

Ti(OiPr)₄-enabled dual photoredox and nickel-catalyzed arylation and alkenylation of cyclopropanols

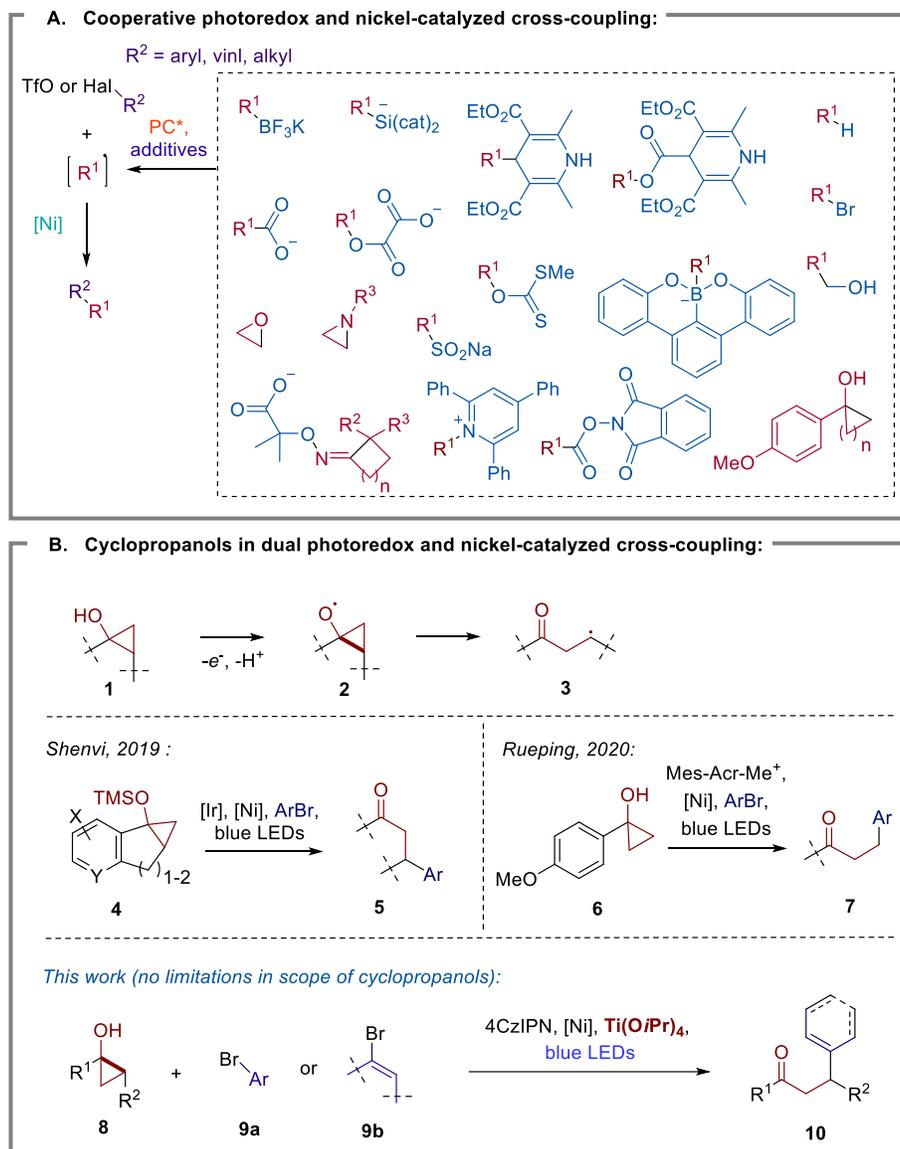
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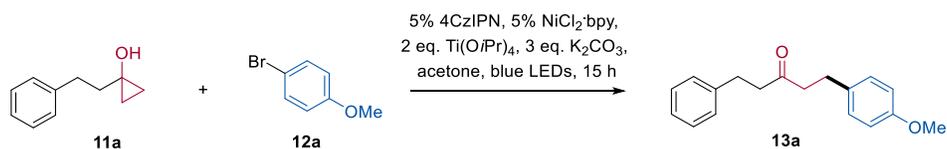
ABSTRACT. Readily available from esters and ketones, cyclopropanols are inclined to undergo diverse ring-opening reactions. Their one-electron oxidation is a conventional way to β -carbonyl radicals. However, despite this fact, their application as a coupling partner in dual photoredox and nickel-catalyzed reactions with organic halides remains underdeveloped. Here, we report that Ti(OiPr)₄ additive enables this elusive cross-coupling with aryl and alkenyl bromides affording β -substituted ketones.

