CHEMISTRY
AN ASIAN JOURNAL
www.chemasianj.org

Accepted Article

Title: Light/Palladium-Promoted Benzylic C–H Acylation Using a Benzoyl Group as the Photo-Directing Group

Authors: Yusuke Masuda, Naoki Ishida, and Masahiro Murakami

To be cited as: *Chem. Asian J.* 10.1002/asia.201801881

Link to VoR: http://dx.doi.org/10.1002/asia.201801881

A Journal of
ACES Asian Chemical Editorial Society

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

10.1002/asia.201801881

WILEY-VCH

Light/Palladium-Promoted Benzylic C–H Acylation Using a Benzoyl Group as the Photo-Directing Group

Yusuke Masuda, Naoki Ishida, and Masahiro Murakami*

Abstract: 2-Methylphenyl ketones undergo site-selective acylation at the benzylic position when treated with acid anhydride under UV irradiation in the presence of a palladium catalyst. The benzoyl carbonyl group serves as the photo-directing group so that the ortho benzylic C–H bond is activated site-selectively.

The C–H functionalization protocol presents a straightforward and efficient method to manipulate organic molecules in an atom- and step-economical manner.[1] It is one of the major issues how to target a specific C–H bond among a multitude of C–H bonds existing in a molecule. It was shown in the seminal report by Murai that an acyl group on a benzene ring directs a metal to activate its ortho C(sp^2)–H bond.[2] This work has triggered a numerous number of studies on utilization of directing groups which bring a metal into close proximity to a targeted C–H bond and site-selectively activate it (Figure 1a).[3,4] We now report that a carbonyl group on a benzene ring acts as the photo-directing group to site-selectively activate a C(sp^3)–H bond at an ortho benzylic position.[5] A palladium catalyst subsequently acylates the activated intermediate with acid anhydride to afford a 1,5-diketone (Figure 1b).[6] This is the first example in which photo-generated *o*-quinodimethane intermediates are combined with transition-metal catalysis.

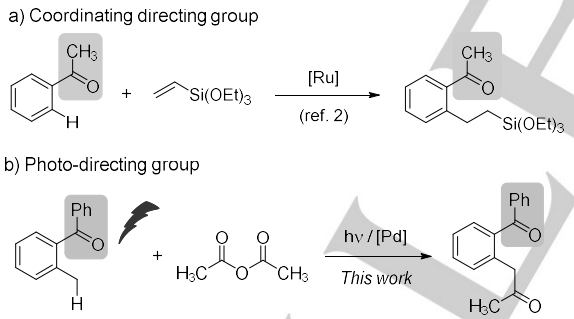
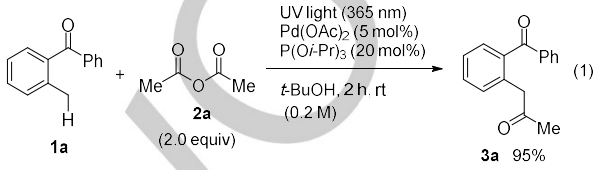
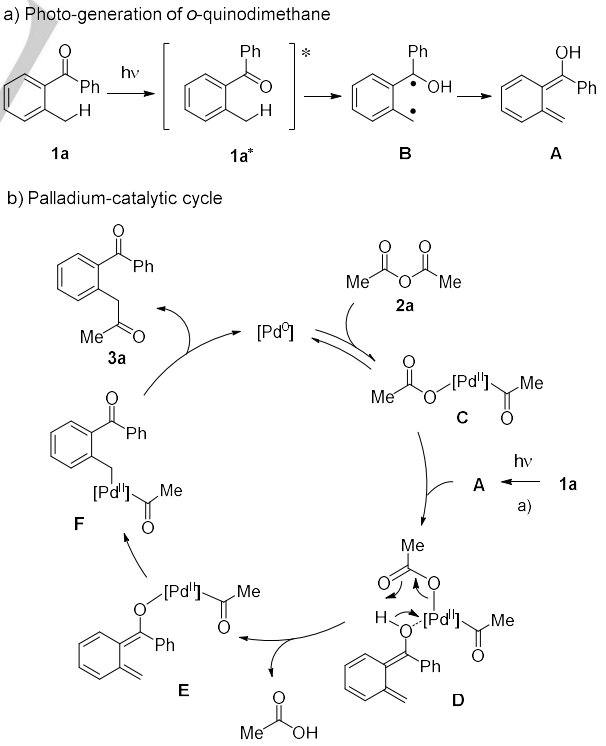


Figure 1. Directing groups for transition-metal catalyzed C–H activations.

