogen moieties are all well tolerated. Besides 1,1-diarylalkenes also silylenolether and enamides can be applied which further increases the synthetic potential of the reaction. The mild reaction conditions, broad substrate scope and an excellent functional-group tolerance deliver an ideal tool for synthetic chemists that can even be used for challenging late-stage modification of complex natural products.

The development of efficient methods for the construction of new C-C bonds is a central problem of organic synthesis. One of the most important tools for C-C couplings is the Pd-catalyzed Heck reaction of alkenes. While the reaction with sp^2-halides is an widespread and well established protocol for synthetic chemistry and organic materials,[1] *unactivated* sp^3-halides are still intractable coupling partners, especially for intermolecular couplings.[2] This can be rationalized by their low rate for oxidative addition and their high tendency to undergo a fast *β*-hydride elimination.[3] To solve this problem, a transition-metal-mediated intermolecular radical alkyl-Heck like coupling was assumed to be a good choice.[4] In 2002, Oshima and co-workers developed an efficient Co-mediated radical Heck coupling of unactivated alkyl bromides with styrenes, but the requirement of stoichiometric alkylmetal reagents generally resulted in a poor functional group tolerance and thus in a limited applicability.[5] Recent efforts elegantly enabled a radical alkyl-Heck reaction of activated alkyl bromides[6] and unactivated alkyl iodides[7] in the absence of alkyl metal reagents. *However, despite these achievements, the use of unactivated alkyl bromides bearing versatile functional groups as starting materials remains a major challenge in this area.* To address this unsolved challenge, a general and efficient catalytic system to enable an alkyl-Heck coupling should meet the following requirements: 1) efficient generation of carbon-centered alkyl radicals from alkyl bromides under mild reaction conditions; 2) prevention of the oxidation of the generated, highly active initial alkyl radical; 3) compatibility with versatile functional groups. In this context we envisioned that the dinuclear gold-complex, which was recently established by Barriault's and our group as highly effective photocatalyst,[8] would allow to achieve this aim. Photoredox catalysis has already proven to be a powerful tool as it offers the opportunity to handle radical chemistry under mild reaction conditions.[9]



Scheme 1. Different strategies for an intermolecular radical Heck coupling of alkyl

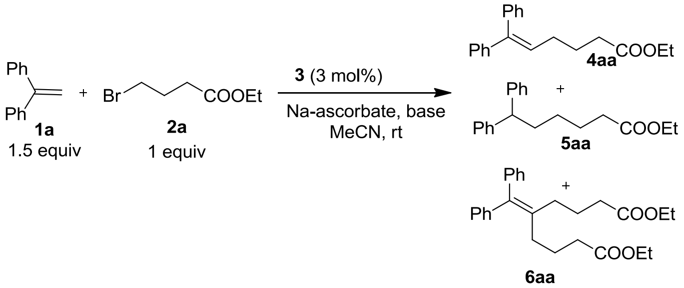
halides.



Scheme 2. Proposed mechanism.

Based on recent work about light-mediated reductive radical couplings of alkyl halides with alkenes in the presence of sacrificial electron and hydrogen donors,[10] we assumed that an oxidative quenching pathway of *unactivated* alkyl bromides might enable an intermolecular alkyl-Heck-like reaction (Scheme 2).[11] We first examined the alkyl-Heck coupling of the unactivated alkyl bromide **2a**[12] and styrene under UVA light (λ = 315-400 nm) with the dinuclear gold-complex **3**, which is known for its ability to form a high-energy photo-excited state with a strong reduction potential.[13] As no desired alkyl-Heck product was detected, we considered that a more stabilized, less reactive and easier oxidizable radical **B** would prevent competing side reactions (Scheme 2). Due to the lower reactivity of this radical, Br-atom transfer, H-atom abstraction, dimerization and oligomerization, all well-reported side reactions of photoredox catalysis, might be prevented that way.

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



Entry	Catalyst (3 mol%)	Base (equiv)	Yield of **4aa**[b]
1[c]	**3**	Et_3N (2)	36% (35% **5aa**)
2[c]	**3**	Bu_3N (2)	37% (36% **5aa**)
3[c]	**3**	$NaHCO_3$ (1.5)	71%
4	**3**	$NaHCO_3$ (1.5)	91%
5[d]	$Ir(ppy)_3$	$NaHCO_3$ (1.5)	0
6[d]	$Ru(bpy)_3Cl_2$	$NaHCO_3$ (1.5)	0
7[c,e]	$Pd(PPh_3)_4$ (10 mol%)	$NaHCO_3$ (1.5)	0
8[f]	**3**	$NaHCO_3$ (1.5)	57%
9	-	$NaHCO_3$ (1.5)	0
10[g]	**3**	$NaHCO_3$ (1.5)	0

