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Letter

Ti(O*i*Pr)$_4$-Enabled Dual Photoredox and Nickel-Catalyzed Arylation and Alkenylation of Cyclopropanols

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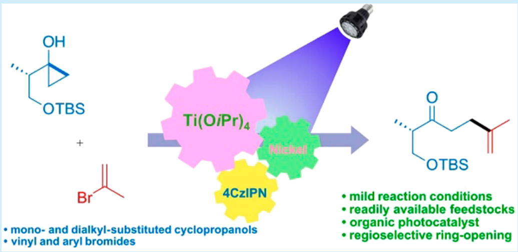
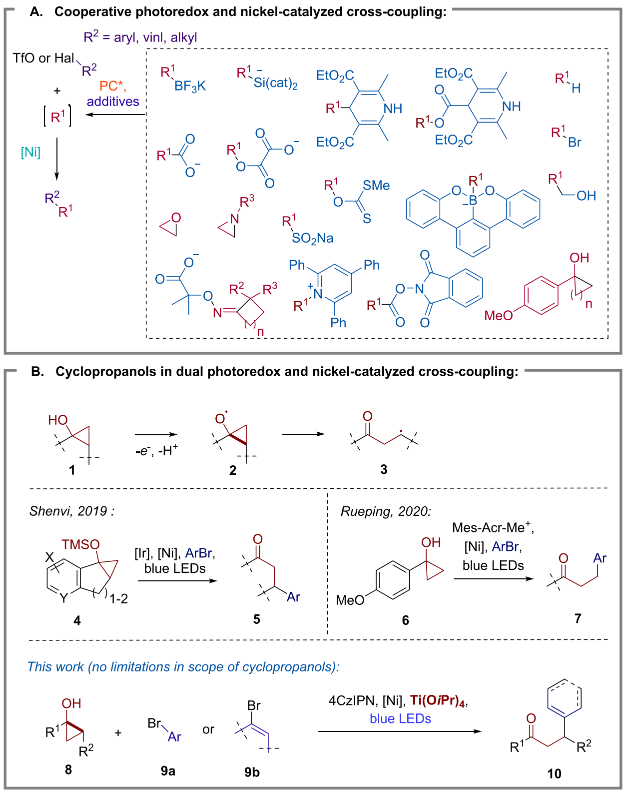
ABSTRACT: Readily available from esters or ketones, cyclopropanols are inclined to undergo diverse ring-opening transformations. Their one-electron oxidation is a conventional way to β-carbonyl radicals. However, despite this fact, their application as a coupling partner in dual photoredox and nickel-catalyzed reactions with organic halides remains underdeveloped. Here, we report that the Ti(O*i*Pr)$_4$ additive enables this elusive cross-coupling with aryl and alkenyl bromides leading to β-substituted ketones.



Nickel-catalyzed coupling of the photochemically generated alkyl radicals[1] with aryl, alkenyl, or alkyl halides has recently emerged as a powerful tool for C−C bond construction (Scheme 1A).[2] Proceeding under mild conditions, these reactions generally tolerate sensitive functional groups and, moreover, can be deployed for the formation of an asymmetric stereocenter.[3] The scope of the radical precursors used in the coupling is exceptionally broad. After the pioneering reports on the arylation of organotrifluoroborates, aliphatic carboxylic acids, and *N*,*N*-dimethylaniline by Molander[4] and MacMillan and Doyle,[5] various alternative coupling partners were utilized, including alkylsylicates,[6] monoalkyl oxalates,[7] dihydropyridines,[8,9] alkyl halides,[10] alkanes,[11] oxiranes,[12] aziridines,[13] cycloalkanone oxymecarboxylates,[14] *N*-hydroxyphthalimide esters,[15] Katritzky salts,[16] alkylsulfinate salts,[17] xanthate esters,[18] boracene-based alkyl borates,[19] and linear[20] and cyclic alcohols.[21] Being a source of β-ketoradicals **3**,[22] cyclopropanols **1** can also undergo the photoredox/nickel dual catalyzed reaction to provide β-substituted ketones (Scheme 1B).[21] However, the scope of cyclopropanols that were engaged in this coupling is rather narrow. Shenvi reported arylation and alkenylation of tricyclic silyloxycyclopropanes **4** promoted by an iridium photocatalyst and a nickel complex.[21a] One of the obtained β-substituted ketones **5** was further efficiently applied in a concise synthesis of natural alkaloid GB-22.[21a] Another example of photoredox-initiated ring-opening arylation was described by Rueping.[21b] The presence of a PMP group in **6** was crucial because the formation of alkoxy radical **2** was initiated by the one-electron oxidation of this moiety. Here, we report that limitations in the scope of photoredox and nickel dual catalyzed cyclopropanol arylation and alkenylation can be overcome when the reaction

