Photochemical and Additive-Free Coupling Reaction of α-Cumyl α-Keto Esters via Intermolecular C–H Bond Activation

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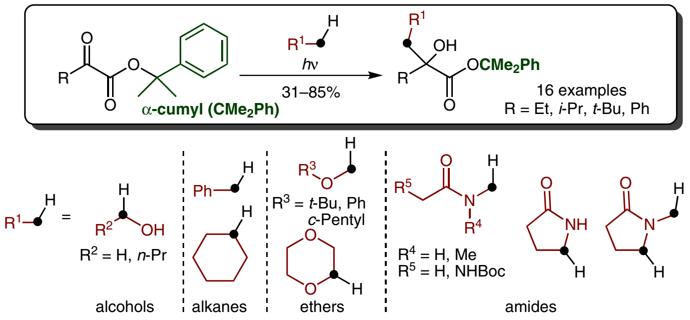

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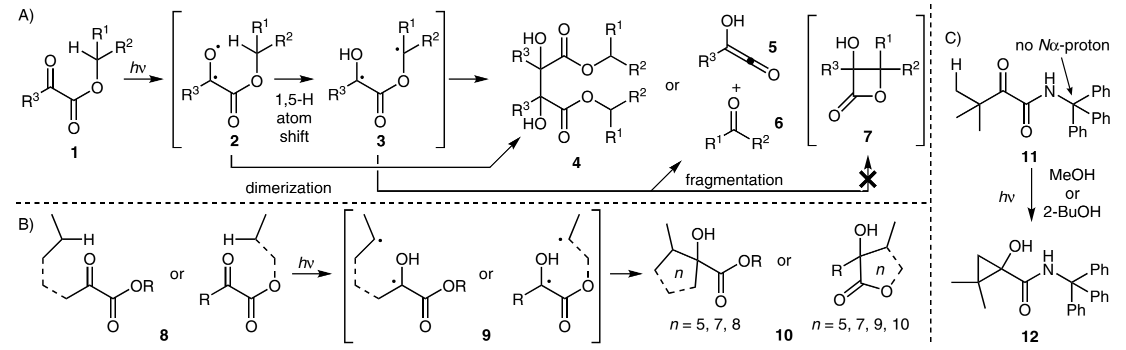
Abstract We developed a photo-chemical coupling reaction of α-keto esters with several simple alcohols, alkanes, ethers, and amides. Use of tertiary alkyl ester, α-cumyl ester, is the key for avoiding the known photo-degradation process. Intermolecular C–H bond activation and subsequent C–C bond formation were promoted by irradiation with an LED lamp (365 nm) without any additives. Among the coupling partners, reactions with sterically less demanding amides proceeded efficiently to provide unique *N*-acyl-β-amino-α-hydroxy acid derivatives. In benzene or acetone as a solvent, the reaction with a solid amino acid derivative provided a precursor of tetrahydro-1,4-diazepine-2,5-dione derivatives.

Key words photo-chemical reaction, α-keto esters, coupling reactions, C–H bond activation, β-amino acid derivatives, α-cumyl esters, tetrahydro-1,4-diazepine-2.5-dione

Photoreaction of α-dicarbonyl systems such as 1,2-diketones and α-keto amides, especially to construct four-membered rings (Norrish–Yang cyclization), has often been utilized in the synthesis of complex molecules,[1–3] because an sp^3 C–H bond is directly functionalized without introduction of a reactive group.[4] However, photo-induced C–C bond formation of the keto group in α-keto esters (**1** or **8**) is less predictable. In contrast to 1,2-diketones or α-keto amides, β-lactone **7** formation has never been reported (Scheme 1,A). Photoexcitation of the keto group of **1** (n–π* transition, **2**) is possible by irradiation at long wavelength (more than 350 nm). Subsequent [1,5] H-atom shift (Norrish-type II reaction) would generate a putative 1,4-diradical species **3**, as with other α-dicarbonyls. However, cyclization of **3** to form **7** appears to be disfavored. Instead, reductive dimerization from **2** to provide **4**[5,6] or degradation from **3** to **5** and **6** (Norrish-type II fragmentation)[7,8] occurs preferentially (Scheme 1,A).[9]



Scheme 1 A) Representative photo-reaction of α-keto esters **1**. B) Intra- or intermolecular photo-induced C–C bond formation of α-keto esters **8** via C–H bond activation. C) Our recent work: Novel photo-induced cyclopropanol formation from α-keto amides **11** via C–H bond activation.

