OL Organic Letters

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C−H Alkylation of Aldehydes by Merging TBADT Hydrogen Atom Transfer with Nickel Catalysis

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Cite This: *Org. Lett.* 2021, 23, 5389−5393 Read Online

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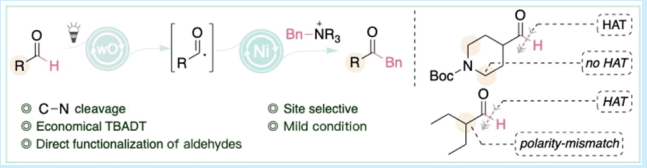
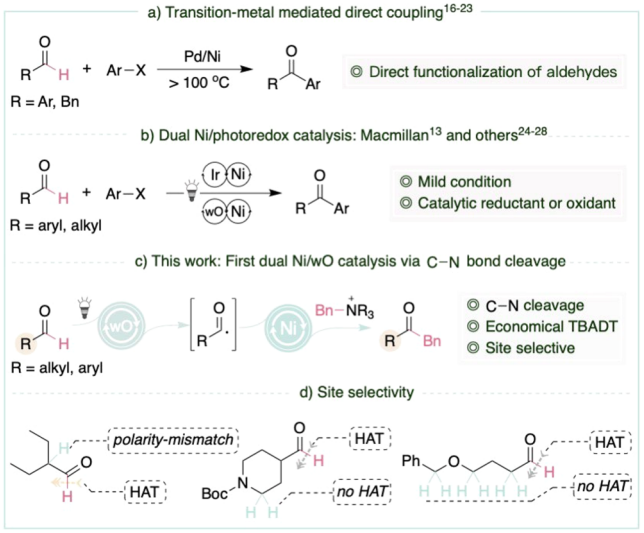
ABSTRACT: Catalyst controlled site-selective C−H functionalization is a challenging but powerful tool in organic synthesis. Polarity-matched and sterically controlled hydrogen atom transfer (HAT) provides an excellent opportunity for site-selective functionalization. As such, the dual Ni/photoredox system was successfully employed to generate acyl radicals from aldehydes via selective formyl C−H activation and subsequently cross-coupled to generate ketones, a ubiquitous structural motif present in the vast majority of natural and bioactive molecules. However, only a handful of examples that are constrained to the use of aryl halides are developed. Given the wide availability of amines, we developed a cross-coupling reaction via C−N bond cleavage using the economic nickel and TBADT catalyst for the first time. A range of alkyl and aryl aldehydes were cross-coupled with benzylic and allylic pyridinium salts to afford ketones with a broad spectrum of functional group tolerance. High regioselectivity toward formyl C−H bonds even in the presence of α-methylene carbonyl or α-amino/oxy methylene was obtained.



The greatest strength of C−H functionalization is the evasiveness of prefunctionalization in organic synthesis, although the vast majority of C−H activation relies on the use of directing groups or intramolecular hydrogen atom abstraction.[1−6] In recent years, there has been an increasing interest in catalyst controlled hydrogen atom transfer (HAT) process since the transition state favors the polarity-matched and sterically controlled hydrogen atom abstraction.[7−15] The site selectivity can be achieved by choice of suitable catalyst and reaction conditions. Of the many HAT reactions known, the generation of acyl radicals from aldehydes stands out to be a unique strategy to offer ketones, a fundamental functional group present in natural and bioactive molecules. Because alkyl aldehydes are easily accessible and inexpensive, the direct coupling of aldehydes via formyl hydrogen atom abstraction is highly desirable. While transition-metal mediated direct cross-coupling of aromatic and benzylic aldehydes with aryl halides exist, in general, these reactions rely on the stoichiometric use of oxidants or reductants and high temperature (Scheme 1a).[16−22]

As such, developing strategies to generate acyl radicals from aldehydes under the mild reaction condition is highly desirable. In this context, Macmillan[13] recently developed a dual Ni/Ir photoredox catalysis that enabled the cross-coupling of alkyl aldehydes via HAT process under mild conditions (Scheme 1b). Murakami and Ishida also developed a similar protocol for dehydrogenative coupling of aldehydes.[23] As an alternative, the inexpensive TBADT (tetrabutylammonium decatungstate) represents a unique and highly attractive photocatalyst in HAT process since the triplet state wO of TBADT selectively abstracts a hydrogen atom from a range of substrates.

