How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 10620–10625
International Edition: doi.org/10.1002/anie.202016051
German Edition: doi.org/10.1002/ange.202016051

Synthetic Methods

Direct α-Tertiary Alkylations of Ketones in a Combined Copper–Organocatalyst System

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Dedicated to Professor Ilhyong Ryu on the occasion of his 70th birthday

Abstract: *Herein, we report an efficient method for the tertiary alkylation of a ketone by using an α-bromocarbonyl compound as the tertiary alkyl source in a combined Cu-organocatalyst system. This dual catalyst system enables the addition of a tertiary alkyl radical to an enamine. Mechanistic studies revealed that the catalytically generated enamine is a key intermediate in the catalytic cycle. The developed method can be used to synthesize substituted 1,4-dicarbonyl compounds containing quaternary carbons bearing various alkyl chains.*

Substituted 1,4-dicarbonyl compounds are very important structures that are often found in natural or related compounds.[1,2] Retrosynthetically disconnecting such a compound reveals two direct synthesis routes from readily available carbonyl compounds: a) the cross-enolate coupling of two different ketones or related enolates, and b) the nucleophilic substitution of a ketone or an enolate with an α-halocarbonyl compound (Figure 1). Cross-enolate coupling is an area that has developed recently, and the number of reports in this field appear to be increasing each year.[3] This methodology provides a direct approach for the construction of a 1,4-dicarbonyl structure, but it is sensitive to steric hinderance at hindered α-carbonyl C–C bonds, resulting in oxidative enolate coupling, while it also suffers from enolate homocoupling (Figure 1a). There are many reports on the α-arylations of carbonyl compounds,[4,5] whereas the α-alkylation of a ketone with an α-halocarbonyl compound is rare. The nucleophilic substitution step can be accomplished using primary or secondary alkyl halides (not α-halocarbonyls and mainly haloalkanes or benzylic halides) (Figure 1b).[6] Tertiary alkyl halides are poorly reactive due to steric hindrance; therefore, the corresponding reaction with an α-halocarbonyl compound, as the electrophile, is challenging.

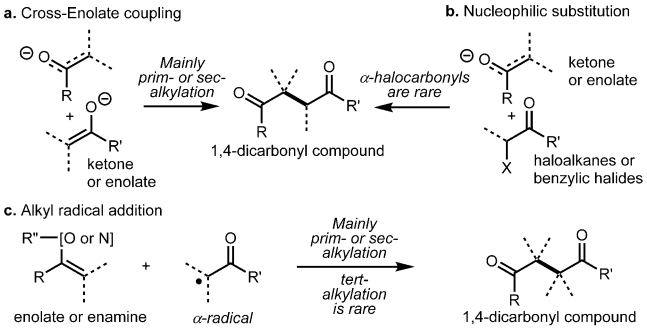

Figure 1. Synthetic approaches to a 1,4-dicarbonyl compound.

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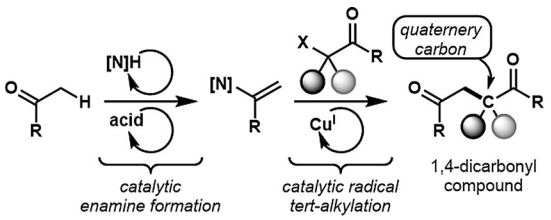
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202016051.

Another promising methodology involves the alkyl radical addition to a reactive C–C double bond (Figure 1c). This methodology uses enol ethers and their derivatives, including silyl enol ethers,[7] stannyl enolates,[8] enamines,[9,10] acetates,[11] and vinyl ethers,[12] as C–C double-bond sources. Despite the importance of substituted 1,4-dicarbonyl compounds, the direct tertiary alkylation of a ketone has not yet been established because it is difficult to control the reactivity of a tertiary alkyl radical (α-radical) due to steric hindrance; it also requires pre-formed highly reactive enolates or their derivatives.

Recently we reported that the reactions of styrenes and α-haloesters involve tertiary alkylative olefinations through atom-transfer radical addition (ATRA) followed by dehydrohalogenation.[13] Although the α-tertiary alkylations of enamides to produce aldehydes has been accomplished,[14] the direct α-tertiary alkylation of a ketone has, to the best of our knowledge, not yet been achieved because the α-carbon of ketone is not directly reactive toward tertiary alkyl radicals.