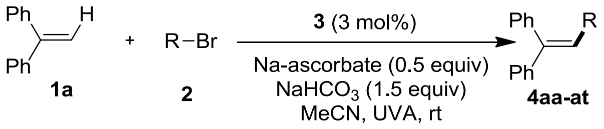
[a] Reaction conditions: 1,1-diphenylethylene **1a** (1.5 equiv), ethyl 4-bromobutanoate **2a** (0.2 mmol), catalyst (0-10 mol%), Na-ascorbate (0.5 equiv), base (1.5-2 equiv), MeCN (0.4 mL), UVA light (λ = 315-400 nm), 30-36 hours; [b] ^1H NMR yield determined with CH_2Br_2 as internal standard; [c] Without Na-ascorbate as additive; [d] Under irradiation with 12 W blue LEDs or 23 W CFL; [e] Heating at 100 ^{o}C for 36 hours; [f] 1.5 equiv **2a** and 1 equiv **1a** were tested; [g] In the dark.

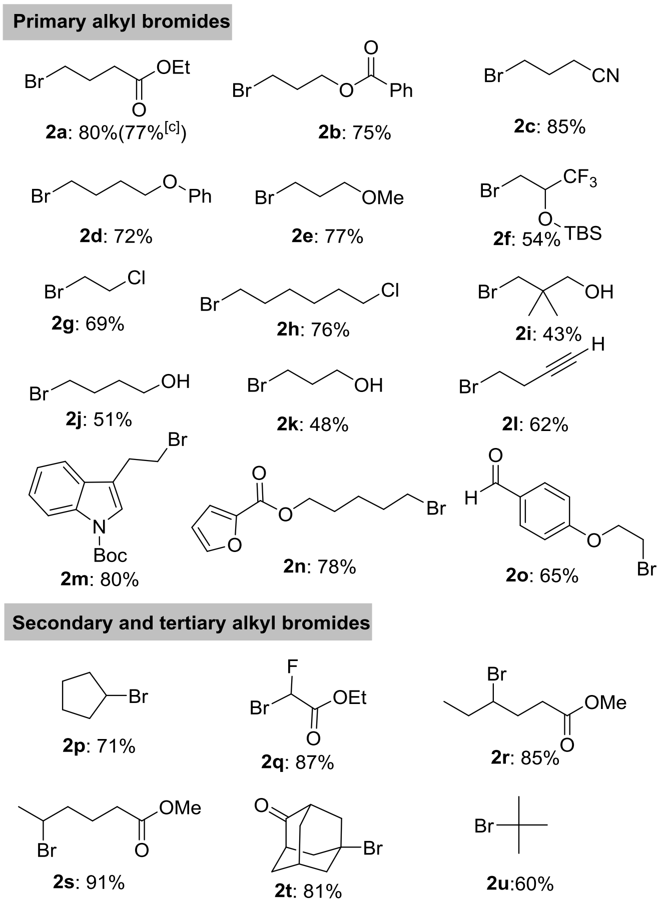
Based on this considerations, we turned our attention to 1,1-disubstituted alkenes in order to obtain a less reactive radical intermediate **B**. Indeed, the gold-catalyzed Heck-like cross coupling of 1,1-diphenylethylene **1a** and 4-bromobutanoate **2a** afforded the desired product **4aa** in moderate yield in the presence of tertiary amines, accompanied by significant amounts of undesired reduction product **5aa** and traces of a two-fold Heck reaction (**6aa**, Table 1, entries 1 and 2). As the poor selectivity could have been due to a competing reduction of the gold catalyst by the amine instead of radical **B**, other bases were considered next. When $NaHCO_3$ was used, the yield of

4aa reached 71% and no reduction product was observed (entry 3). Remarkably, the use of 0.5 equiv Na-ascorbate as additive could deliver **4aa** in an excellent yield of 91% (entry 4). We assumed that trace soluble Na-ascorbate in MeCN would inhibit the decomposition of unstable gold intermediate **D**. Other applied bases and solvents did not improve this alkyl-Heck coupling further (see Supporting Information for reaction condition optimization). Not surprisingly, photocatalysts with a weaker reduction ability failed to undergo the radical alkyl-Heck-like reaction (entries 5 and 6). When [Pd(PPh_3)$_4$] was used as catalyst, even upon heating to 100 °C no product **4aa** was observed (entry 7).[14] In addition, it was found that a slight excess of 1,1-diphenylethylene was beneficial for the Heck-like reaction (entry 4 *vs* entry 8). The control experiments demonstrated that the radical alkyl-Heck coupling could proceed neither in the absence of a dinuclear gold photocatalyst **3** nor in absence of light.