When 2-methylbenzophenone **1a** was treated with acetic anhydride **2a** in the presence of a $Pd(OAc)_2$/$P(O\textit{i}\text{-}Pr)_3$ catalyst under photo-irradiation for 2 h, 1,5-diketone **3a** was produced in 95% yield [Eq. (1)]. For comparison, a same reaction was carried out without photo-irradiation to confirm that no reaction occurred.[7]



Among various mechanistic possibilities conceivable for the formation of **3a** from 2-methylbenzophenone **1a** and acetic anhydride **2a** under photo-irradiation, Scheme 1 shows one of the plausible pathways. Initially, the *o*-quinodimethane **A** is generated from **1a** upon photo-excitation.[8,9] This process mechanistically consists of three steps; (i) photoexcitation of the carbonyl group, (ii) 1,5-hydrogen shift, which is the most facile mode for hydrogen shift,[10] to the excited carbonyl oxygen generating 1,4-biradical **B**, and (iii) isomerization of **B** to *o*-quinodimethane **A** which has a closed-shell structure.[11] On the other hand, acetic anhydride **2a** undergoes oxidative addition



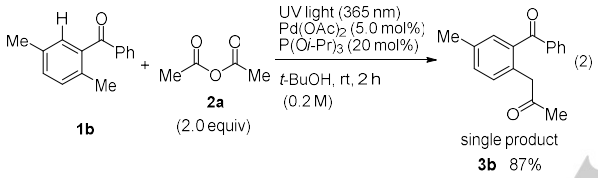
Scheme 1. Proposed mechanism.

[*] Dr. Y. Masuda, Dr. N. Ishida, Prof. Dr. M. Murakami
Department of Synthetic Chemistry and Biological Chemistry
Kyoto University, Katsura, Kyoto 615-8510 (Japan)
E-mail: murakami@sbchem.kyoto-u.ac.jp

Supporting information and the ORCID identification numbers for the authors of this article can be found under:

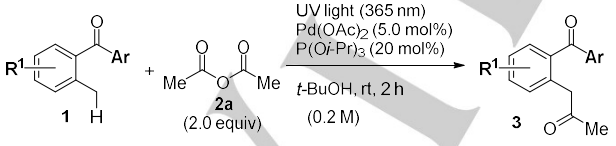
onto palladium(0) to form acetyl(acetato)palladium(II) **C**.[12] The photo-generated enol **A** coordinates onto palladium to form the intermediate **D** followed by elimination of acetate acid.[13] The resulting acetyl(enolato)palladium(II) **E** tautomerizes into acetyl(benzyl)palladium(II) **F**, thereby regaining aromatization energy. Finally, a carbon–carbon bond is formed by reductive elimination to furnish the 1,5-diketone **3a** with regeneration of Pd(0).[14,15]

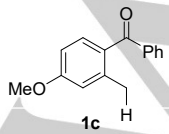
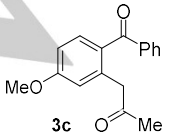
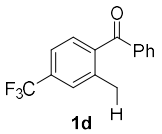
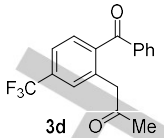
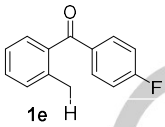
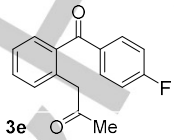
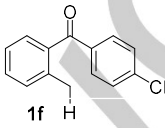
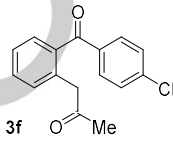
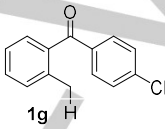
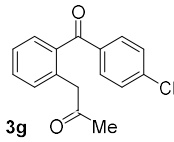
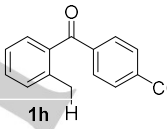
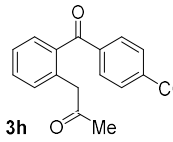
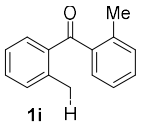
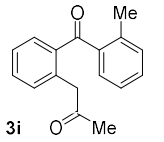
The directing effect of the carbonyl group was corroborated by the reaction using 2,5-dimethylbenzophenone **1b**, which had two methyl groups at different positions, i.e., ortho and meta positions on the benzene ring [Eq. (2)]. Acetylation took place site-selectively at the methyl group ortho to the carbonyl group to form the product **3b**. No acetylation occurred at the meta methyl group. It is also notable that the ortho C(sp^2)–H bond on the benzene ring, which is often activated with the aid of directing groups based on coordination, remained intact. This unique site-selectivity originates from the privileged mode of 1,5-hydrogen shift at the photo-excited state.