Based on this background, including our chemistry, we hypothesized that an enamine catalytically generated through the reaction of a ketone and an amino organocatalyst will react with a tertiary alkyl radical to give the corresponding α-tertiary-alkylated ketone (i.e., a 1,4-dicarbonyl compound possessing a quaternary carbon center). Progress in radical chemistry involving catalytically generated enamines has recently been reported by Melchiorre, Nicewicz, and MacMillan,[15] who showed that a catalytically generated enamine from a cyclic ketone or aldehyde can be used in radical α-alkylation chemistry. On the other hand, the reaction involves a simple ketone and a functionalized tertiary alkyl reagent, which remains challenging for this chemistry.[16] Herein, we report the development of a reaction system that combines an organocatalyst and a transition-metal catalyst; that is, a dual catalyst system, that facilitates the direct α-tertiary alkylation of ketones (Scheme 1).

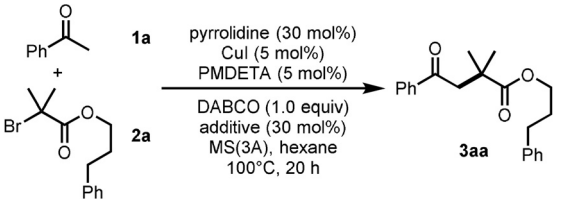
Optimization studies employed a combination of acetophenone (**1a**, 3 equiv) and 2-bromoester **2a** (1 equiv) in the presence of pyrrolidine (30 mol%), CuI (5 mol%), PMDETA (5 mol%, *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylene-



Scheme 1. This work: Dual catalyst system.

triamine), DABCO (1 equiv, 1,4-diaza bicyclo[2.2.2]octane), and molecular sieves (MS 3A) in hexane at 100 °C for 20 h (Table 1). At this stage, we expected that generating the enamine from **1a** and the tertiary alkyl radical derived from **2a** is critical in this catalyst system. Indeed, **3aa** was not obtained in the absence of a Cu catalyst and pyrrolidine, and the yield of **3aa** depended on the amount of pyrrolidine (Runs 1–4). These results revealed that enamine formation affects the yield of **3aa**. Various acids were examined with the aim of accelerating the formation of the enamine. *p*-TsOH and CF_3CO_2H gave moderate yields of **3aa** (Runs 5 and 6), while the reaction involving AcOH resulted in 64% yield of **3aa** (Run 7). Although we examined some acetic acid derivatives, no improvement in yield was observed. On the other hand, phenol derivatives were effective (Runs 8–14), with 80% yield of **3aa** obtained when methyl 4-hydroxybenzoate was used (Run 11). Other acids with pK_a values of around 9 were ineffective (Runs 15 and 16). It is well known that copper complexes with PMDETA efficiently generate alkyl radical species from alkyl halides in ATRP or ATRA chemistry;[17] however, the addition of an acid did not affect the coordination of PMDETA to copper. This reaction required the use of DABCO, a strong base, with 17% yield of **3aa** obtained in the absence of DABCO (Run 12). A dramatically lower yield of **3aa** was obtained when K_2CO_3, *i*-Pr_2EtN, or 4-dimethylaminopyridine (DMAP) was used instead of DABCO (for optimization details, see Supporting Information).

Table 1: Additive effect.[a]



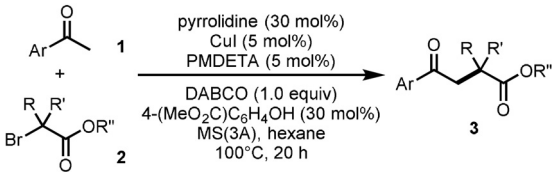
Run	Additive	Yield of **3aa** [%][b]
1	none	26
2[c]	none	0
3[d]	none	59
4[e]	none	81
5	*p*-TsOH	47
6	CF_3CO_2H	43
7	AcOH	64
8	*p*-MeC_6H_4OH	51
9	phenol	55
10	C_6F_5OH	49
11	*p*-$MeO_2CC_6H_4OH$	80 (70)
12	*p*-$MeO_2CC_6H_4OH$	17[f]
13	*m*-$MeO_2CC_6H_4OH$	66
14	*o*-$MeO_2CC_6H_4OH$	32
15	2-(benzo[*d*]oxazol-2-yl)phenol	48
16	(*S*)-binol	71

[a] All reactions were conducted with **1a** (3.0 equiv), **2a** (1.0 equiv), pyrrolidine (30 mol%), CuI (5 mol%), PMDETA (5 mol%), DABCO (1.0 equiv), additive (30 mol%) and MS 3Å in hexane for 20 h at 100 °C. [b] Yield determined by ^{1}H NMR spectroscopy, 1,1,2,2-tetrachloroethane used as internal standard; yield of isolated product shown in parenthesis. [c] Without pyrrolidine. [d] 50 mol% of pyrrolidine. [e] 100 mol% of pyrrolidine. [f] Without DABCO.