On the other hand, some specific examples of intramolecular C–C bond formation for α-keto esters such as **8**, bearing a C–H bond in close proximity to a keto group, have been reported.[10] As shown in Scheme 1 (B), C–C bond formation would proceed via diradical species **9**, which would be generated by H-atom abstraction from the neighboring C–H bond in a diradical species like **2** prior to degradation. These precedents suggest the potential utility of photo-induced coupling of α-keto esters, but only a few examples of intermolecular photochemical coupling of α-keto esters via C–H bond activation have been reported, and they are limited to specific substrates[11] (methyl, ethyl, or allyl α-keto ester) and reactants such as cyclohexene,[12] HMPA,[13] or a 4*H*-pyran derivative.[14] The scope of photo-induced C–C bond-forming coupling reaction of α-keto esters remains unclear. Herein, we report photo-coupling reactions of α-keto esters with alcohol, ether, alkanes, and amides.

We recently found a novel type of photoreaction of bulky α-keto amides **11** without Nα protons, which should not undergo Norrish-type II reaction, providing cyclopropanol **12** (Scheme 1,C).[15] This result prompted us to investigate the photoreaction of α-keto ester **13a** with α-cumyl ester, instead of trityl ester.[16] We initially assumed that similar cyclopropanol formation from **13a** might proceed, at least to some degree, but the expected reaction did not occur. Instead, interestingly, irradiation of **13a** with an LED lamp (365 nm) produced the methanol adduct **14a** in reasonably good yield (Table 1, entry 1).[17] This result indicates that, unlike α-keto amides, avoiding the Norrish-type II process allows intermolecular H-atom abstraction followed by C–C bond formation to occur in the case of α-keto esters. Indeed, in contrast to the reaction of **13a**, irradiation of α-keto esters **13b** and **13c** with primary or secondary alkyl ester substituents, rapidly afforded messy mixtures, including small amounts of methanol adducts **14b** and **14c**. In both cases, the corresponding dimers **15b** or **15c** were detected by MS analysis of the mixtures.

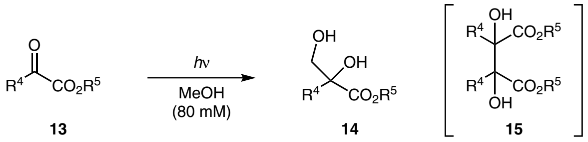
Next, we investigated the scope of the keto substituent. Photolysis of phenyl derivative **13d** in methanol gave the corresponding adduct **14d** in 25% yield. A complex mixture was formed from thienyl derivative **13e**, and the adduct **14e** was not detected. Photoreaction of isopropyl derivative **13f** proceeded smoothly to give **14f** in 68% yield, whereas ethyl derivative **13g** gave **14g** in lower yield (15%) with partial recovery of **13g** (23%). Thus, a tertiary or secondary alkyl group appears to be better as a keto substituent in the case of the photochemical coupling reaction with alcohols.

We next investigated the photo-reaction of α-keto ester **13f** with various coupling partners (Scheme 2). Photolysis in 1-butanol provided the corresponding diol **16f** in 33% yield (d.r. = 1.6:1). In this case, dimer **15f** was produced in 52% yield, together with a trace (5%) of α-hydroxy ester **17f**, which would be formed by disproportionation of the intermediate radical species.[18] With 2-propanol as a coupling partner, adduct **18f** was formed in only 8% yield. Instead, dimer **15f** was the major product (64%) along with α-hydroxy ester **17f** (5%).

Coupling of **13f** with toluene (bond-dissociation energy, BDE: 89.7 kcal/mol)[19] produced **19f** in moderate yield. It was found that coupling proceeded even with cyclohexane (BDE: 99.5 kcal/mol)[19] to provide **20f** (40%), along with **15f** and **17f**.