Scheme 1. Cross-Coupling of Aldehydes



Fagnoni[24] and Orfanopoulos[25] employed TBADT to generate acyl radical from alkyl aldehydes, and subsequently employed

Received: May 21, 2021
Published: June 25, 2021

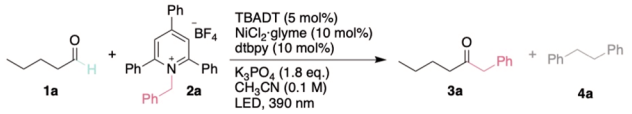
them in Giese-addition. Lately, TBADT has also been employed in dual Ni/Pd/photoredox catalysis to cross-couple the aldehydes and aryl halides.[26,27]

Despite these initial findings, the scope of the electrophile remains rather confined to aryl halides (Scheme 1b).[26−28] As such, developing strategies to accommodate more electrophiles would be beneficial. The use of alkyl amines as an electrophilic coupling partner in dual TM-photoredox catalysis is underdeveloped despite its widespread availability.[29,30] On the basis of recent studies on Katritzky pyridinium salts[31] by various research groups including Watson,[32−38] Glorius,[39−41] Aggarwal,[42,43] Martin,[44] Rueping,[45] and our group,[46] we anticipated that the pyridinium salts could be cross-coupled with alkyl aldehydes under a suitable TM-photoredox catalytic system. However, the undesired homocoupling of pyridinium salts and site selectivity in C−H abstraction must be addressed (Scheme 1d). As a part of our ongoing studies in nickel mediated cross-coupling reactions,[46−48] herein we describe the Ni/TBADT dual catalysis for the successful realization of coupling between alkyl aldehydes and benzylic pyridinium salts.

At the outset of our studies, aldehyde **1a** was chosen to identify a suitable reaction condition. An extensive library of nickel catalysts, ligands, photocatalysts, and solvents was screened (see SI-4) to suppress the formation of undesired homocoupled product **4**. Of the several nickel catalysts screened (entries 1−7, Table 1), only $NiCl_2$·glyme and $NiBr_2$·glyme (entries 1−2) afforded the cross-coupled product **3a** in very good yields. $NiCl_2$ and $NiBr_2$·bpy afforded the ketone **3a** only in 37% and 20% yields (entries 3−4), and the undesired homocoupling of **2a** to **4** was seen as a major byproduct. The other nickel catalysts were also ineffective (entries 5−7). Having identified $NiCl_2$·glyme as the optimal catalyst, a small group of ligands were further screened (entries 8−11). Interestingly, the reaction afforded 60% of **3a** in the absence of added ligand dtbpy (entry 8). However, the simple bpy (entry 9), 1,10-phen (entry 10), and DMAP (entry 11) ligands led to a significant reduction in the yields affording **3a** only in 53%, 38%, and 75% yields. When K_2CO_3 or Li_2CO_3 was employed as a base, the yield of **3a** was drastically reduced (entries 12−13). Lowering the amount of either K_3PO_4 (entry 14) or catalyst (entry 15−16) also lowered the yield. The high dielectric constant solvent CH_3CN was more efficient than the other solvents (SI-5). Several photocatalysts were subsequently investigated. Despite the fact that the absorption spectrum of TBADT is centered at 324 nm,[49] the broad range of its absorption allows the use of visible light for the excitation. We obtained excellent yields with both 390 and 365 nm LED lights (entries 1 and 22), although the use of long-wavelength 410 nm LED light significantly reduced the efficiency of the reaction (entry 21). Virtually no cross-coupled product was seen when TBADT was replaced with Eosin Y or Mes-Acr-ClO_4 (entries 17−18). The more efficient $Ir[dF(CF_3)ppy_2(dtbpy)]PF_6$ ($E_{1/2}$ = 1.21 V vs SCE in CH_3CN)[50] afforded the ketone **3a** only in 58% yield (entry 19), and the organic photocatalyst benzophenone gave traces of cross-coupled product (entry 20). The amount of aldehyde **1a** cannot be lowered as it significantly reduces the yield of **3a** (entry 23). In general, the dimerization of **2a** accounts for all the inefficient reactions. Control experiments revealed that there was no reaction in the absence of K_3PO_4 or $NiCl_2$·dtbpy or TBADT or LED (entries 24−27).