The acetylation reaction was examined using various 2-methylphenyl ketones (Table 1). Both electron-rich and electron-deficient benzene rings were suitable as the core aromatics (entries 1 and 2). Functional groups such as fluoro, chloro, and methoxycarbonyl groups were all tolerated on the aromatic rings (entries 3-6). The reaction of those having electron-withdrawing substituents was slower than that of electron-rich substrates.[16] Bis(*o*-tolyl) ketone underwent the acylation only once to produce the diketone **3i**, and no bis-acetylated product was formed (entry 7).[17] 2-Ethylbenzophenone failed to participate in the acylation reaction.[18]

Table 1. Scope of 2-methyl benzophenones.[a]

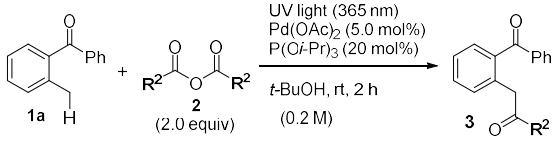


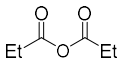
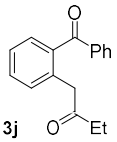
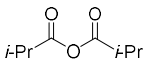
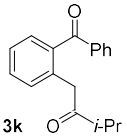
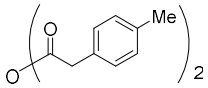
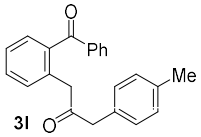
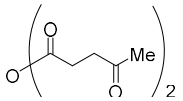
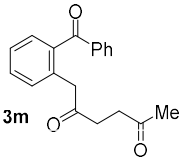
Entry	Substrate **1**	Product **3**	yield[b]
1			83%
2			51%
3			72%
4			75%
5[c]			73%
6[c]			62%
7			72%

[a] Reaction conditions: 2-methylphenyl ketone (0.20 mmol), acetic anhydride (0.40 mmol), $Pd(OAc)_2$ (0.01 mmol), P(O*i*-Pr)$_3$ (0.04 mmol), *t*-BuOH (1.0 mL), UV light (365 nm, LED lamp), room temperature, 2 h. [b] Isolated yield. [c] 0.02 mmol of P(O*i*-Pr)$_3$, 1 h.

The substrate scope was investigated also using various carboxylic anhydrides (Table 2). Propanoic anhydride **2b** and isobutylic anhydride **2c** successfully participated in the reaction as the acylating reagent (entries 1 and 2), whereas pivalic anhydride failed to give the acylated ketone, presumably due to the steric reasons. Levulinic anhydride **2d** was a suitable substrate to give triketone **3m** in 48% yield (entry 4).

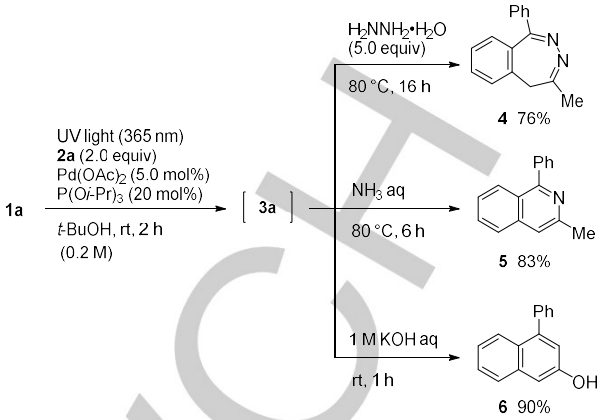
Table 2. Scope of acid anhydrides.[a]



Entry	Acid anhydride **2**	Product **3**	yield[b]
1	 **2b**	 **3j**	80%
2	 **2c**	 **3k**	59%
3	 **2c**	 **3l**	63%
4	 **2d**	 **3m**	48%

[a] Reaction conditions: 2-methylphenyl ketone (0.20 mmol), acetic anhydride (0.40 mmol), $Pd(OAc)_2$ (0.01 mmol), $P(O\textit{i}\text{-}Pr)_3$ (0.04 mmol), *t*-BuOH (1.0 mL), UV light (365 nm, LED lamp), room temperature, 2 h. [b] Isolated yield.