Under the optimized reaction conditions, a wide variety of unactivated alkyl bromides **2a-u** were examined (Table 2). In general, this protocol tolerates a broad scope of alkyl bromides. A number of versatile functional groups, such as, esters, aldehydes, ketones, nitriles, alcohols, heterocycles, alkynes, ethers and halogens, were compatible, and all of these test substrates delivered the desired alkyl-Heck-like coupling products **4aa-au** in moderate to good yields. The versatility of this gold-catalyzed alkyl-Heck-like coupling is also shown by its good tolerance of primary, secondary and tertiary alkyl bromides. This is noteworthy as it overcomes the difficulties of Pd-catalyzed *β*-elimination processes and thus enables the applicability of unactivated alkyl bromides bearing functional groups in alkyl-Heck reactions. When bromobenzene was used instead of alkyl bromides, little Heck product was produced.

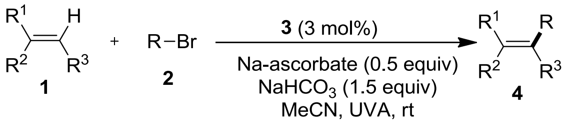
Table 2: The reaction scope with regard to alkyl bromides.[a]

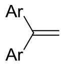
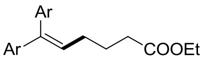
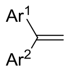
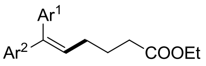


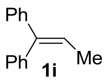
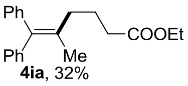
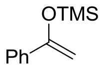
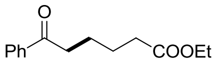
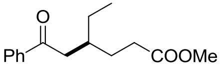
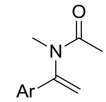
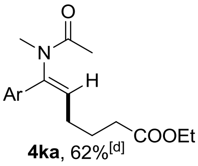
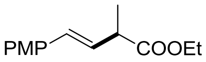
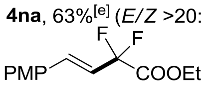
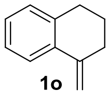
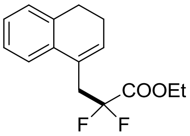


[a] Reaction conditions: Alkene **1a** (1.5 equiv), alkyl bromide (0.2 mmol), photocatalyst **3** (3 mol%), Na-ascorbate (0.5 equiv), $NaHCO_3$ (1.5 equiv), MeCN (0.4 mL), UVA light (λ = 315-400 nm), 30-36 hours. [c] 0.5 mmol scale.

Table 3: Reaction scope with regard to alkenes.[a]



Alkenes	Product and yield[b]
 **1a**: Ar = C_6H_5 **1b**: Ar = C_6H_4(4-F) **1c**: Ar = C_6H_4(4-OMe) **1d**: Ar = C_6H_4(4-Me) **1e**: Ar = C_6H_4(4-Cl)	 **4aa**, 80% **4ba**, 79% **4ca**, 54% **4da**, 81% **4ea**, 62%
 **1f**: Ar^1 = C_6H_5, Ar^2 = C_6H_4(2-OH) **1g**: Ar^1 = C_6H_5, Ar^2 = C_6H_4(2-OTBS) **1h**: Ar^1 = C_6H_5, Ar^2 = C_6H_3(3,4-diCl)	 **4fa**, 81% **4ga**,77% **4ha**, 65%

 **1i**	 **4ia**, 32%
 **1j**	 **4ja**, 68%[c]  **4jb**, 60%[c]
 **1k**: Ar = C_6H_5 **1l**: Ar = C_6H_4(4-Cl) **1m**: Ar = C_6H_4(4-Me)	 **4ka**, 62%[d] **4la**, 51%[d] **4ma**, 69%[d]
 **1n**	 **4na**, 63%[e] (*E/Z* >20:1)  **4nb,** 70%[e] (*E/Z* =10:1)
 **1o**	 **4oa,** 73%[e]

[a] Reaction conditions as mentioned in Table 2. *E/Z* ratio of **4fa-ha** range from 1.2:1 to 1:1. [b] Isolated yields. [c] 2.5 equiv **1j** were used. [d] 48 hours. [e] Alkene (0.2 mmol), activated alkyl bromides (1.5 equiv), $NaHCO_3$ (1.5 equiv), sunlight, 6-8 hours.

