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Acylation of Aryl Halides and α-Bromo Acetates with Aldehydes Enabled by Nickel/TBADT Cocatalysis

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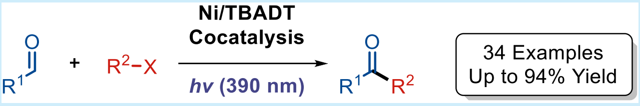
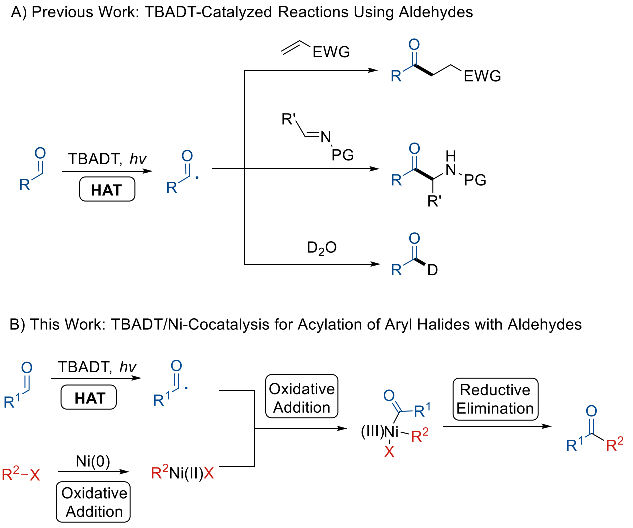
ABSTRACT: In this protocol aryl halides and α-bromo acetates are efficiently cross-coupled with an array of (hetero)aromatic and aliphatic aldehydes under the cooperative catalysis of nickel and tetrabutylammonium decatungstate as a hydrogen-atom-transfer photocatalyst. This method provides a concise approach to a variety of ketones with high compatibility of various functional groups.



Because aldehydes are abundant, inexpensive, and easily accessible precursors, the preparation of ketones in one single step using aldehydes as acyl source is a concise and appealing method. Therefore, many organic reactions have been established following this concept, such as Benzoin reaction,[1] Stetter reaction,[2] and transition-metal catalyzed hydroacylation of alkenes or alkynes.[3] Furthermore, cross-couplings of aldehydes with aryl (pseudo)halides[4] or organometallics[5] were also achieved under the catalysis of Pd, Ni, Ru, or Rh. Generally, these reactions required high reaction temperature. In contrast, a Ni/photo cocatalytic acylation of aryl and alkyl halides with aldehydes under mild reaction conditions was developed by MacMillan and his co-worker.[6] However, the use of an expensive noble-metal photocatalyst is less desirable. Very recently, König et al. reported that the photochemical Ni-catalyzed acylation of aryl bromides still proceeded smoothly even in the absence of an external photocatalyst.[7] The major disadvantage of this method is that the substrate scope is limited to aromatic aldehydes.

Tetrabutylammonium decatungstate (TBADT) is a well-known hydrogen-atom-transfer (HAT) photocatalyst, which is able to promote numerous reactions involving C−H bond activation of a radical type.[8,9] Notably, TBADT can be prepared in one single step from the inexpensive precursor.[10] The pioneering work of Fagnoni et al. disclosed that acyl radicals can be generated from aldehydes via homolytic acyl C−H bond cleavage under the photocatalysis of TBADT,[9c] and this elementary reaction has been engaged as a key step in hydroacylation of alkenes[9c,e,g,q] and imines[9p] as well as deuteration[9r] of aldehydes (Scheme 1A). On the other side, Ni(0) is able to undergo oxidative addition with aryl or alkyl halides, to afford a Ni(II)-species. We envisage that the generated Ni(II) intermediate could be further oxidized by an acyl radical in a Ni/TBADT-cocatalyzed reaction,[11] to provide a Ni(III) species,[6] which upon reductive elimination results in a variety of ketones (Scheme 1B).

Scheme 1. (A) TBADT-Catalyzed Reactions Using Aldehydes; (B) Ni/TBADT-Cocatalyzed Acylation of Aryl or Alkyl Halides



To realize the nickel/TBADT-cocatalyzed acylation reaction, we utilized 4-bromo acetophenone (**1a**) and butanal (**2a**) as standard substrates for optimizing the reaction conditions (Table 1). Systematic screening of various parameters including solvents, temperature, reaction time, catalyst loading, and concentration provided us the optimal reaction conditions as follows: 5 mol % TBADT and 10 mol % NiI_2 with the bipyridine **L1** as ligand and K_3PO_4 as base in MeCN (0.2 M) at room temperature under the irradiation (390 nm) for 4 h. In this case, the reaction afforded the desired product **3a** in 94%