The present reaction was driven only by light and a catalytic amount of palladium, and no stoichiometric amounts of other reagents were employed. Consequently, it was possible to dispense with a work-up and isolation procedure before carrying out further derivatization of the produced 1,5-dicarbonyl compounds. Instead, reagents were directly added to the reaction mixture containing the diketone **3a** to successfully prompt subsequent reactions (Scheme 2). For example, hydrazine was added to a same reaction flask after **1a** was reacted with **2a**, and the resulting mixture was heated at 80 °C for 16 h. An aqueous work-up followed by chromatographic purification afforded 2,3-benzodiazepine **4**. In general, 2,3-benzodiazepine is a versatile pharmacophore, often constituting psychotropic drugs such as Tofisopam and Girisopam.[19] When the in-situ generated **3a** was treated with an aqueous ammonia solution, isoquinoline **5** was obtained in 83% yield. Diketone **3a** underwent also an intramolecular aldol condensation reaction upon treatment with potassium hydroxide to form 2-naphthol **6** in 90% yield.



Scheme 2. Sequential transformations from 2-methylbenzophenone **1a** to 2,3-benzodiazepine **4**, isoquinoline **5**, and 2-naphthol **6** in one-pot..

In conclusion, we disclosed that a benzylic C–H bond of 2-methylbenzophenone is activated under photo-irradiation to be acylated with carboxylic anhydrides in the presence of a palladium catalyst. A benzoyl carbonyl group acts as the photo-directing group to activate the benzylic C–H bond site-selectively. A number of reactions of 2-methyl benzophenones forming C–C bond at the benzylic position has been reported.[5,20] However, *o*-quinodimethane **A** has never been used in combination with transition-metal catalysis. We demonstrated that the cooperation of light and transition-metal catalysts gives rise to the powerful methods for site-selective C–C bond formations of 2-methyl benzophenones.

Experimental Section

A typical procedure for synthesis of diketones: $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol%) was placed in a Pyrex flask, which was subsequently filled with an argon by vacuum-refill cycles. 2-Methylbenzophenone **1a** (39 mg, 0.20 mmol), acetic anhydride **2** (41 mg, 0.40 mmol, 2.0 equiv), $P(O\textit{i}\text{-}Pr)_3$ (8.4 mg, 0.04 mmol, 20 mol%), and *t*-BuOH (1.0 mL) were added into the flask, which was pre-stirred for 5 minutes at room temperature.[21] After irradiated with LED lamp (365 nm) for 2 h at ambient temperature, the resulting mixture was passed through a pad of Florisil® and eluted with diethyl ether. Volatiles were removed under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/ethyl acetate = 3/1) to give the acylated product **3a** (46.0 mg, 0.19 mmol, 96% yield, colorless oil).

Acknowledgements

This work was supported by JSPS KAKENHI Grants Numbers JP15H05756 (M.M.) and 18H04648 (N.I.) (Hybrid Catalysis). Y.M. acknowledged JSPS fellowship for young scientists (14J03286).

Keywords: photoreaction • palladium • acylation • C–H activation • directing group

[1] Selected reviews and perspectives: a) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev.* **2011**, *40*, 1976; b) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; c) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; d) J. F. Hartwig, *J. Am. Chem. Soc.* **2016**, *138*, 2.

[2] S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529.

[3] For selected reviews of directing group-assisted C–H bond activations, see: a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; b) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; c) Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong, *Chem. Soc. Rev.* **2015**, *44*, 7764.

[4] For directing group-assisted C–H bond acylations, see: a) N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai, *J. Am. Chem. Soc.* **2000**, *122,* 12882; b) S. Yu, Y. Li, L. Kong, X. Zhou, G. Tang, Y. Lan, X. Li, *ACS Catal.* **2016**, *6*, 7744.