Then, we examined the reaction with ethers commonly used as solvents, in the expectation that Oα–C–H bond activation would be accelerated by electron transfer from the O atom (Scheme 2,B).[20] As we expected, photolysis of **13f** in *t*-BuOMe provided the unique tertiary alcohol derivative **21f** in good yield (73%). Coupling with anisole or 1,4-diox-

Table 1 Photo-Induced Coupling of α-Keto Esters **13** with Methanol

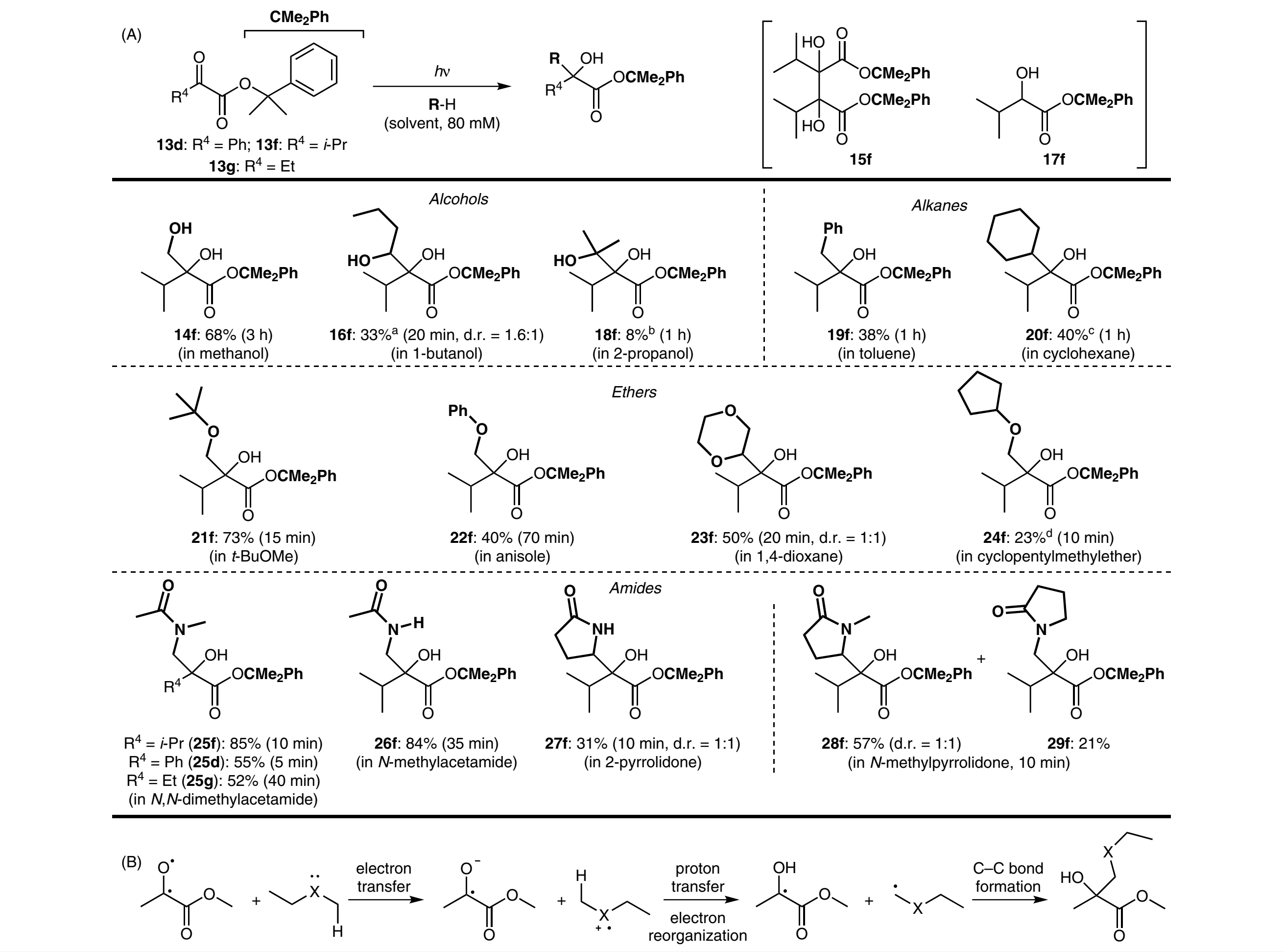


Entry	Substrate	R⁴	R⁵	Time	Product **14**	Yield (%)
1	**13a**	*t*-Bu	$C(CH_3)_2Ph$	4 h	**14a**	54
2	**13b**	*t*-Bu	CH_2CH_2Ph	20 min	**14b**	3
3	**13c**	*t*-Bu	$CH(CH_3)Ph^a$	5 min	**14c**	10 (d.r. = 1:1)
4	**13d**	Ph	$C(CH_3)_2Ph$	1 h	**14d**	25
5	**13e**	thienyl	$C(CH_3)_2Ph$	1 h	**14e**	0
6	**13f**	*i*-Pr	$C(CH_3)_2Ph$	3 h	**14f**	68
7	**13g**	Et	$C(CH_3)_2Ph$	1 h	**14g**	15[b]

[a] (*R*)-phenethyl ester was used.
[b] 23% recovery of the starting material **13g**.

ane similarly afforded **22f** and **23f** in reasonable yields. When the reaction was carried out in cyclopentylmethylether (CPME), formation of **15f** and **17f** also occurred, and coupling product **24f**, which is formed by H-atom abstraction from the less hindered methyl group followed by C–C bond formation, was obtained in only 23% yield. The results of the photoreactions with CPME and *i*-PrOH indicated that photocoupling with an Oα-methine group is disfavored, probably for steric and/or electronic reasons, allowing dimerization and disproportionation reactions to occur in competition with photocoupling. Comparison of the reactions with *t*-BuOMe and anisole suggested that BDE is unlikely to be the dominant factor for the coupling reaction (BDE; CH_3OCH_2–H: 96.1 kcal/mol, $PhOCH_2$–H: 92.0 kcal/mol).[19] In case of heteroatom-containing coupling partners, an electron-transfer process may also contribute to this coupling reaction.

