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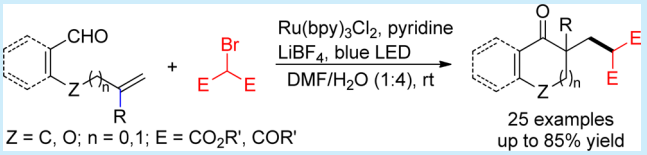
Visible-Light-Induced Tandem Radical Addition−Cyclization of Alkenyl Aldehydes Leading to Indanones and Related Compounds

Danyang Lu, Yimei Wan, Lichun Kong, and Gangguo Zhu*

Department of Chemistry, Zhejiang Normal University, 688 Yingbin Road, Jinhua 321004, China

Supporting Information

ABSTRACT: Herein we describe a novel, visible light-induced tandem radical addition−cyclization of alkenyl aldehydes with α-bromocarbonyl compounds. A set of cyclic ketones, including indanones, cyclopentenones, 3,4-dihydronaphthalen-1(2*H*)-ones, and chroman-4-ones, are synthesized at room temperature with high efficiency and good functional group compatibility. It represents the first report on the catalytic 1,2-acylalkylation of unactivated alkenes.



Indanones are found in numerous natural products, drugs, and bioactive molecules, such as the cytotoxic pterosine B,[1] antitumor active indenoindolone,[2] antiosteoporosis active (+)-isopaucifloral F,[3] and donepezil,[4] a drug for the treatment of Alzheimer's disease (Figure 1). In addition, they can serve as

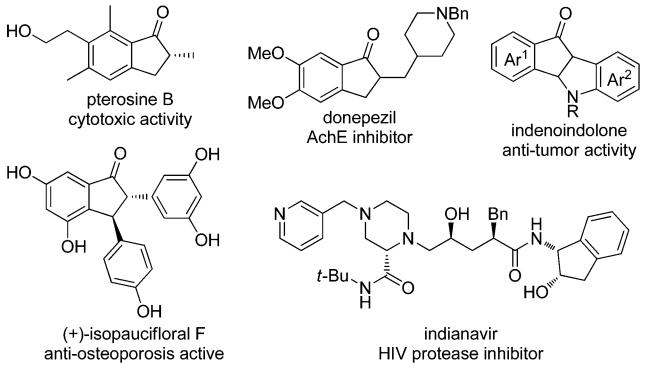
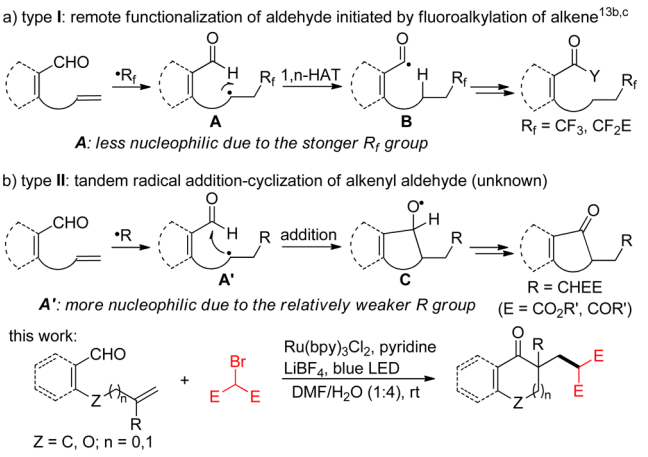


Figure 1. Significance of indanones.

versatile intermediates for the synthesis of HIV protease inhibitor indianavir,[5] a drug for the treatment of AIDS disease, and other pharmaceutical compounds. Consequently, a series of methods have been developed for the assembly of these scaffolds, including the Pd-,[6] Rh-,[7] Ag-,[8] or In-catalyzed[9] annulation, intramolecular Friedel−Crafts reaction,[10] Nazarov cyclization,[11] and others.[12] However, efficient and mild methods, especially those that can be performed at room temperature, are still in high demand.