Having the optimized conditions in hand, we screened a broad spectrum of aldehydes, and the results are summarized

Table 1. Optimization Table[a]



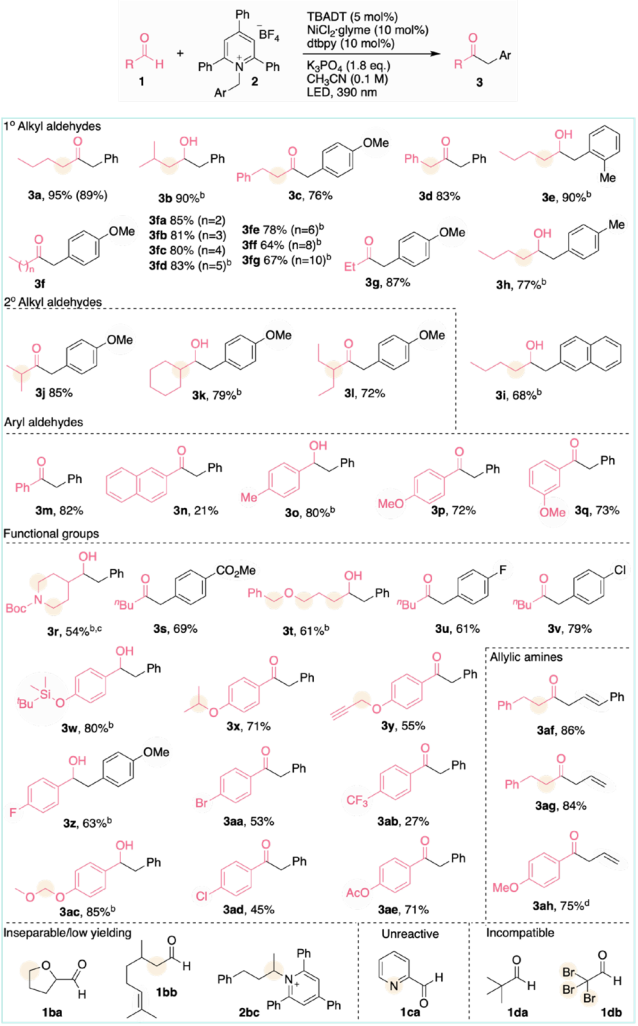
entry	deviation from above	4[b]	3a[b]
1	none	3	95, 89[c]
2	10 mol % of $NiBr_2$·glyme	9	88
3	10 mol % of $NiCl_2$	20	37
4	10 mol % of $NiBr_2$·bpy	23	20
5	10 mol % of $Ni(cod)_2$	28	43
6	10 mol % of $Ni(OTf)_2$	21	13[d]
7	10 mol % of $Ni(OAc)_2·4H_2O$	6	19[d]
8	without dtbpy	8	60
9	10 mol % of bpy	42	53
10	10 mol % of 1,10-phen	27	38
11	20 mol % of DMAP instead of dtbpy	2	75
12	1.8 equiv of K_2CO_3 instead of K_3PO_4	27	25[e]
13	1.8 equiv of Li_2CO_3 instead of K_3PO_4	21	37[e]
14	1.0 equiv K_3PO_4	2	78
15	2.5 mol % of TBADT	3	86[f]
16	2.5 mol % of TBADT	14	60[g]
17	5 mol % of Eosin Y	25	ND[h]
18	5 mol % of Mes-Acr-ClO_4	5	ND[h]
19	2 mol % of $Ir[dF(CF_3)ppy_2(dtbpy)]PF_6$	10	58[h]
20	30 mol % of Benzophenone	27	6[e]
21	410 nm with 2 equiv of **1a**	12	67
22	365 nm with 2 equiv of **1a**	2	96, 81[c]
23	2 equiv of **1a**	10	87, 80[c]
24	without K_3PO_4	ND	ND[d]
25	without $NiCl_2$·dtbpy	ND	ND[d]
26	without TBADT	28	<5[d]
27	without light source	ND	ND[d]

[a]0.0075 mmol of TBADT, 0.015 mmol of $NiCl_2$·glyme, 0.015 mmol of dtbpy, 0.15 mmol of **2a**, 0.45 mmol of **1a**, 0.27 mmol of K_3PO_4, CH_3CN (0.1 M), 390 nm. [b]GC yield. [c]Isolated yield. [d]Unreacted **2a** was observed in TLC analysis. [e]365 nm instead of 390 nm LED light source was used. [f]7.5 mol % of $NiCl_2$·glyme, 7.5 mol % of dtbpy. [g]5.0 mol % of $NiCl_2$·glyme, 5.0 mol % of dtbpy. [h]445 nm instead of 390 nm LED light source was used. DMAP: 4-(Dimethylamino)pyridine. dtbpy: 4,4′-Di-*tert*-butyl-2,2′-dipyridyl. bpy: 2,2′-Bipyridine. 1,10-Phen: 1,10-Phenanthroline. ND: not detected.