The reactivities of various ketones **1** were next examined under the optimized reaction conditions (Table 2). Although the alkylation mechanism is discussed later (vide infra), the formation of the enamine is an important step in the catalytic cycle. Pyrrolidine reacted smoothly with electron-poor and sterically less-hindered ketones **1** to produce the enamine intermediate, which reacted with the *tert*-alkyl radical generated from the reaction of the copper catalyst with the α-bromocarbonyl compound **2**. Therefore, relatively electron-rich ketones **1** (as in **1b**, **1c**, **1r**, and **1s**) resulted in lower yields of **3**, while the reactions proceeded smoothly with relatively electron-poor ketones **1** bearing (pseudo) halogens (i.e., **1d**, **1m**, and **1q**) and esters (i.e., **1f**–**1j**) to produce **3** in good yields. Ketones bearing aminocarbonyl groups (as in **1k** and **1l**), however, resulted in moderate yields. Ketones bearing electron-poor aryl and phenyl groups (as in **1n**, **1o**, and **1p**) also provided **3** in good yields. We examined various solvents with the aim of increasing the yield, with hexane/CPME (cyclopentyl methyl ether) found to be the better solvent in the case of **1b**. Sterically hindered ketone **1e** gave a low yield of **3ea**, but similarly hindered ketone **1r** gave a higher yield of **3ra**. Higher yields of **3** were obtained when 50 mol% pyrrolidine was included in the reactions of **1c** and **1r**. Acetophenones bearing thiophene or pyridine (**1t**, **1u**), which can poison the catalyst, afforded **3ta** or **3ua** in 38% or 52% isolated yield, respectively. In the case of **1u**, increasing amount of pyrrolidine was effective to obtain high yield.

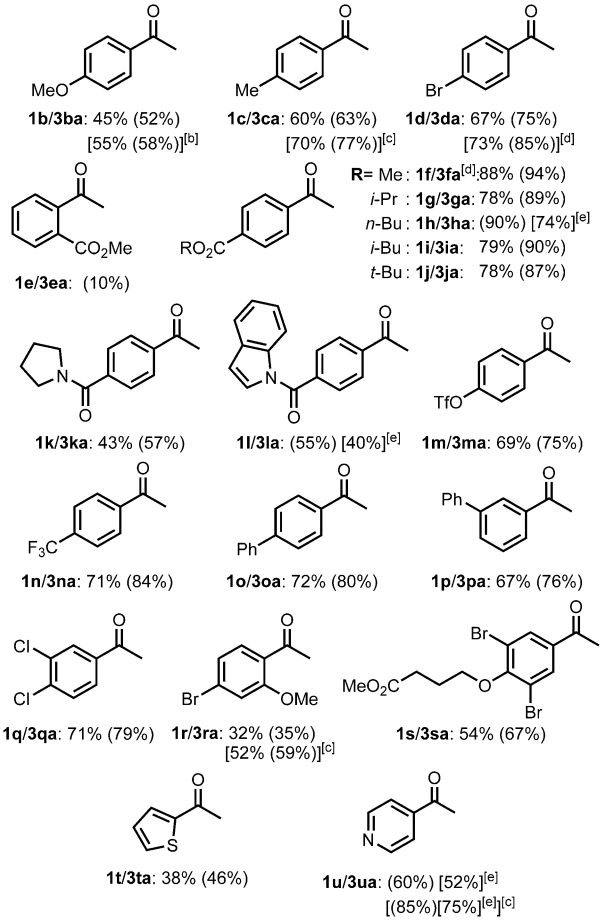
We next examined the reactivities of α-bromocarbonyl compounds **2** (Table 3). To check functional group compatibility, **2b**–**2j** bearing alkyl, substituted benzyl, ester, bromine, alcohol, and amino functional groups were examined, with our alkylation reaction exhibiting good functional group compatibility. We also checked the reactivities of substrates **2k**–**2o** bearing alkyl chains of various length, including cyclobutyl, cyclohexyl, ethyl, propyl, butyl, and other longer chains at the α-position, which revealed that this radical reaction is basically insensitive to steric bulk at the reaction site. Therefore, even **2o** substituted with both *n*-octyl and *n*-hexyl groups afforded **3jo** in 48% yield. Increasing the amount of pyrrolidine was also effective in the reactions of **2n** and **2o**, to give **3jn** and **3jm** in yields of 62% and 60%, respectively. 2-Bromolactone **2p** gave 53% yield of **3jp**. We found that 2-bromocarboxamide **2q** was a limitation of this reaction. Indeed, we examined various 2-bromocarboxamides, with the corresponding reduction, HBr elimination, and 1,4-HAT-like (hydrogen-atom-transfer-like) side-reactions observed. Although our radical methodology was not applicable to primary- and secondary-alkyl halide but sec-