Nickel-catalyzed coupling of the photochemically generated alkyl radicals¹ with aryl, alkenyl or alkyl halides has recently emerged as a powerful tool for the 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 Molander⁴ and MacMillan and Doyle,⁵ various alternative coupling partners were utilized including alkylsilicates,⁶ monoalkyl oxalates,⁷ dihydropyridines,^{8,9} alkyl halides,¹⁰ alkanes,¹¹ oxiranes,¹² aziridines,¹³ cycloalkanone oxime-carboxylates,¹⁴ N-hydroxyphthalimide esters,¹⁵ Katritzky salts,¹⁶ alkylsulfinate salts,¹⁷ xanthate esters,¹⁸ boracene-based alkyl borates,¹⁹ linear²⁰ and cyclic alcohols.²¹ Being a source of β -keto radicals **3**,²² cyclopropanols **1** can also undergo the photoredox/nickel dual catalyzed reaction to provide β -substituted ketones (Scheme 1B).²¹ However, scope of cyclopropanols that can be 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 the photoredox initiated ring-opening arylation was described by Rueping.^{21b} The presence of 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 is carried out in the presence of Ti(O*i*Pr)₄ as an additive. Under these conditions, β -substituted ketones **10** can be obtained from cyclopropanols **8** and aryl- or vinyl- bromides **9**.



one-electron oxidation by the photoexcited acridinium salts ($E_{1/2}(\text{P}^*/\text{P}^-) = +2.08 \text{ V}$),²⁴ but our attempts to use them in the ring-opening arylation of **8** with **9** were unsuccessful. Nevertheless, we found that addition of $\text{Ti}(\text{OiPr})_4$ to the reaction mixture enables the reaction even when 4CzIPN ($E_{1/2}(\text{P}^*/\text{P}^-) = +1.35 \text{ V}$)²⁵ is employed as a photocatalyst. The highest yield in the arylation of **11a** with *p*-bromoanisole (**12a**) was achieved when the reaction was run in acetone in the presence of the photocatalyst, nickel chloride bipyridine complex, potassium carbonate as a base and titanium isopropoxide as an additive. Changing the solvent with acetonitrile and DMA resulted in a slight drop in yield, but in THF, the arylation was significantly less efficient. When di-*tert*-butylbipyridine, batophenanthroline, neocuproine or dimethoxybipyridine were used as alternative ligands, the yield of **13a** diminished. While inorganic salt K_3PO_4 can be employed as a base of choice, the reaction in the presence of 2,6-lutidine proceeded giving the product in a low 23% yield. The yield of **10a** in the reaction promoted by $\text{Ti}(\text{OtBu})_4$ additive with bulk *tert*-butoxide ligands was slightly lower than that under the standard conditions. 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 $\text{Ti}(\text{OiPr})_4$ or a photocatalyst.