We have recently developed a new method for the direct access to carbonyl compounds via the radical transformation of unsaturated aldehydes.[13] In the case of alkenyl aldehydes, the remote C−H functionalization of aldehydes has been realized through an intramolecular 1,n-hydrogen atom transfer (1,n-HAT) (Scheme 1a, type **I**).[13b,c] In contrast, the tandem radical addition−cyclization of alkenyl aldehydes has not been achieved. We envisioned that the formation of a more

Scheme 1. Summary of This Work



nucleophilic carbon radical **A′** might favor the intramolecular addition of carbon radicals to aldehydes, thus permitting the realization of tandem radical addition−cyclization of alkenyl aldehydes (Scheme 1b, type **II**).

On the other hand, the visible-light-driven photoredox catalysis has become a powerful tool for organic synthesis because of its inherent green and sustainable features.[14] The photocatalytic methods generally proceed at ambient temperature, thereby providing extremely mild alternatives to the existing protocols. Inspired by these works, we report here a novel, visible light photocatalyzed tandem radical addition−cyclization of alkenyl aldehydes with α-bromocarbonyls,[15] which successfully generates indanones, cyclopentenones, 3,4-dihydronaphthalen-1(2*H*)-ones, chroman-4-ones, and related cyclic ketones in moderate to high yields at room temperature. The facile transformation of resultant products into 6−5−6 tricyclic compounds, including 5*H*-indeno[1,2-*b*]pyridines and

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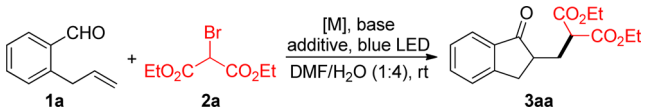
9*H*-fluorenes, has also been demonstrated. As far as we know, it is the first report on the 1,2-acylalkylation of unactivated alkenes.

Initially, the reaction was conducted with 2-allyl benzaldehyde (**1a**) and diethyl bromomalonate (**2a**) in the presence of 2 mol % of $Ru(bpy)_3Cl_2$ under a 15 W blue LED irradiation. After being stirred at room temperature in a 1:4 mixture of DMF/H_2O for 24 h, the 2-alkylated indanone **3aa** was obtained in 45% yield, while no reaction was observed with DMF as the solvent, suggesting the importance of effects of water solvation (Table 1, entries 1 and 2). The replacement of $Ru(bpy)_3Cl_2$ with either $Ru(bpy)_3(PF_6)_2$ or $[Ir(ppy)_2(dtbbpy)]PF_6$ led to comparable yields (entries 3 and 4). To improve the reaction yield, a variety of bases were examined (entries 5−10). In the presence of Et_3N and *i*-Pr_2NEt, only a trace amount of **3aa** was formed (entries 8 and 9). In contrast, the yield was improved to 55% when pyridine was employed as the base (entry 11). It was reported that Lewis acid additives might promote the reduction of carbon−halide bonds via coordination, thus facilitating the formation of carbon radicals.[15b] Therefore, an array of additives were tested, and gratifyingly, full consumption of **1a** was observed with the addition of 1 equiv of $LiBF_4$, and **3aa** was isolated in 81% yield (entries 12−16). Furthermore, the reaction could be scaled up by 20 times without erosion of the efficiency.

Table 1. Optimization of the Reaction Conditions[a]