Table 2: Substrate scope I.[a]



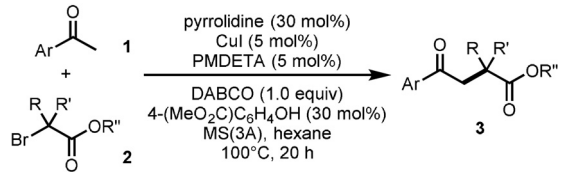
Substrates / Isolated yields of **3** (NMR yield)

Reactions of ketones (**1**) with $BrC(Me)_2CO_2(CH_2)_3Ph$ (**2a**)



[a] All reactions were conducted with **1** (3.0 equiv), **2** (1.0 equiv), pyrrolidine (30 mol%), CuI (5 mol%), PMDETA (5 mol%), DABCO (1.0 equiv), methyl 4-hydroxybenzoate (30 mol%) and MS 3Å in hexane for 20 h at 100°C. Isolated yields are shown. Yields in parentheses were determined by ^{1}H NMR analysis. [b] Reaction in hexane:CPME (10:1). [c] 50 mol% pyrrolidine was used. [d] Reaction at 80°C. [e] Isolated yield by GPC.

Table 3: Substrate scope II.[a]

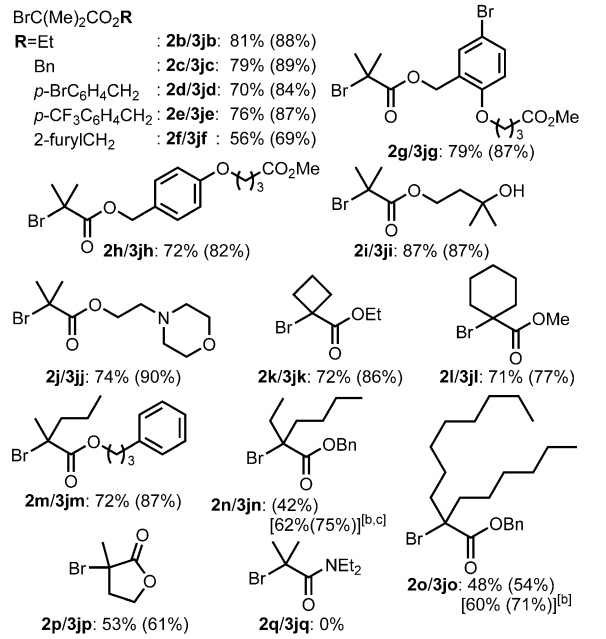


Substrates / Isolated yields of **3** (NMR yield)

Reactions of alkyl-Br (**2**) with p-(t-BuO_2C)C_6H_4COMe (**1j**)

$BrC(Me)_2CO_2$**R**

R=Et	: **2b/3jb**: 81% (88%)
Bn	: **2c/3jc**: 79% (89%)
p-$BrC_6H_4CH_2$	: **2d/3jd**: 70% (84%)
p-$CF_3C_6H_4CH_2$	: **2e/3je**: 76% (87%)
2-furylCH$_2$	: **2f/3jf** : 56% (69%)