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 ₃ PO ₄ instead of K ₂ CO ₃	56%
10	2,6-lutidine instead of K ₂ CO ₃	23%
11	Ti(<i>O<i>t</i></i> Bu) ₄ instead of Ti(<i>O<i>i</i></i> Pr) ₄	47%
12	B(OMe) ₃ instead of Ti(<i>O<i>i</i></i> Pr) ₄	19%
13	Al(<i>O<i>i</i></i> Pr) ₃ instead of Ti(<i>O<i>i</i></i> Pr) ₄ or no Ti(<i>O<i>i</i></i> Pr) ₄ or no 4CzIPN	0%

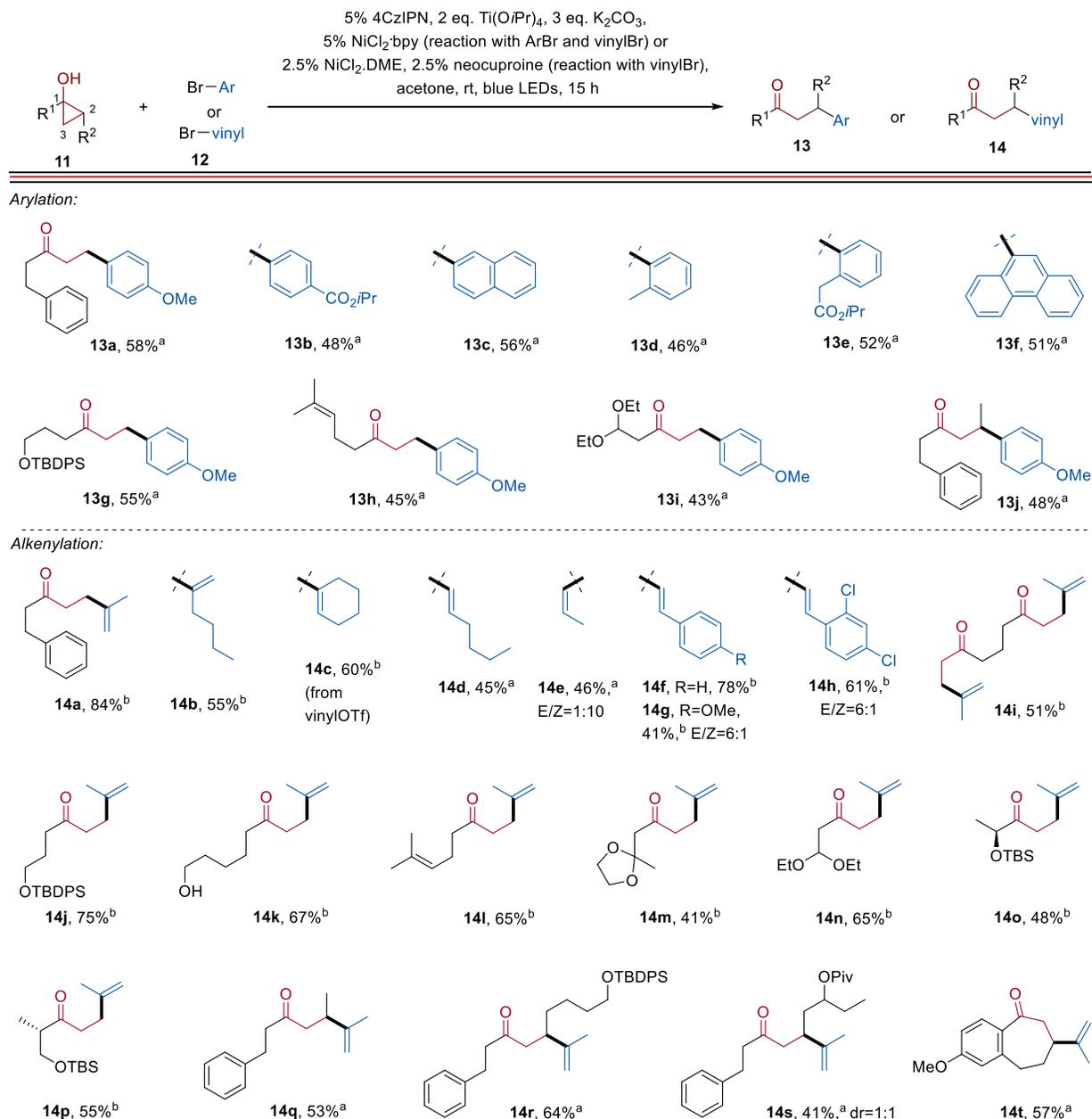
^aReaction conditions: **11a** (0.1 mmol), **12a** (0.2 mmol), photocatalyst (0.005 mmol), NiCl₂·bpy (0.005 mmol) or NiCl₂·DME (0.005 mmol), ligand (0.005 mmol), additive (0.2 mmol), base (0.3 mmol) and solvent (1 mL), blue LEDs, 15h. ^bCrude ¹H NMR yield with CH₂Br₂ as internal standard; 4CzIPN = 2,4,5,6-Tetra(9H-carbazol-9-yl)isophthalonitrile; 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.