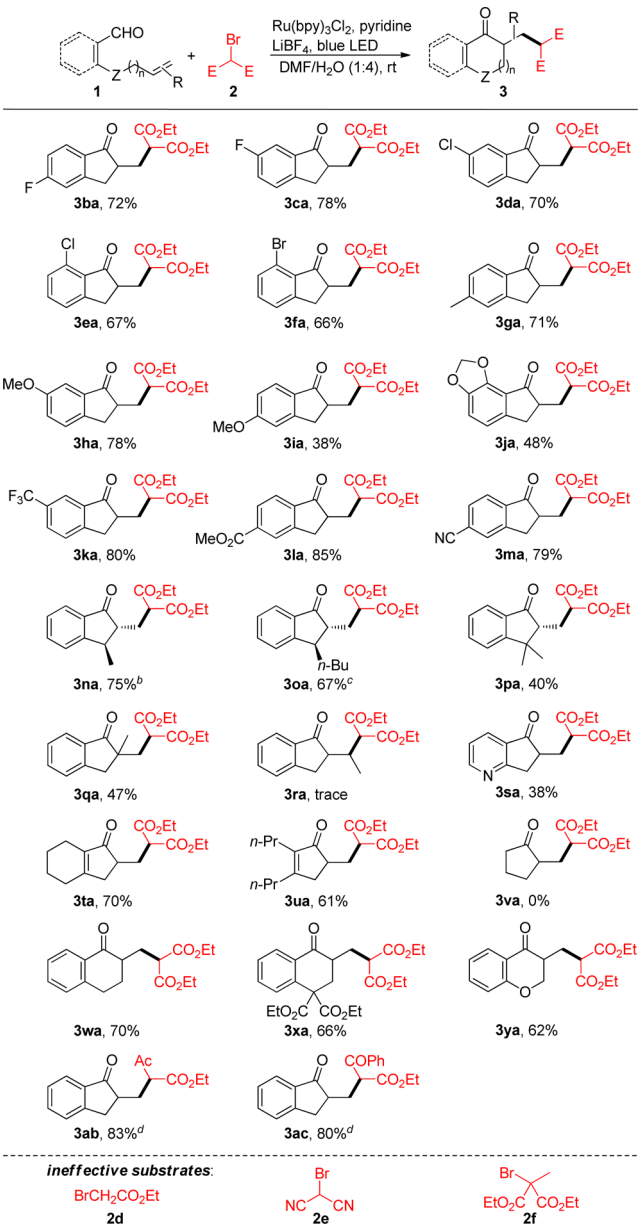


entry	[M]	base	additive	yield (%)
1[b]	$Ru(bpy)_3Cl_2$	none	none	0
2	$Ru(bpy)_3Cl_2$	none	none	45
3	$Ru(bpy)_3(PF_6)_2$	none	none	39
4	$[Ir(ppy)_2(dtbbpy)]PF_6$	none	none	43
5	$Ru(bpy)_3Cl_2$	$NaHCO_3$	none	17
6	$Ru(bpy)_3Cl_2$	K_2HPO_4	none	21
7	$Ru(bpy)_3Cl_2$	NaH_2PO_4	none	30
8	$Ru(bpy)_3Cl_2$	Et_3N	none	trace
9	$Ru(bpy)_3Cl_2$	*i*-Pr_2NEt	none	trace
10	$Ru(bpy)_3Cl_2$	DBU	none	13
11	$Ru(bpy)_3Cl_2$	pyridine	none	55
12	$Ru(bpy)_3Cl_2$	pyridine	LiCl	5
13	$Ru(bpy)_3Cl_2$	pyridine	LiBr	46
14	$Ru(bpy)_3Cl_2$	pyridine	LiI	11
15	$Ru(bpy)_3Cl_2$	pyridine	$LiBF_4$	81 (77)[c]
16	$Ru(bpy)_3Cl_2$	pyridine	KPF_6	trace

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), [M] (2 mol %), base (0.50 mmol), additive (0.25 mmol), DMF/H_2O (v/v = 1:4), 25 °C, 24 h. Yields of the isolated products are given. [b]DMF was used as the solvent. [c]5 mmol scale.