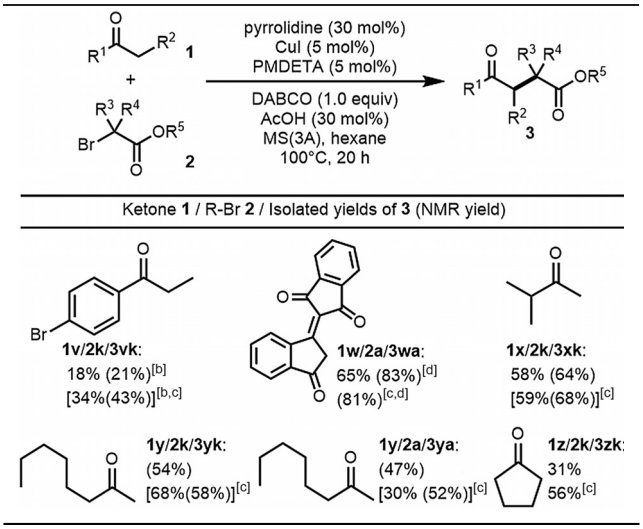
[a] All reactions were conducted with **1** (3.0 equiv), **2** (1.0 equiv), pyrrolidine (30 mol%), CuI (5 mol%), PMDETA (5 mol%), DABCO (1.0 equiv), methyl 4-hydroxybenzoate (30 mol%) and MS 3Å in hexane for 20 h at 100°C. Isolated yields are shown. Yields in parentheses were determined by ^{1}H NMR analysis. [b] 50 mol% pyrrolidine was used. [c] Isolated yield by GPC.

alkyl halides are basically reactive for enamines under classical ionic conditions.

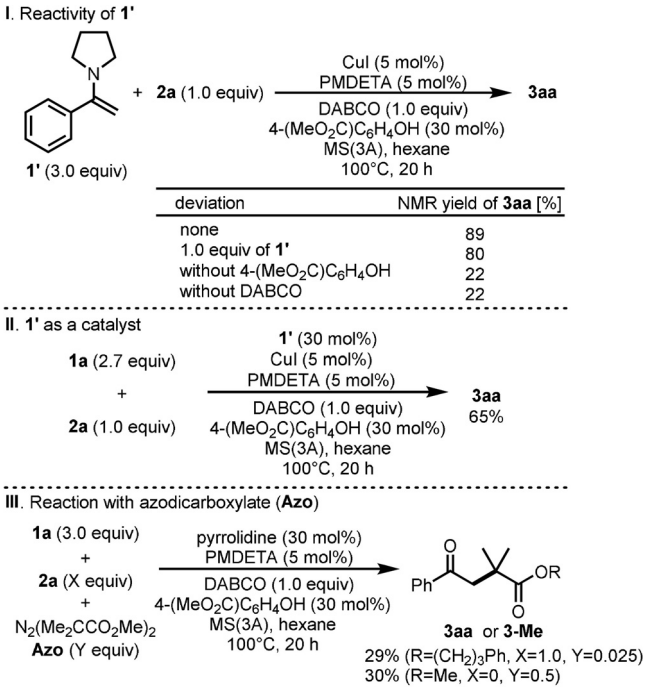
We next tried miscellaneous combinations of aliphatic, and β-functionalized ketones (**1v**–**1aa**) under modified optimized conditions. AcOH or TfOH gave smooth enamine formation (Table 4). The NMR yields of **3** were basically good but isolated yields were moderate to good because the isolations were sometimes problematic due to inseparable (or difficult to separate) side products such as reduction and H-Br elimination of **2**. Although β-ethylated ketone (**1v**) reacted with **2k** to give 34% yield of **3vk** in the presence of TfOH, β-alkenylated ketone (**1w**) reacted smoothly with **2a** to produce the corresponding product (**3wa**) in 65% yield in the presence of methyl 4-hydroxy benzoate that is the optimal acid. The reactions of acyclic aliphatic ketones (**1x** and **1y**) can be applied to this reaction and the yields ranged from 42–68% (**3xk**, **3yk**, and **3ya**). Cyclic ketone **1z** gave single alkylated product **3zk** in 56% yield. Interestingly, 3-methylcyclohex-2-en-1-one **1aa** gave γ-alkylated product **3aak** in 63% yield (See SI). In this case, α-alkylation was not observed.