As shown in Table 3, a series of different alkenes was investigated next. All of the applied 1,1-diarylalkenes delivered the desired products **4aa-ha** in moderate to good yields, while trisubstituted alkene **1i** only gave a moderate yield most probably due to its steric hindrance. Importantly, electron-rich trimethylsiloxyethylene **1j** and enamides **1k-m** turned out to be good coupling partners, too. They directly yielded the long-chained ketones **4ja-jb** and enamides **4ka-ma** in satisfactory yields. Although styrene gave poor efficiency with the unactivated alkyl bromides, we found that they can smoothly undergo the alkyl-Heck coupling with activated alkyl bromides to deliver products **4na**, **4nb** and **4oa** in 63%-73% yield.

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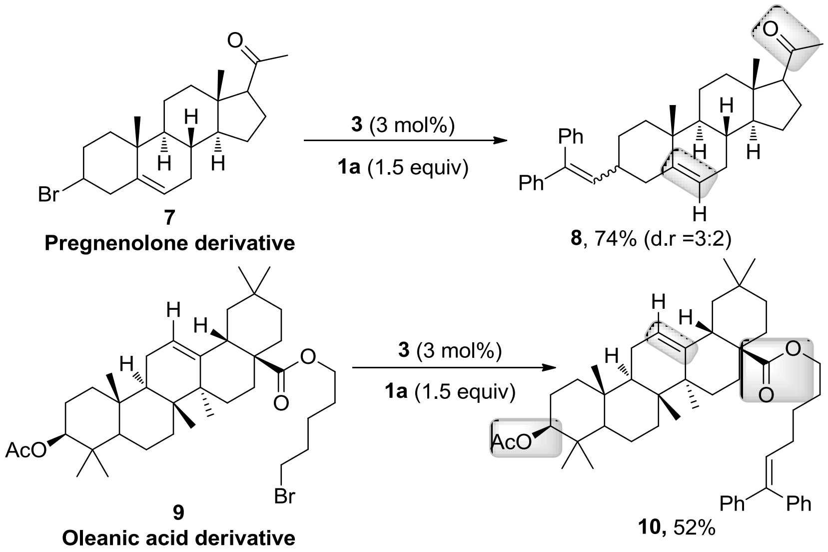
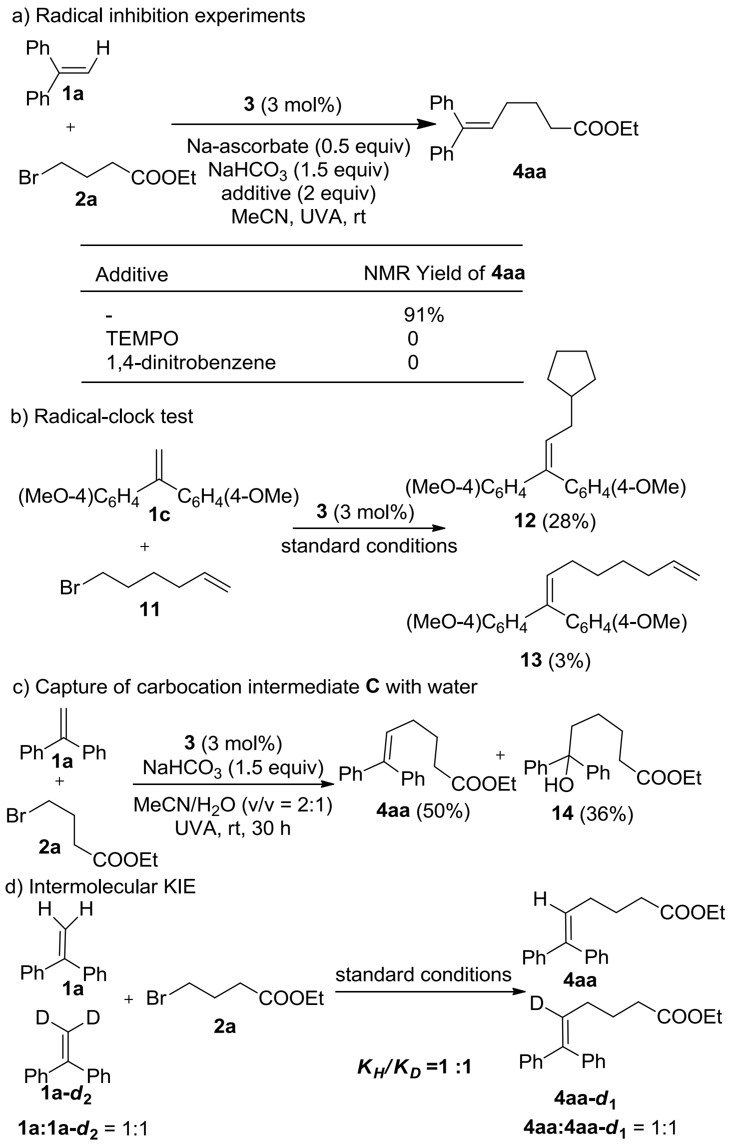


Scheme 3. Late-stage functionalization of bioactive molecules.