Having identified the optimized reaction conditions, the scope and limitations of this reaction were investigated in detail using a variety of alkenyl aldehydes (Scheme 2). Halides, such as F, Cl, and Br, were tolerated rather well under the reaction conditions, thereby offering great opportunities for the downstream derivations (**3ba**−**3fa**). In particular, 2-allyl-4-chlorobenzaldehyde (**1d**) afforded **3da** in 70% yield, while 2-allyl-6-chlorobenzaldehyde (**1f**) was converted into the corresponding product **3fa** in 66% yield, implying that the steric hindrance near the aldehyde group has little impact on the reaction. Substrates **1i** and **1j**, bearing the strong electron-donating OMe group, were transformed to the desired products in decreased yields (**3ia** and **3ja**). In comparison, aldehydes **1k**−**1m**, having strong electron-withdrawing substituents such as CF_3, CO_2Me, and CN on the benzene ring, were viable substrates and provided indanones **3ka**−**3ma** in high yields. These results indicated that the electrophilicity of the aldehyde group has a significant correlation with the reaction yield.

Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.50 mmol), $Ru(bpy)_3Cl_2$ (2 mol %), pyridine (0.50 mmol), $LiBF_4$ (0.25 mmol), DMF/H_2O (v/v = 1:4), 25 °C, 24 h. Yields of the isolated yields are given. [b]dr = 88:12. [c]dr > 98:2. [d]dr = 50:50.

Pleasingly, 2,3-disubstituted indanones could be synthesized in a diastereoselective manner. For example, the reaction of **1n** occurred uneventfully to deliver **3na** in 75% yield with high diastereoselectivity (dr = 88:12). In the case of **1o**, a single *trans*-diastereoisomer **3oa** was assembled, presumably owing to

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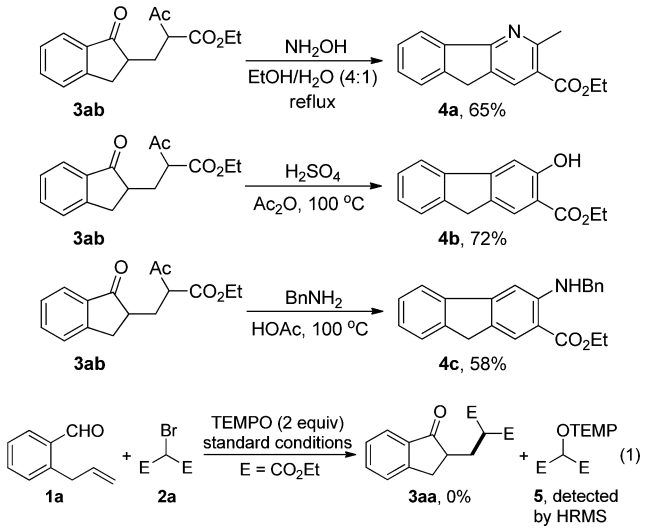
the increased steric hindrance. Moreover, alkenyl aldehyde **1q**, with a disubstituted terminal C−C double bond, was a competent substrate for the indanone synthesis, albeit in a moderate yield (**3qa**). In contrast, the substrate **1r**, possessing an internal alkene, failed to provide the desired product under the reaction conditions.

The reaction of 2-allylnicotinaldehyde (**1s**) took place smoothly, forming **3sa** in a moderate yield. In addition to 2-allyl benzaldehydes, other alkenyl aldehydes such as **1t** and **1u** were also effective coupling partners and gave polysubstituted cyclopentenones **3ta** and **3ua** in good yields. The tandem radical addition−cyclization of hex-5-enal (**1v**) was sluggish, probably because of the absence of conjugation effect between the carbon radical and the adjacent double bond (see the intermediate **IV** of the proposed mechanism). When 2-homoallyl benzaldehyde **1w** was subjected to the reaction conditions, the 3,4-dihydronaphthalen-1(2*H*)-one derivative **3wa** was assembled in 70% yield. The construction of chroman-4-one was also feasible, as exemplified by the production of **3ya**. Of note, in all cases we tested, byproducts derived from the intramolecular hydrogen atom abstraction of aldehydic hydrogen atom were not observed. Meanwhile, the bromide component was varied. For instance, the coupling of **1a** with ethyl 2-bromo-3-oxobutanoate (**2b**) occurred efficiently to produce **3ab** in 83% yield. The structure of products **3** was determined by the H−H COSY, HMBC, DEPT, NOE, and other NMR measurements (see the Supporting Information). Unfortunately, substrates **2d**−**2f** were incompatible for the reaction.