A plausible organo- and copper-catalyzed *tert*-alkylation mechanism is outlined in Figure 2. Enamine **1′** is formed by the pyrrolidine ([N]H) and ArOH catalysts, and reacts with **A**, generated from the reaction of **2** with Cu^I, to form **B**. The reaction in the presence of TEMPO did not result in the formation of product **3**, which suggests that radical species **A** exists. **B** is then oxidized by Cu^{II} to produce cationic intermediate **C**. Here, ATRA provides an alternative pathway. Key intermediate **E** is obtained from **D** by the elimination of ArOH with DABCO. Finally, the hydrolysis of **E** provides **3** with concomitant formation of pyrrolidine to

Table 4: Substrate scope III.[a]



[a] All reactions were conducted with **1** (3.0 equiv), **2** (1.0 equiv), pyrrolidine (30 mol%), CuI (5 mol%), PMDETA (5 mol%), DABCO (1.0 equiv), AcOH (30 mol%) and MS 3Å in hexane for 20 h at 100 °C. Isolated yields are shown. Yields in parentheses were determined by ^{1}H NMR analysis. [b] TfOH was used instead of AcOH. [c] 50 mol% pyrrolidine and acid were used. [d] Methyl 4-hydroxy benzoate was used instead of AcOH.



Scheme 2. Control experiments.

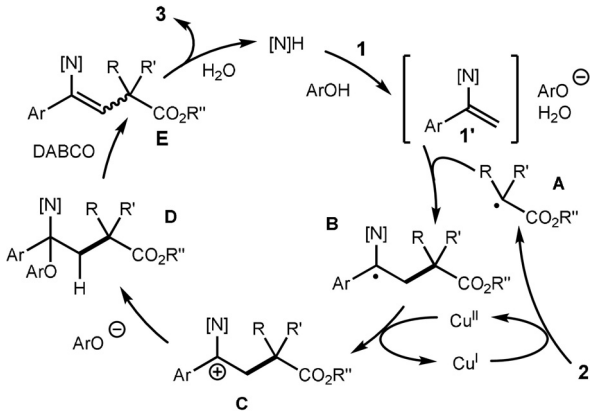


Figure 2. Proposed mechanism.

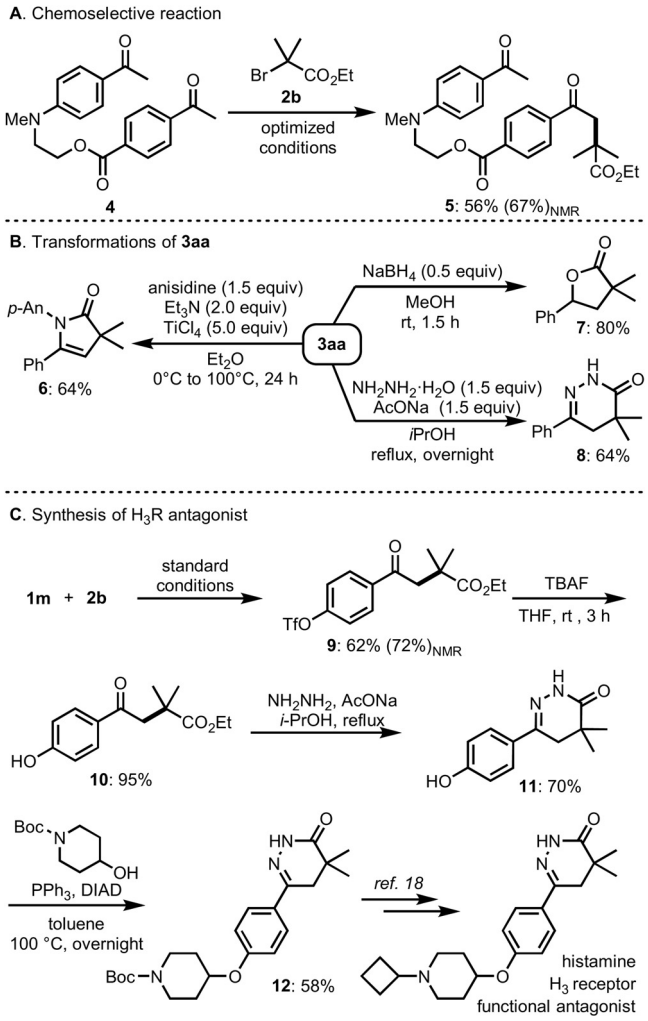
complete the catalytic cycle. Cationic intermediate **C** can also give **3** through an E1-like elimination reaction.