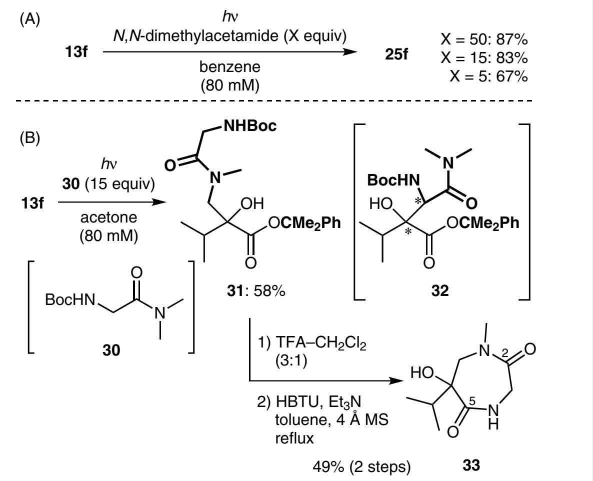
Therefore we next examined the reaction of *N*,*N*-dimethylacetamide. If the electron-transfer process significantly contributes to the reaction, the NαC–H bond should be preferentially activated over the C–H bond of the acetyl group, despite its higher BDE [BDE; $HCON(CH_2$–**H**$)_2$: 105 kcal/mol, **H**–CH_2CONMe_2: 91.0 kcal/mol].[19] As expected, photolysis of **13f** in *N*,*N*-dimethylacetamide cleanly and selectively afforded **25f** in excellent yield (85%); this represents a direct synthesis of a β-amino-α-hydroxy acid derivative containing a tetrasubstituted α-carbon center.[21] Coupling reactions of phenyl or ethyl derivative **13d** and **13g** also successfully proceeded to give **25d** and **25g** in good yields. *N*-Methylacetamide also afforded the adduct **26f** in 84% yield. With cyclic 2-pyrrolidone, H-atom abstraction and C–C bond formation occurred to provide **26f** in 31% yield, indicating that coupling reaction with the *N*α-methylene group was possible, as well as at the Oα-position (like **23f**). In the case of the reaction with *N*-methylpyrrolidone, the coupling products were formed in 78% total yield. The regioisomer **28f**, the coupling product at the *N*α-methylene group, was formed preferentially (57% yield,



Scheme 2 (A) Photo-induced coupling reactions of α-keto esters **13**. (B) Plausible mechanism of coupling reaction via an electron transfer process. Isolated yields are shown unless otherwise noted: a) **15f** (52%, calcd yield) and **17f** (5%, calcd yield) were obtained; b) **15f** (64% calcd yield) and **17f** (5% calcd yield) were obtained; c) **15f** (20%, calcd yield) and **17f** (8%) were obtained; d) **15f** (20%) and **17f** (19%) were obtained.

d.r. = 1:1), and the coupling product at the methyl group **29f** was also obtained (21% yield).