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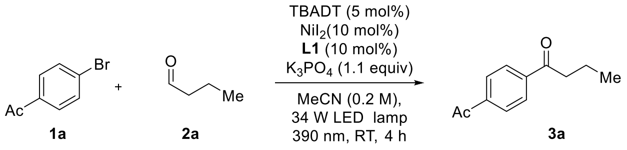
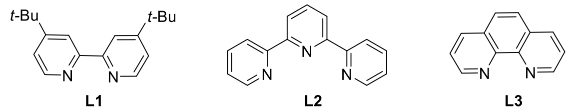
Table 1. Variation from the Optimal Reaction Conditions[a]





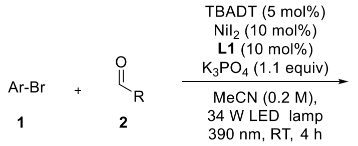
Entry	Variation from the Optimal Conditions	Yield (%)[b]
1	none	94
2	w/o TBADT	0
3	w/o NiI_2	0
4	w/o light	0
5	$NiBr_2$ instead of NiI_2	82
6	$NiBr_2$·dme instead of NiI_2	80
7	**L2** instead of **L1**	trace
8	**L3** instead of **L1**	trace
9	2 mol % TBADT instead of 5 mol % TBADT	81
10	DABCO instead of K_3PO_4	<10
11	acetone instead of MeCN	68

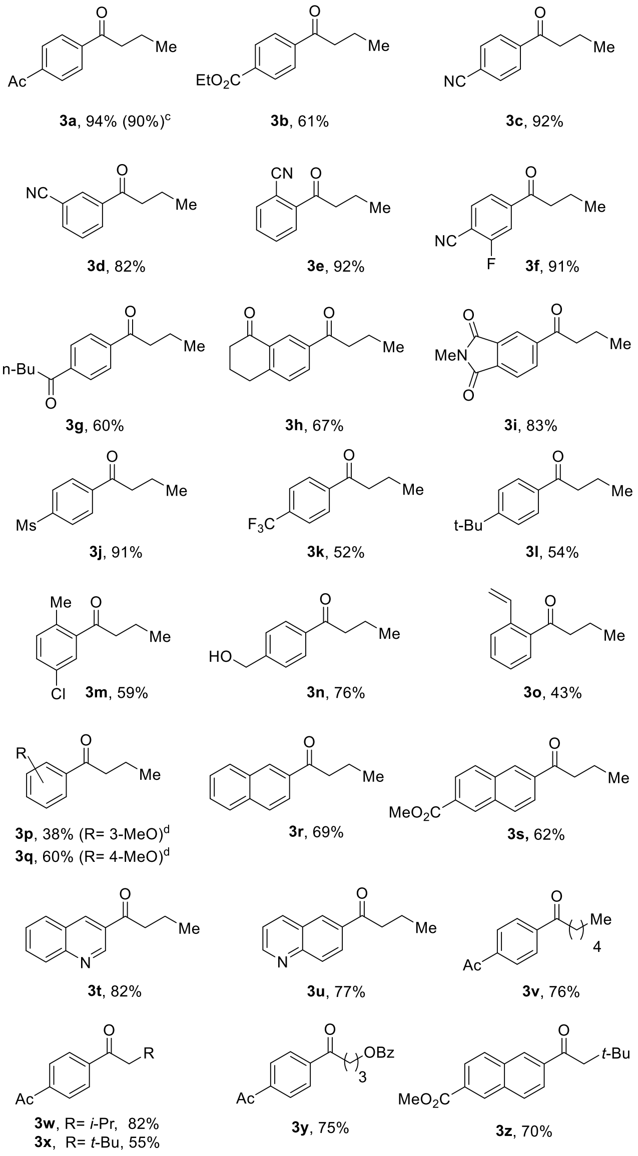
[a] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of 4-bromo acetophenone (**1a**) with 3 equiv of butanal (**2a**) using 5 mol % TBADT, 10 mol % NiI_2, 10 mol % **L1**, and 1.1 equiv of K_3PO_4 irradiated by a 34 W LED lamp (390 nm) in 1 mL of MeCN at room temperature for 4 h. [b] Yield of the isolated product after column chromatography.

yield (entry 1). Conducting the reactions without either TBADT or NiI_2 gave rise to the complete shutdown of the cross-coupling reaction (entries 2 and 3). Moreover, the formation of the desired product **3a** was not observed when the reaction was carried out in the dark (entry 4). The use of other Ni-salts resulted in lower yields (entries 5 and 6). In the case of terpyridine (**L2**) or 1,10-phenanthroline (**L3**) as ligand, only a trace amount of product was produced (entries 7 and 8). Lowering the catalyst loading of TBADT to 2 mol % led to a decreased yield (entry 9). When K_3PO_4 was replaced by the organic base DABCO, the yield diminished dramatically (entry 10). Furthermore, the reaction using acetone as solvent also provided the product, albeit with lower efficiency (entry 11).