[5] For carbonyl addition reactions of ortho-alkylphenyl ketones at the benzylic positions under irradiation, see: a) T. L. Burkoth, E. F. Ullman, *Tetrahedron Lett.* **1970,** *11*, 145; b) D. M. Findlay, M. F. Tchir, *J. Chem. Soc., Chem. Commun.* **1974**, 514; c) K. Takaki, T. Fujii, H. Yonemitsu, M. Fujiwara, K. Komeyama, H. Yoshida, *Tetrahedron Lett.* **2012**, *53*, 3974; d) Y. Masuda, N. Ishida, M. Murakami, *J. Am. Chem. Soc.*, **2015**, *137*, 14063; e) S. Cuadros, L. Dell'Amico, P. Melchiorre, *Angew. Chem. Int. Ed.* **2017**, *56*, 11875; *Angew. Chem.* **2017**, *129*, 12037, and references cited therein.

[6] For direct C–H acylations by photoredox catalysis, see: a) D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 8094; b) C. L. Joe, A. G. Doyle, *Angew. Chem. Int. Ed.* **2016**, *55*, 4040; *Angew. Chem.* **2016**, *128*, 4108.

[7] See supporting information for the details.

[8] a) N. C. Yang, C. A. Rivas, *J. Am. Chem. Soc.* **1961**, *83*, 2213; b) *Tetrahedron* **1976**, *32*, 405; c) R. Haag, J. Wirz, P. J. Wagner, *Helv. Chim. Acta* **1977**, *60*, 2595; d) P. K. Das, J. C. Scaiano, *J. Photochem.* **1980**, *12*, 85.

[9] The generation of **A** under UV irradiation was confirmed by a separate reaction of **1a** with methyl vinyl ketone. See supporting information for the mechanistic investigations.

[10] For selected reviews, see: a) G. Majetich, K. Wheless, *Tetrahedron* **1995**, *51*, 7095; b) J. Robertson, J. Pillai, R. K. Lush, *Chem. Soc. Rev.* **2001**, *30*, 94; c) S. Chiba, H. Chen, *Org. Biomol. Chem.* **2014**, *12*, 4051.

[11] Stereoisomeric *o*-quinodimethane having inward-oriented hydroxy group would revert to **1a** without participating in the palladium-catalyzed process.

[12] a) K. Nagayama, F. Kawataka, M. Sakamoto, I. Shimizu, A. Yamamoto, *Chem. Lett.* **1995**, *24,* 367; b) A. Jutand, S. Négri, J. G. De Vries, *Eur. J. Inorg. Chem.* **2002**, *2002,* 1711.

[13] The replacement of the acetate ligand with **A** might be initiated by π-coordination of the diene moiety of **A** rather than anionic displacement.

[14] All experiments to detect the intermediate **E** or **F** failed, probably because tautomerization and reductive elimination steps were fast.

[15] Single electron transfer from the palladium complex to acetic anhydride forming acetyl radical species is also conceivable. For recent examples of the palladium-catalyzed coupling reactions through single electron transfer, see: a) D. Kurandina, M. Parasram, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2017**, *56*, 14212; *Angew. Chem.* **2017**, *129*, 14400; b) G.-Z. Wang, R. Shang, W.-M. Cheng, Y. Fu, *J. Am. Chem. Soc.* **2017**, *139*, 18307.

[16] Whereas the reaction of **1d** was slow, the product **3d** gradually decomposed upon irradiation for a long period of time.

[17] A deuterium experiment using the mono-acetylated product **3i** suggested that it fails to generate an *o*-quinodimethane intermediate with the remaining *o*-methylbenzoyl moiety; see supporting information for details.

[18] No styrene derivatives, possibly generated through β-hydride elimination, was formed. We assumed that the generation of a benzyl palladium species corresponding to **F** would be hampered by sterics.

[19] E. J. Horváth, K. Horváth, T. Hámori, M. I. Fekete, S. Sólyom, M. Palkovits, *Prog. Neurobiol.* **2000**, *60*, 309.

[20] Selected reviews: a) J. L. Segura, N. Martin, *Chem. Rev.* **1999**, *99*, 3199; b) M. D. Kärkäs, J. A. Porco, Jr., C. R. J. Stephenson, *Chem. Rev.* **2016**, *116*, 9683.

[21] The reaction mixture was melted by heating when the temperature was below the melting point of *t*-BuOH (25 °C)