in Table 2. The linear alkyl aldehydes **1a**−**1i**, including long alkyl chain **1fa**−**1fg** and benzylic aldehyde **1d**, underwent cross-coupling reactions with high levels of efficiency to afford the corresponding ketones **3**. The α-branched secondary alkyl aldehydes **1j**−**1l** including cyclohexanecarbaldehyde **1k** and 4-piperidinecarbaldehyde **1r** did not impede the reaction; the corresponding cross-coupled products were isolated in 85%, 79%, 72%, and 54% yields, respectively. As expected, aryl aldehydes (**1m**−**1q** and **1w**−**1ae**) including 2-naphthaldehyde **1n** were also compatible under the optimized reaction condition. The milder reaction condition granted us to incorporate various functional groups, including ethers, alkyl amine **1r**, esters **2s** and **1ae**, medicinally relevant fluorides (**1u** and **1z**), trifluoromethyl **1ab**, chlorides (**1v** and **1ad**), and propargyl **3y** are compatible under the optimized condition. Similarly, protecting groups such as TBDMS **1w**, MOM **1ac**, acetate **1ae**, and benzyl **1t** groups are also compatible and afforded the corresponding cross-coupled product in good yields. This provides us with an opportunity for the further

https://doi.org/10.1021/acs.orglett.1c01716
Org. Lett. 2021, 23, 5389−5393

Table 2. Substrate Scope[a]



[a]0.035 mmol of TBADT, 0.07 mmol of $NiCl_2$·glyme, 0.07 mmol of dtbpy, 0.7 mmol of **2**, 2.1 mmol/1.4 mmol of **1** (alkyl/aryl), 1.26 mmol of K_3PO_4, CH_3CN (0.1 M), 390 nm. [b]Reduced with $NaBH_4$ and isolated as alcohol. [c]10 mol % of TBADT, 7.5 mol % of $NiCl_2$·glyme and dtbpy. [d]NMR yield.

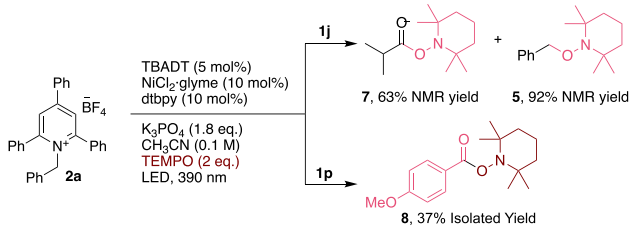
functionalization of the cross-coupled products. Our protocol has also been extended to pyridinium salts derived from allyl amines, thus giving rise to synthetically useful ketones **3af**–**3ah** in 86%, 84%, and 75% isolated yields. The moderate yields concerning few substrates can be attributed to the formation of homocoupled product **4** from pyridinium salt **2**, traces of proto-deaminated seen during the synthesis of **3i**, and proto-dehalogenated products for substrates **1aa** and **1ad**. A further attempt to improve the yield was not successful.

The aldehydes **1n** and **1ab** exhibited diminished reactivity, and incomplete consumption of aldehydes were observed. The cross-coupled products from tetrahydrofuran-2-carboxaldehyde **1ba** and citronellal **1bb** were inseparable from impurities (see SI-32). Pyridium salt **2bc** derived from secondary alkyl amine was inefficient to cross-couple with aldehyde **1a**, and a further attempt to improve the yield was unsuccessful. Pyridine-2-carbaldehyde **1ca** was found to be completely unreactive; coordination of pyridine's nitrogen to the nickel center might be deactivating the catalyst. In fact addition of pyridine-2-carbaldehyde **1ca** in the standard reaction greatly suppressed the efficiency of the reaction (SI-41). The tertiary alkyl pivalaldehyde **1da** remained intact, most likely because of its steric hindrance. Tribromoacetaldehyde **1db** was found to be incompatible; numerous byproducts including proto-dehalogenation were observed. Pyridinium salts derived from primary alkyl amines are poorly reacting (see SI-33). In order to expand the synthetic application, we have carried a large scale reaction with 1.2 mmol of **2fb** and obtained **3j** in 84% isolated yield.

As mentioned earlier, the presence of multiple C−H bonds with a small difference in BDEs could lead to the formation of regioisomers. It has been shown that the polar nature of HAT event can selectively abstract hydrogen atom from electron-rich sp^3 C−H bonds in the presence of weak methylene/methyl/methine C−H bonds (polarity mismatch), and the kinetic control does not necessarily reflect BDEs of C−H bonds.[13,51] As expected, substrates with an α-methylene carbonyl group (see Table 2) were compatible and smoothly reacted at formyl C−H bond to afford the cross-coupled product **3**. However, substrates having C−H bonds next to the heteroatom are prone to undergo hydrogen atom abstraction since the polar transition state of HAT can be stabilized by the α-heteroatom. Although the N-Boc protected substrate **1r** may not undergo α C−H abstraction, it has been reported[13] that the high dielectric solvents such as CH_3CN promote α-amino C−H functionalization for the substrate **1r** under the photocatalytic condition. Fortunately, we observed selective HAT at the formyl C−H bond for the aldehydes with α-amino methylene **1r** and α-oxy methylene groups (**1ac** and **1t**).