To demonstrate further the general applicability, the derivatives of biologically important pregenenolone and oleanic acid were subjected to the standard conditions (Scheme 3). Several important functional groups (alkene, ketone and ester moieties) are involved in these complex molecules, but despite this fact clean gold-catalyzed radical alkyl-Heck-like reactions furnished the desired products **8** and **10** in acceptable yields.

To support the proposed mechanism from Scheme 2, some mechanistic experiments were performed (Scheme 4). The addition of radical inhibitor TEMPO and electron-transfer scavenger 1,4-dinitrobenzene fully inhibited the alkyl-Heck reaction, which indicates that a radical pathway that proceeds through a single-electron transfer process is highly possible in this transformation. A radical-clock experiment with 6-bromohex-1-ene **11** further verifies a radical mechanism as the cyclic coupling product **12** was observed as the main product with only 3% of linear coupling product **13** (Scheme 4b). To capture a possible carbenium ion intermediate **C**, water was added to the reaction mixture and indeed the resulting tertiary alcohol **14** was isolated in 36% yield. The intermolecular competition KIE experimental result indicates that C-H bond cleavage is not involved in the rate-determining step of the alkyl-Heck process. At present, the mechanism depicted in Scheme 2 appears highly probable.



Additive	NMR Yield of **4aa**
-	91%
TEMPO	0
1,4-dinitrobenzene	0

Scheme 4. Studies to probe the reaction mechanism.

In conclusion, the new and practical protocol for a photocatalyzed alkyl-Heck-like reaction of unactivated alkyl bromides and different alkenes by dinuclear gold photoredox catalysis in the presence of an inorganic base overcomrd the inherent limitation of Pd-catalyzed Heck reactions of unactivated alkyl bromides. We anticipate that it will become a powerful protocol for the formation of such C(sp^2)-C(sp^3) bonds. Further studies on substrate scope and detailed mechanism are in progress.

Acknowledgement: Prof. Samir Zard at Ecole Polytechnique is kindly acknowledged for his helpful discussion on this chemistry.

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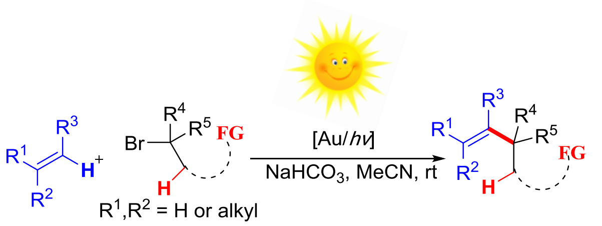
[13] Pioneering work: a) C.-M. Che, H.-L. Kwong, C.-K. Poon, V. W.-W. Yam, *J. Chem. Soc., Dalton Trans.* **1990**, 3215-3219; b) C.-M. Che, H.-L. Kwong, V. W.-W. Yam, K.-C. Cho, *J. Chem. Soc., Chem. Comm.* **1989**, 885-886; c) C. King, J. C. Wang, M. N. I. Khan, J. P. Fackler, *Inorg. Chem.* **1989**, *28*, 2145-2149.

[14] Alexanian et al. recently notified that unactivated alkyl bromides under their standard conditions ([PdCl$_2$(dppf)], K$_2$CO$_3$, 100 ^{o}C) failed to undergo Heck-like coupling, see 7d.

TOC graphic



FG = functional groups

- ☑**Unactivated alkyl bromides with β-hydrogens**
- ☑**Excellent functional groups tolerance**
- ☑**Broad reaction scope, >30 examples, up to 91% yield**
- ☑**Late-stage application**
- ☑**Mild reaction conditions**

Abstract: A general and mild method for an intermolecular radical Heck-like coupling of unactivated primary, secondary and tertiary alkyl bromides catalyzed by a dinuclear gold complex is presented. A variety of alkenes and densely functionalized unactivated alkyl bromides tolerated the reaction conditions well, including substrates containing esters, aldehydes, ketones, nitriles, alcohols, heterocycles, alkynes, alkenes, ethers and halogens moieties. This notable features offer an ideal protocol for challenging late-stage intermolecular C-C couplings of complex molecules.