Scheme 1. Reactions of Cyclopropanols under Dual Photoredox and Nickel Catalysis



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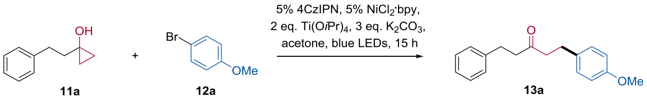
is carried out in the presence of Ti(O*i*Pr)$_4$ as an additive. Under these conditions, diverse β-substituted ketones **10** were obtained from cyclopropanols **8** and aryl or vinyl bromides **9**.

Transformation of cyclopropanol **1** (E^{ox} = +1.66 V)[23] to oxycyclopropyl radical **2** requires a relatively strong oxidant. For comparison, the reduction potential of the excited photocatalysts commonly used in the cooperative photoredox and nickel-catalyzed reactions lies between +0.77 and +1.35 V.[2a] Thus, either a photocatalyst with stronger oxidative properties or an alternative way of oxycyclopropyl radical **2** generation was required to initiate the cross-coupling. Recently, we found that cyclopropanols undergo one-electron oxidation by the photoexcited acridimium salts [$E_{1/2}(P^*/P^-)$ = +2.08 V],[24] but our attempts to use them in the ring-opening arylation of **8** with **9** were unsuccessful. Nevertheless, we found that addition of Ti(O*i*Pr)$_4$ to the reaction mixture enables the reaction even when 4CzIPN [$E_{1/2}(P^*/P^-)$ = +1.35 V][25] is employed as a photocatalyst. The highest yield in the arylation of **11a** with *p*-bromoanisole (**12a**) was achieved when the reaction was performed in acetone in the presence of the photocatalyst, the nickel chloride bipyridine complex, potassium carbonate as a base, and titanium isopropoxide as an additive. Changing the solvent to acetonitrile and DMA led to a slight decrease in yield, but in THF, the arylation was significantly less efficient. When di-*tert*-butylbipyridine, batophenanthroline, neocuproine, or dimethoxybipyridine was used as an alternative ligand, the yield of **13a** decreased compared to that under the standard conditions. While inorganic salt K_3PO_4 can be employed as a base of choice, the reaction in the presence of 2,6-lutidine afforded the product in a low 23% yield. The yield of **13a** in the reaction promoted by the Ti(O*t*Bu)$_4$ additive with bulk *tert*-butoxide ligands was slightly lower than in the presence of Ti(O*i*Pr)$_4$. Trimethyl borate also promoted the cross-coupling, though significantly less efficiently. No reaction was observed when aluminum isopropoxide was used as an additive or when the arylation was carried out in the absence of Ti(O*i*Pr)$_4$ or a photocatalyst (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