We also tried photolysis of **13f** in actetone, benzene, *t*-BuOH, MeCN, *t*-BuOAc, and CF_3Ph, but no coupling product with these molecules was detected. Instead, only degradation of **13f** was observed. We found that the degradation rates of **13f** in acetone and benzene were slower than those in *t*-BuOH, MeCN, *t*-BuOAc, and CF_3Ph.[22] In using reactive amide substrates as a coupling partner, the reaction can be diluted with acetone or benzene (Scheme 3,A). Irradiation of **13f** in the presence of 50, 15, and even 5 equivalents of *N*,*N*-dimethylacetamide in benzene successfully afforded the coupling product **25f** in good yields.[23]



Scheme 3 A) Coupling reactions of α-keto esters **13f** in diluted *N*,*N*-dimethylamide with benzene. B) Reaction with the glycine derivative **30** and transformation of the major product into compound **33**.

The use of solvent permits us to carry out reactions with solid substrates such as *N*-Boc-protected glycinedimethylamide **30** (Scheme 3,B). The photoadduct **31** was obtained in 58% yield as the major product of photolysis of **13f** in the presence of **30** (15 equiv) in acetone.[24] It should be noted that only a trace amount of regioisomer **32** was detected, although radical species at the *N*α-methylene group next to the carbonyl group in **30** should be also stabilized by captodative effect.[25]

The α-cumyl group is labile under mild acidic conditions,[26] and the Boc and α-cumyl groups in **31** were removed simultaneously to generate the amino acid derivative. Treatment of the crude material under condensation reaction conditions at elevated temperature afforded the biologically intriguing tetrahydro-1,4-diazepine-2.5-dione (homodiketopiperazine) derivative **33** containing a tetrasubstituted carbon center.[27]

In conclusion, we have achieved photoinduced coupling of α-keto esters by utilizing bulky α-cumyl esters. This reaction expands the synthetic utility of α-keto esters as building blocks. *N*,*N*-Dimethylamides were found to be excellent coupling partners of α-keto esters, enabling rapid access to β-amino-α-hydroxyacid derivatives. Our method does not require additives[28] and is operationally simple. Further applications are being examined.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561098.

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(16) Trityl ester was prone to be hydrolyzed.

(17) **Typical Experimental Procedure for the Synthesis of 14f**
A degassed 80 mM solution of **13f** in MeOH (700 μL) was irradiated with a 365 nm LED lamp until the starting material was consumed (3 h for **13f**). Silica gel column chromatography gave **14f** (10.2 mg, 68%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.9 Hz, 3 H), 1.81 (s, 3 H), 1.86 (s, 3 H), 2.06 (sept, J = 6.9 Hz, 1 H), 2.06 (m, 1 H), 3.40 (br d, J = 1.8 Hz, 1 H) 3.76 (d, J = 11.0 Hz, 1 H), 3.88 (br m, 1 H), 7.27 (m, 1 H), 7.32–7.37 (m, 2 H), 7.40–7.43 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.5, 17.2, 27.9, 28.9, 32.7, 66.7, 80.9, 84.3, 124.6 (2 C), 127.6, 128.4 (2 C), 144.8, 174.4. IR: 3485, 2969, 1727, 1270, 1225, 1134, 1102, 1077, 1031 cm^{-1}. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $C_{15}H_{22}NaO_4$: 289.1416; found: 289.1412.

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(22) Recovery of **13f** after irradiation for 1 h: 77% (in acetone), 80% (in benzene), 69% (in *t*-BuOH), 54% (in MeCN), 44% (in *t*-BuOAc), and 59% (in CF_3Ph).

(23) Formation of the dimer **15f** was also observed (X = 5, 15%; X = 15, 15%; X = 50, 8%).

(24) Compound **30** was insoluble in benzene.

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(26) The α-cumyl group in **14f** was easily removed by using 2% TFA in the presence of *i*-Pr_3SiH. See Supporting Information.

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