Having optimized the reaction conditions, we next investigated the scope of the reaction. Aryl bromides with donor or acceptor functional groups, as well as an ortho-substituent reacted with **11a** giving desired β-arylketones **13a-f**. 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-catalysed arylation which leads to α-branched products,²⁶ the investigated radical reaction proceeded with cleavage of the 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 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**. In synthesis of γ,δ -unsaturated ketones **14d** and **14e** from 2-alkylsubstituted vinyl bromides and cyclopropanol **11a**, 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 little isomerization of the double bond, which caused drop in *Z/E* ratio to 8:1. Diminishing of the isomeric purity was more significant for the products **14g** and **14h** bearing the alkene unit conjugated with an electron-rich aromatic ring. After completion of the coupling, **14g** was isolated as a 6:1 mixture of *E/Z* stereoisomers. This ratio further dropped to 1.7:1 when the reaction time was increased to 48h. Ketone product **14f** with the unsubstituted benzene ring was obtained as a single *E*-isomer. Aryl chloride units were found to be 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, 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 enantiomerically pure alkenylketones **14o-p** 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 bipyridine ligand instead of neocuproine. Finally, β -isopropenylcycloheptanone **14t** was obtained from the bicyclic cyclopropanol in 57% yield.

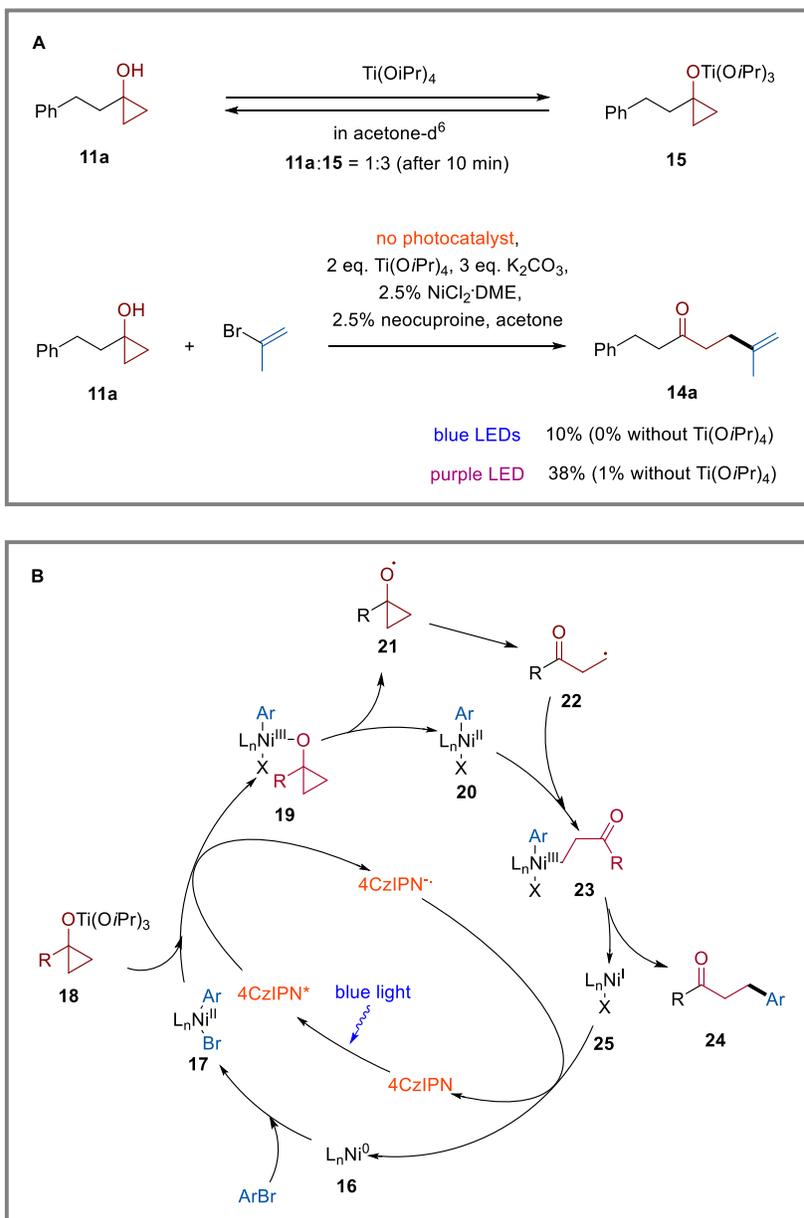
Table 2. The scope of the reaction ^{a,b}