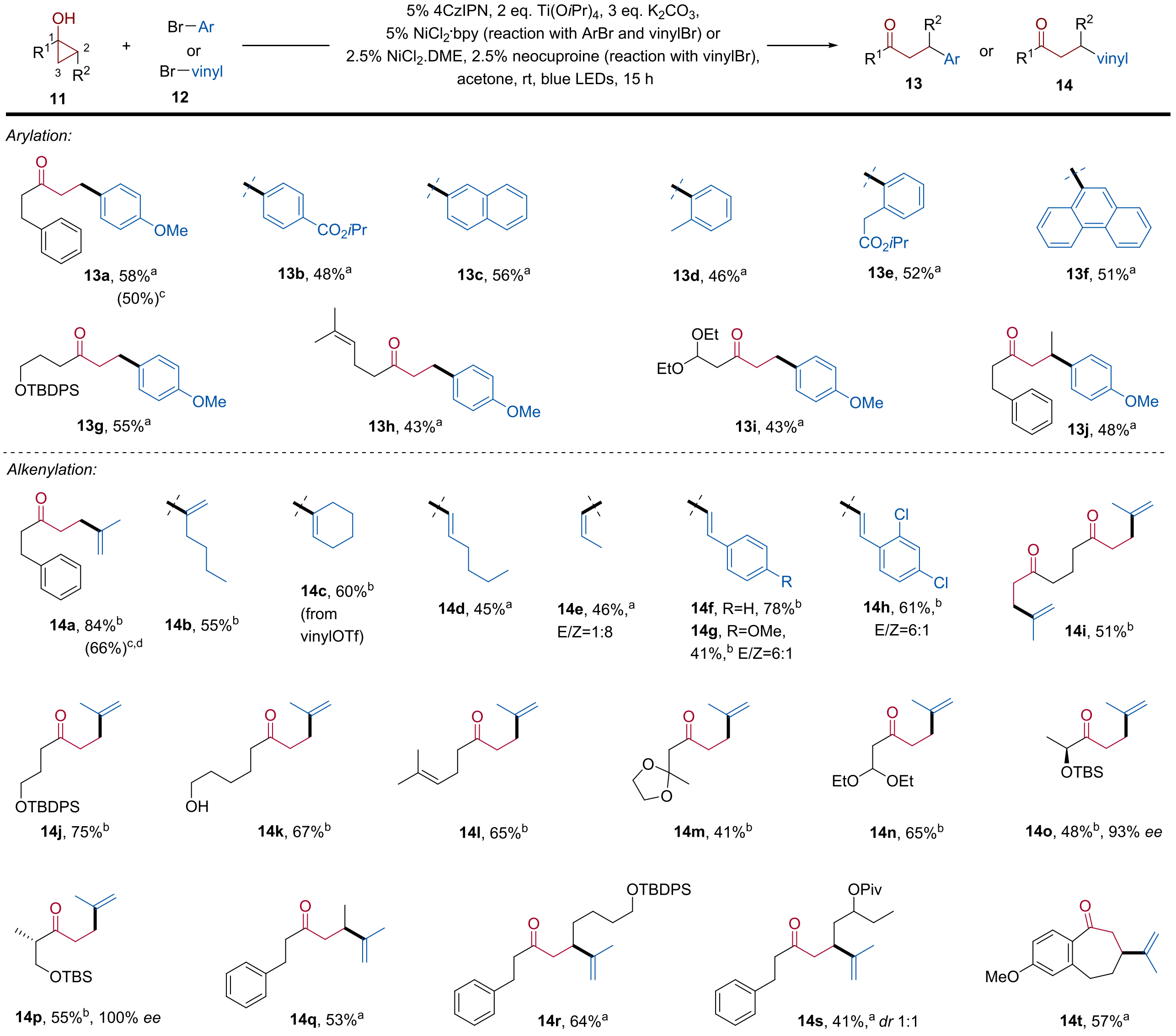
entry	reaction conditions	yield of **13a** (%)[b]
1	standard conditions	60
2	THF instead of acetone	28
3	MeCN instead of acetone	49
4	DMA instead of acetone	51
5	NiCl$_2$·DME and dtbbpy instead of NiCl$_2$·bpy	47
6	BPhen·NiCl$_2$·2DMF instead of NiCl$_2$·bpy	47
7	NiCl$_2$·DME and neocuproine instead of NiCl$_2$·bpy	21
8	NiCl$_2$·DME and dMeObpy instead of NiCl$_2$·bpy	30
9	K_3PO_4 instead of K_2CO_3	56
10	2,6-lutidine instead of K_2CO_3	23
11	Ti(O*t*Bu)$_4$ instead of Ti(O*i*Pr)$_4$	47
12	B(OMe)$_3$ instead of Ti(O*i*Pr)$_4$	19
13	Al(O*i*Pr)$_3$ instead of Ti(O*i*Pr)$_4$ or no Ti(O*i*Pr)$_4$ or no 4CzIPN	0

[a] Reaction conditions: **11a** (0.1 mmol), **12a** (0.2 mmol), photocatalyst (0.005 mmol), NiCl$_2$·bpy (0.005 mmol) or NiCl$_2$·DME (0.005 mmol), ligand (0.005 mmol), additive (0.2 mmol), base (0.3 mmol), solvent (1 mL), blue LEDs (2 × 20 W), 15 h. Abbreviations: 4CzIPN, 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile; bpy, 2,2′-bipyridine; dtbbpy, 4,4′-di-*tert*-butyl-2,2′-bipyridine; BPhen, 4,4′-diphenyl-2,2′-bipyridine; DME, 1,2-dimethoxyethane; DMA, *N*,*N*-dimethylacetamide; dMeObpy, 4,4′-dimethoxy-2,2′-bipyridine. [b] Crude ^1H NMR yield with CH_2Br_2 as the internal standard.