After establishing the optimal reaction conditions, we started to evaluate the substrate spectrum of this Ni/TBADT-cocatalyzed reaction by varying the structure of both aryl halides and aldehydes (Table 2). All the reactions employing bromobenzene with electron-withdrawing substitution proceeded smoothly under the standard reaction conditions, furnishing the products **3a**−**k** in moderate to excellent yields. Furthermore, the use of alkyl- or vinyl-substituted bromobenzenes as precursors also posed no problem, and the corresponding products **3l**−**o** were obtained in moderate to good yields. In contrast, the reactions using methoxy-substituted phenyl bromides failed to deliver the products in acceptable efficiency. In this case, the corresponding iodides were utilized, instead, giving the products **3p** and **3q** in moderate yields. Moreover, naphthyl and heteroaryl bromides also turned out to be pertinent substrates for this Ni/TBADT-cocatalyzed reaction, providing the products **3r**−**u** in good to high efficiency. Subsequently, a variety of aliphatic aldehydes were surveyed, and the products **3v**−**z** were afforded in moderate to good yields. Generally, the undesired dehalogenation of aryl halides accounts for all the above-mentioned low-yielding reactions. In addition, aromatic aldehydes also undergo the arylation under the standard conditions. However, control studies found that these reactions proceed in the absence of Ni-catalyst, and therefore these substrates were not the focus of this manuscript.

Table 2. Evaluation of the Substrate Scope of Aryl Halides and Aliphatic Aldehydes[a,b]

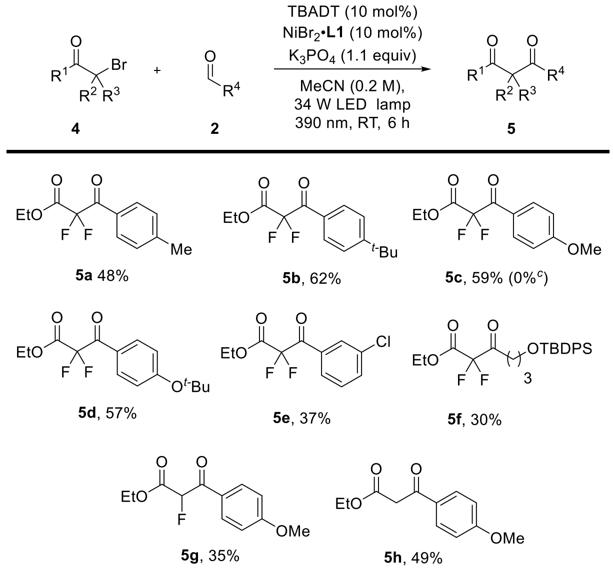




[a] Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the aryl bromides **1** with 3 equiv of aldehydes **2a** using 5 mol % TBADT, 10 mol % NiI_2, 10 mol % **L1**, and 1.1 equiv of K_3PO_4 irradiated by a 34 W LED lamp (390 nm) in 1 mL of MeCN at room temperature for 4 h. [b] Yields of the isolated products. [c] Reaction was performed on 1 mmol scale. [d] Reaction was performed with the corresponding iodides.

Next, we continued to investigate the substrate scope of this Ni/TBADT cocatalyzed reaction by using aliphatic bromides as the coupling partner with aldehydes. Unfortunately, in the case of unactivated alkyl halides the desired acylation reaction failed to deliver the cross-coupling product at a synthetically useful level. Gratifyingly, ethyl 2-bromo acetate and its fluorinated analogues turned out to be competitive coupling partners with both substituted benzaldehydes and an aliphatic aldehyde under modified reaction conditions (10 mol % TBADT, $NiBr_2$**L1** complex as catalyst instead of the precatalyst NiI_2 and **L1**), providing an array of β-keto esters **5a−h** in moderate yields (Table 3). Moreover, we performed a control experiment for the reaction using aromatic aldehyde, in which no TBADT was employed. In this case, no acylation reaction occurred, confirming the indispensable role of TBADT in the cocatalysis.

Table 3. Evaluation of the Substrate Scope of α-Bromo Acetates[a,b]



[a]Unless otherwise specified, reactions were performed on a 0.2 mmol scale of the aldehydes **2** with 3 equiv of the α-bromo acetates **4** using 10 mol % TBADT, 10 mol % $NiBr_2{\cdot}$**L1**, and 1.1 equiv of K_3PO_4 irradiated by a 34 W LED lamp (390 nm) in 1 mL of MeCN at room temperature for 4 h. [b]Yields of the isolated products. [c]Reaction was performed without TBADT.

In summary, we developed a nickel/photo cocatalyzed acylation of aryl halides and α-bromo acetates with both aromatic and aliphatic aldehydes under mild reaction conditions, providing a convenient and efficient access to a variety of ketones. Notably, a series of sensitive functional moieties are well tolerated in this reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01121.

Description of experimental procedures, NMR spectra, and ESI-MS data (PDF)

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Notes

The authors declare no competing financial interest.

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