Experiments that illustrate the synthetic utility of this method were carried out (Scheme 3). Upon treatment of **3ab** with 3

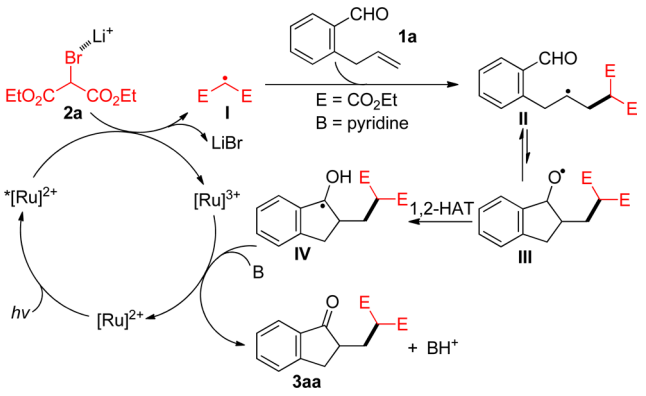
Scheme 3. Derivatization of Compound 3ab



equiv of NH_2OH in a 4:1 mixture of EtOH/H_2O at reflux for 4 h, the 5*H*-indeno[1,2-*b*]pyridine product **4a**[16] was synthesized in a good yield. In the presence of catalytic concentrated H_2SO_4, the intramolecular condensation of **3ab** delivered the 9*H*-fluorene derivative **4b**[17] in 72% yield. In addition, the reaction between **3ab** and $BnNH_2$ generated the amino 9*H*-fluorene **4c** in 58% yield.

Subsequently, a radical trapping experiment was performed with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 2 equiv) as the radical scavenger. The formation of **3aa** was completely inhibited, and the TEMPO-adduct **5**[18] was detected by the HRMS analysis (eq 1), implying the involvement of a carbon radical intermediate. Based on the above results and previous reports,[15b,c] a putative mechanism is proposed as described in Scheme 4. First, the photocatalyst Ru(II) is elevated to its

Scheme 4. Proposed Catalytic Cycle



excited state Ru(II)* under blue LED irradiation. The generated Ru(II)* species may act as a single electron transfer (SET) reagent and reduce **2a** to form an electrophilic carbon radical **I**, with the concurrent production of Ru(III) species. Afterward, the addition of radical **I** across the electron-rich C−C double bond of **1a**, followed by an intramolecular addition to aldehyde, produces an alkoxy radical **III**, which is transformed to the carbon-centered radical **IV** via a formal 1,2-hydrogen atom transfer (1,2-HAT).[13a,19] In the presence of pyridine, the SET oxidation[20] of **IV** by Ru(III) species provides the indanone product **3aa**, together with the regeneration of the Ru(II) catalyst.

In summary, an operationally simple and mild visible light-induced tandem radical addition−cyclization of alkenyl aldehydes with activated bromides has been developed. To the best of our knowledge, it is the first report of 1,2-acylalkylation of unactivated alkenes. A variety of cyclic ketones, such as indanones, cyclopentenones, 3,4-dihydronaphthalen-1(2*H*)-ones, and chroman-4-ones, are successfully synthesized in moderate to high yields at room temperature. Various functional groups, such as F, Br, Cl, OMe, CF_3, CO_2Me, CN, and Ac, are compatible for the current process. The resultant products can be smoothly converted into the synthetically attractive 6−5−6 tricyclic compounds, including 5*H*-indeno-[1,2-*b*]pyridines and 9*H*-fluorenes, which may be valuable for the rapid access to complex molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01162.

Detailed experimental procedures, characterization data for new products **1**, **3**, and **4** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gangguo@zjnu.cn.

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ORCID

Gangguo Zhu: 0000-0003-4384-824X

Notes

The authors declare no competing financial interest.

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