Having optimized the reaction conditions, we next investigated the scope of the reaction (Scheme 2). Aryl bromides with donor or acceptor functional groups as well as an *ortho* substituent reacted with **11a** giving desired β-arylketones **13a–f** in 46–58% yields. Silylated hydroxyl group, alkenyl, and diethylacetal units in the cyclopropanol substrate were tolerated, but formation of **13h** and **13i** was slightly less efficient. The reaction of the 1,2-disubstituted cyclopropanol afforded arylketone **13j** as a single β-branched regioisomer. In contrast to the palladium-catalyzed arylation that leads to α-branched products,[26] the investigated radical reaction proceeded with the cleavage of a more substituted bond of the three-carbon ring. Next, cross-coupling of cyclopropanols with vinyl halides was investigated. Generally, yields of the alkenylation were better when the reaction was carried out in the presence of neocuproine instead of a bipyridine ligand. The reaction between cyclopropanol **11a** and 2-bromoalkenes provided ketones **14a** and **14b** in 84% and 55% yields, respectively. Alkenylation of **11a** with vinyl triflate also proceeded efficiently to produce β-cyclohexenylketone **14c**. During the synthesis of γ,δ-unsaturated ketones **14d** and **14e** from 2-alkyl-substituted vinyl bromides and cyclopropanol **11a**, the bipyridine ligand was more favorable than neocuproine and the products were isolated in 45% and 46% yields, respectively. Formation of *Z*-alkenylketone **14e** was accompanied by a slight isomerization of the double bond, which caused a decrease in the *Z*:*E* ratio to 8:1. A decrease in the isomeric purity was more significant in the course of the reaction affording products **14g** and **14h**, which bear the alkene unit conjugated with an electron-rich aromatic ring. After completion of the coupling, **14g** was isolated as a 6:1 *E*/*Z* mixture. This ratio further decreased to 1.7:1 when the reaction time was increased to 48 h. Ketone product **14f** with the unsubstituted benzene ring was obtained as a single *E* isomer. Aryl chloride units were inert under the reaction conditions, and ketone **14h** was prepared from the corresponding vinyl bromide in a good 61% yield. Then, diverse 1-mono- and 1,2-disubstituted cyclopropanols were tested in the reaction with 2-bromopropene. The substrate bearing two hydroxycyclopropyl groups underwent smooth coupling giving diketone **14i** in 51% yield. Silylated and unprotected hydroxyl groups, the alkenyl unit, and acetal protecting groups were tolerated, and corresponding products **14j–n** were isolated in 41–75% yields. The reaction conditions were mild enough for the preparation of chiral alkenylketones **14o** and **14p** that contain sensitive α-stereocenters. Alkenylation of 1,2-disubstituted cyclopropanols provided regioisomerically pure β-branched products **14q–s** in 41–64% yields. These reactions proceeded more efficiently in the presence of the bipyridine ligand. Finally, β-isopropenylcycloheptanone **14t** was obtained from the bicyclic cyclopropanol containing an aryl substituent at C1 in 57% yield.

To gain insight into the role of Ti(O*i*Pr)$_4$ in the ring-opening cross-coupling, additional control experiments were carried out (Scheme 3A). First, we investigated the reaction between cyclopropane **11a** and Ti(O*i*Pr)$_4$ in acetone-d_6. A fast exchange between the isopropoxide and cyclopropyloxy ligands

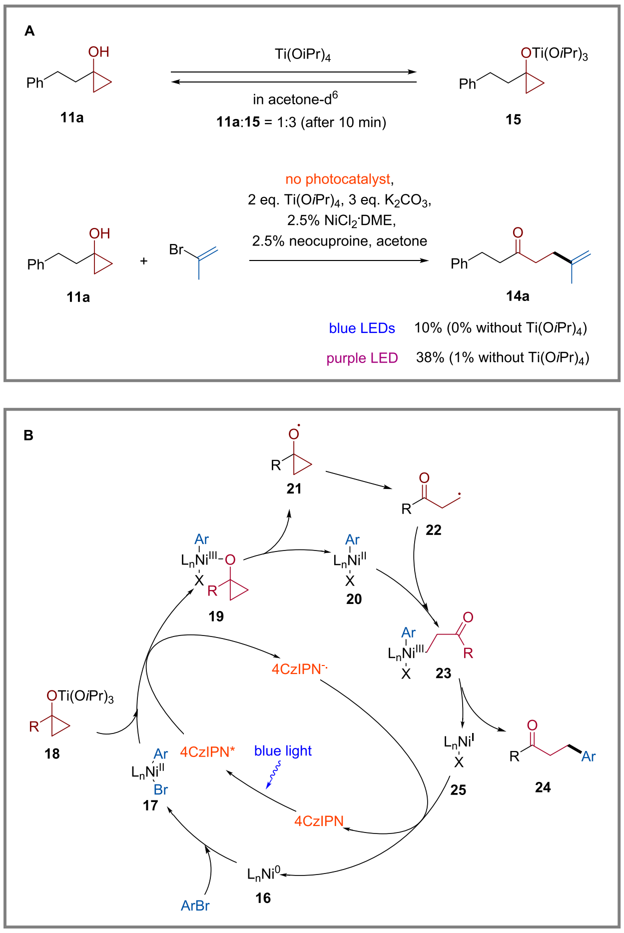
Scheme 2. Scope of the Reaction[a,b]