^aReaction conditions A: **11** (0.25 mmol), **12** (0.5 mmol), 4CzIPN (0.0125 mmol), NiCl₂bpy (0.0125 mmol), Ti(OiPr)₄ (0.5 mmol), K₂CO₃ (0.75 mmol), acetone (2.5 mL), blue LEDs, 15h;
^bReaction conditions B: the same as reaction conditions A, but NiCl₂DME (0.00625 mmol) and neocuproine (0.00625 mmol) were used instead of NiCl₂bpy (0.0125 mmol).

To get insight into the role of $\text{Ti}(\text{O}i\text{Pr})_4$ in the ring-opening cross-coupling, additional control experiments were carried out (Scheme 2A). First, the reaction between cyclopropane **11a** and $\text{Ti}(\text{O}i\text{Pr})_4$ in acetone- d^6 was investigated. We observed a fast exchange between the isopropoxyde and cyclopropyloxy ligands leading to 1:3 mixture of **11a** and **15**. 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, voltamperograms of **11a** and its 1:1 mixture with $\text{Ti}(\text{O}i\text{Pr})_4$ were nearly identical suggesting that the additive played another role in the reaction. Alternatively, $\text{Ti}(\text{O}i\text{Pr})_4$ could serve as a co-catalyst that assists formation of cyclopropyloxy nickel(III) complexes.²⁷ Homolytic cleavage of RO-Ni^{III} bond could provide cyclopropyloxy radicals, which could further undergo the ring-opening and cross-coupling.^{28,29,30} Bering in mind that formation of RO-Ni^{III} intermediates is possible even in the absence of a photocatalyst and this reaction proceeds more efficiently under the irradiation with 390-395 nm LEDs,^{27e} 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 $\text{Ti}(\text{O}i\text{Pr})_4$. Under the irradiation with purple LEDs, the yield increased significantly to 38% and 1% of the product was formed in the absence of $\text{Ti}(\text{O}i\text{Pr})_4$. Based on these experiments, we proposed a catalytic cycle in which 4CzIPN* oxidizes the nickel complex rather than cyclopropanol or its titanium alkoxide while $\text{Ti}(\text{O}i\text{Pr})_4$ assists the formation of RO-Ni^{III} intermediates (Scheme 2B). After the oxidative addition of aryl or vinyl bromide to **16**, aryl nickel complex **17** would undergo oxidation by the photoexcited 4CzIPN* and ligand exchange with titanium alkoxide **18** to provide Ni^{III} complex **19**. Next, 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** affording

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 2. Control experiments and 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 photoredox 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 $\text{Ti}(\text{OiPr})_4$ additive. The cross-coupling is compatible with functional groups including unprotected hydroxyl and proceeds under conditions mild enough for the preparation of enantiomerically pure ketones bearing a sensitive α -stereocenter.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures and characterization of all new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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