As we expected the generation of radical intermediates from both the aldehyde **1** and pyridinium salt **2a**, we employed TEMPO in the optimized reaction condition and observed (GC-MS and NMR) the formation of TEMPO-adducts **5**, **7**, and **8** from both acyl and alkyl radical intermediates as shown in Scheme 2. Our attempt to isolate the TEMPO-adducts **5** and **7** was unsuccessful; however, the adduct **8** was successfully isolated in 37% yield. As we anticipate the reduction of pyridinium salt **2a** by low valent nickel complex, **2a** was treated with $Ni(cod)_2$ and observed the homocoupled product **4**. However, **2a** was intact when treated with TBADT (SI-40).

Scheme 2. Radical Trap Experiments



On the basis of the available literature data and our observations, a mechanistic hypothesis is shown in Figure 1. Upon subjecting TBADT (I) to 390 nm, a LMCT (oxygen → tungsten) populates a short-lived (lifetime: ca. 30 ps) S_1 excited state TBADT* (**II**), which decays (ISC) to long-lived triplet state wO (lifetime: 55 ± 20 ns) with 0.5−0.6 quantum yield.[52] The triplet state wO (**III**) abstracts a hydrogen atom from aldehyde to generate the corresponding acyl radical (**IV**) and the intermediate $[W_{10}O_{32}]^{5-}$ (**V**). Recently Macmillan et al. described that the reduction potential of $[W_{10}O_{32}]^{5-}$ (**V**) is insufficient to reduce high

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Org. Lett. 2021, 23, 5389−5393

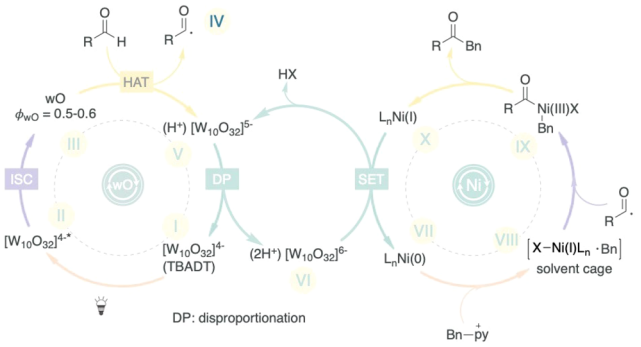

Figure 1. Mechanistic hypothesis.

valent nickel to Ni(0),[14] and it undergoes disproportionation to deliver $[W_{10}O_{32}]^{4-}$ (**I**) and $[W_{10}O_{32}]^{6-}$ (**VI**).[8,52] The high valent $[W_{10}O_{32}]^{6-}$ (**VI**) reduces the Ni(I) species to the low valent Ni(0) intermediate (**VII**), which rapidly reduces the pyridinium salt **2** to generate the intermediate complex **VIII** where the alkyl radical expected to be bound in the solvent cage. The Ni(I) intermediate complex **VIII** further reduces the acyl radical **IV** to generate the intermediate Ni(III) complex **IX**, which undergoes reductive elimination to deliver the acylated product **3** and regenerates Ni(I) intermediate to continue the catalytic cycle.

In summary, for the first time, we demonstrated a milder and efficient method for the cross-coupling of alkyl and aryl aldehydes with benzylic and allylic pyridinium salts via C−N bond cleavage. This dual catalysis accommodates a broad spectrum of functional groups, thus providing access to synthetically versatile ketones. Site selectivity was achieved in the presence of various C−H bonds with similar BDEs. α-Amino and α-oxy methylene groups were intact. The generation of acyl and benzyl radical in the mechanistic cycle was confirmed via the TEMPO trap experiment. Further study to expand the scope of dual catalysis is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01716.

Additional observations and data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Science and Engineering Research Board, Ramanujan Fellowship SB/S2/RJN059/2015, CSIR (Council of Scientific and Industrial Research) 02(0409)/21/EMR-II and IISER-Trivandrum for financial support. V.M., A.G., and A.K. acknowledge IISER, Trivandrum for fellowship.

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https://doi.org/10.1021/acs.orglett.1c01716
Org. Lett. 2021, 23, 5389−5393