[a]Reaction conditions A: **11** (0.25 mmol), **12** (0.5 mmol), 4CzIPN (0.0125 mmol), $NiCl_2$·bpy (0.0125 mmol), Ti(O*i*Pr)$_4$ (0.5 mmol), K_2CO_3 (0.75 mmol), acetone (2.5 mL), blue LEDs, 15 h. [b]Reaction conditions B: same as reaction conditions A but $NiCl_2$·DME (0.00625 mmol) and neocuproine (0.00625 mmol) were used instead of $NiCl_2$·bpy (0.0125 mmol). [c]Reaction run on a 1 mmol scale. [d]With 1% $NiCl_2$·DME and 1% neocuproine.

leading to a 1:3 mixture of **11a** and **15** was observed. Initially, we assumed that the formed titanium cyclopropoxide complex **15** could undergo one-electron oxidation by the photoexcited 4CzIPN* more efficiently than free cyclopropanol **11a**. However, voltammograms of **11a** and its 1:1 mixture with Ti(O*i*Pr)$_4$ were nearly identical, suggesting that the additive played another role in the reaction. Alternatively, Ti(O*i*Pr)$_4$ could serve as a co-catalyst that assists in the formation of cyclopropyloxy nickel(III) complexes.[27] Homolytic cleavage of the RO−Ni^{III} bond could provide cyclopropyloxy radicals, which would further undergo ring opening and cross-coupling.[28−30] Bearing in mind that the formation of RO−Ni^{III} intermediates is possible even in the absence of a photocatalyst and this reaction proceeds more efficiently under irradiation with 390−395 nm LEDs,[27b] we carried out additional control experiments without 4CzIPN. When blue LEDs were used as a source of light, the alkenylation of **11a** by 2-bromopropene gave product **14a** in 10% yield, while no reaction was observed in the absence of Ti(O*i*Pr)$_4$. Under irradiation with purple LEDs, the yield increased significantly to 38% and 1% of the product was formed in the absence of Ti(O*i*Pr)$_4$. On the basis of these experiments, we proposed a catalytic cycle in which 4CzIPN* oxidizes the nickel complex rather than cyclopropanol or its titanium alkoxide while Ti(O*i*Pr)$_4$ assists in the formation of RO−Ni^{III} intermediates (Scheme 3B). After the oxidative addition of aryl or vinyl bromide to **16**, aryl nickel complex **17** would undergo oxidation by photoexcited 4CzIPN* and ligand exchange with titanium alkoxide **18** to provide Ni^{III} complex **19**. Next, the Ni^{III}−O bond in **19** would break, providing Ni^{II} complex **20** and oxycyclopropyl radical **21**. Ring opening of **21** would give *β*-ketoradical **22**, which would further react with **20** to afford Ni^{III} complex **23**. Reductive elimination from **23** would lead to coupling product **24** and Ni^{I} species **25**, reduction of which would close the catalytic cycle.

Scheme 3. Control Experiments and a Plausible Catalytic Cycle



In conclusion, we have developed a general approach to β-aryl- and β-alkenylketones from cyclopropanols and aryl or alkenyl bromides or triflates. We found that this 4CzIPN and nickel dual catalyzed reaction becomes general for a broad scope of 1-mono- and 1,2-disubstituted cyclopropanols when carried out in the presence of the Ti(O*i*Pr)$_4$ additive. The cross-coupling is compatible with functional groups including an unprotected hydroxyl and proceeds under conditions mild enough for the preparation of enantiomerically pure ketones bearing a sensitive α-stereocenter.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01795.

Experimental procedures and compound characterization (PDF)

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[§]N.V. and M.B. contributed equally to this work.

Notes

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The authors declare no competing financial interest.

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