While speculative, we conducted some control experiments to support of the overall reaction mechanism (Scheme 2). We examined the reactivity of enamine **1′**, with the desired product **3aa** obtained in 89% yield under the optimized conditions; an 80% yield was obtained even when one equivalent of **1′** was used (Scheme 2 I). Although isolated enamines are reactive and pyrrolidine is cheap and readily available, the reaction of a catalytically generated enamine obtained by reacting a ketone with pyrrolidine is much more attractive than the reaction involving an isolated enamine. However, there appear to be no reports of reactions of α-bromocarbonyls with catalytically generated enamines since Zhang reported reactions of enamines with α-bromocarbonyls in the presence of a Ru catalyst,[9a] which is possibly attributable to the low reactivities of radical species toward unstable or short life-time molecules, such as aliphatic enamines. Low yields of **3aa** were obtained in the absence of 4-(MeO_2C)C_6H_4OH or DABCO. These results are consistent with those in Table 1 (Runs 1 and 12). We expected 4-(MeO_2C)C_6H_4OH to play an important role in the formation of the enamine; however, this result suggests that 4-(MeO_2C)C_6H_4OH affects or accelerates some of the elemental steps in the catalytic cycle, for example, by stabilizing cation **C**. DABCO is required for the hydrogen-elimination step in the catalytic cycle.

We also used enamine **1′** as a catalyst instead of pyrrolidine, which resulted in 65% yield of **3aa** (Scheme 2 II); in this case, the reaction did not proceed in the absence of **1′**. Pyrrolidine is consumed to generate **1′** and is reformed after the addition/elimination reaction.

An azodicarboxylate (**Azo**) generates the corresponding *tert*-alkyl radical when heated; hence, we used **Azo** to determine whether this reaction is a radical chain reaction or not (Scheme 2 III). When the reaction using **Azo** (as a catalyst or reagent) was carried out in the presence/absence of **2a**, low yield of **3aa** or **3-Me** (R = Me) was obtained. This result suggests that a chain mechanism may be involved, but as a minor pathway. As a key catalyst, a Cu salt is required to complete or repeat the catalytic cycle.

The reaction conditions associated with these α-alkylations can be further exploited for chemoselectivity. Hence, the alkylation of **4**, which possesses two different ketone moieties, exclusively afforded **5**, the singly alkylated product (Scheme 3 A). We next demonstrated that **3aa** can undergo three chemical transformations, as shown in Scheme 3 B. The reaction of **3aa** in the presence of *p*-anisidine, Et_3N, and $TiCl_4$ resulted in the formation of lactam derivative **6** in 64% yield, while the reduction of **3aa** with $NaBH_4$ led to cyclization and



Scheme 3. Synthetic application.

the corresponding lactone in 80% yield. Furthermore, the reaction of **3aa** with hydrazine gave pyridazinone derivative **8** in 64% yield. This amination reaction was used to formally synthesize the functional antagonist of the histamine H_3 receptor (Scheme 3C).[18] The alkylation of **1m** with **2b** under the optimized conditions provided **9** in 62% yield. Heterocyclic product **11** was obtained after the deprotection of **9** followed by the cyclization of **10** with hydrazine. The key intermediate **12** for the synthesis of the antagonist was obtained in 58% by the Mitsunobu reaction of **11**.

Starting with acetophenone (**1m**) and α-bromocarbonyl compound (**2b**), the corresponding tert-alkyl was incorporated smoothly, and only four steps were required to synthesis of the key intermediate **12**. In contrast, beginning with anisole in the previous route,[18] in which tert-alkyl was incorporated via Friedel–Crafts reaction, **12** was synthesized in five steps.

In summary, we successfully demonstrated the direct α-tertiary alkylations of ketones with α-bromocarbonyl compounds in a Cu- pyrrolidine combined-catalyst system. This dual catalyst system realizes the synthesis of tertiary alkylated ketones bearing quaternary carbons. Control experiments revealed that the catalytically generated enamine is a key intermediate. This combined catalyst system enabled the efficient synthesis of highly congested organic molecules through radical chemistry. Further applications, including asymmetric reactions, are currently being explored.

Acknowledgements

We warmly thank Yamaguchi University, Naito foundation and JSPS KAKENHI Grant Number JP20H04823 in Hybrid Catalysis for Enabling Molecular Synthesis on Demand.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkylation · copper · ketones · organocatalysis · radicals

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Manuscript received: December 2, 2020
Version of record online: April 7, 2021

