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Letter

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Photoredox Ni-catalyzed Branch-Selective Reductive Coupling of Aldehydes with 1,3-Dienes

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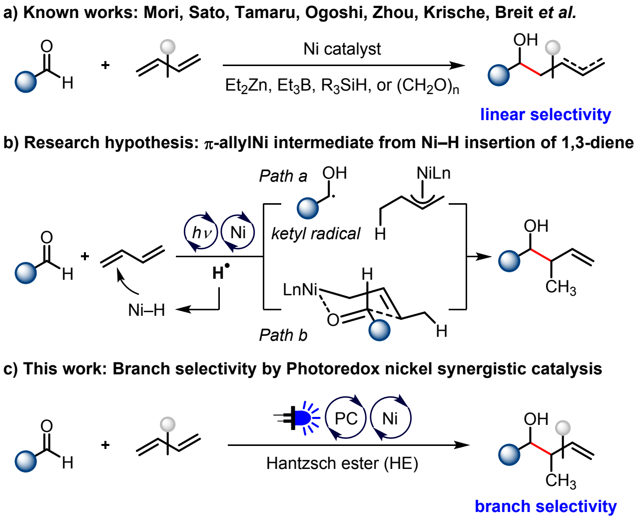
ABSTRACT: We report here a Ni-catalyzed reductive coupling of aldehydes with widely available 1,3-dienes under visible light photoredox dual catalysis. The homoallyic alcohols are obtained in broad scope with complete branched regioselectivity. Hantzsch ester is used as the hydrogen radical source to oxidize low-valent nickel salt affording Ni−H species. Preliminary mechanistic studies indicate a successive single-electron transfer (SET) pathway and the generation of a key π-allylnickel intermediate via Ni−H insertion of 1,3-diene in this synergistic catalytic process.

Allylation of aldehydes is one of the most important and reliable C−C bond-forming reactions for the production of homoallylic alcohols in synthetic chemistry. Traditionally, these valuable compounds are synthesized via addition of aldehydes with premetalated C-nucleophiles (from organometallic reagents or organic halides).[1] These methods often pose issues of safety, cost, and multi-step pre-synthesis. Alternatively, 1,3-butadiene, an abundant petrochemical feedstock, has been applied to the reductive coupling with aldehydes producing homoallylic alcohols under various transition-metal catalysts.[2] Remarkably, Ru or Ir-catalyzed borrowing hydrogen strategy with alcohol as reductant (or as both reductant and aldehyde precursor) reported by Krische and others is a tremendous improvement in the diene-aldehyde reductive coupling reactions.[3-5]

As a base metal catalyst, nickel has also been applied in reductive coupling reactions, as well as diene-aldehyde couplings (Scheme 1a).[6] In 1994, Mori, Sato and colleagues reported the seminal Ni-catalyzed intramolecular coupling of 1,3-dienes with carbonyl groups in the presence of silanes giving homoallylic or bishomoallylic alcohols.[7] Shortly after that Tamaru et al. disclosed intermolecular reductive coupling reactions of 1,3-dienes with aldehydes by using BEt_3 as reducing reagents to produce bishomoallylic alcohols.[8] Elegant enantioselective reactions were also reported independently by the groups of Zhou and Sato.[9] Recently, Breit and Krische realized that Ni-catalyzed reductive coupling of 1,3-dienes and formaldehyde afforded linear bishomoallylic alcohols with formaldehyde as both coupling partner and reductant.[10] To the best of our knowledge, all of these reactions produce allylation or homoallylation products with linear regioselectivity. In addition, most of these reactions require toxic and flammable organometallic reagents (Et_2Zn/Et_3B) or silanes as reductants. The origin of the linear selectivity has been recognized to be Ni(0)-mediated oxidative coupling of diene with aldehyde generating an isolable π-allyloxanickelacycle intermediate.[11] Therefore, exploring new nickel based catalytic systems may enable branched selectivity, and this would highly broaden the synthetic utility of this diene-aldehyde coupling further.

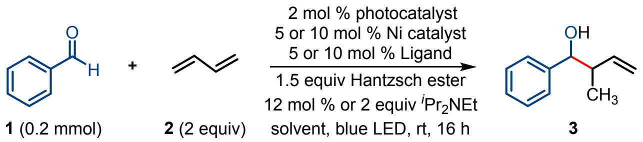
Scheme 1. Ni-catalyzed Reductive Coupling of Aldehydes with 1,3-Dienes



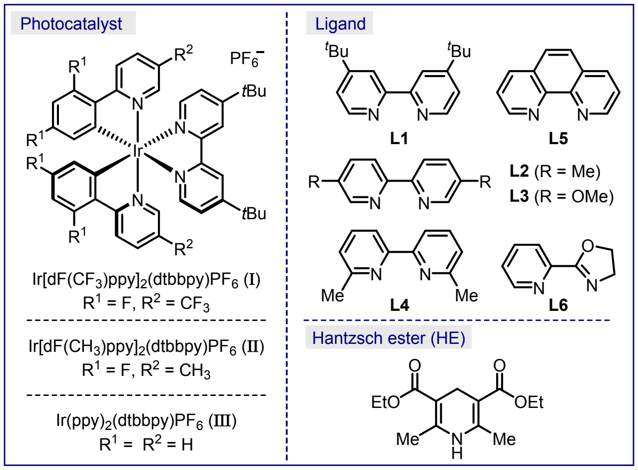
Recently, the photocatalytic reductive coupling of aldehyde with electron-deficient olefins, such as acrylic ester and vinyl pyridine, generating alcohols via ketyl radicals has been disclosed by Chen, Ngai, and others using Hantzsch ester (HE) as reducing reagents.[12] In addition, König and co-workers reported a photoredox Ni-catalyzed hydrocarboxylation of styrenes via nickel hydride intermediate using HE as the hydrogen source.[13] Inspired by these elegant works, we aimed to develop a base metal catalyzed reductive allylation of aldehydes with 1,3-dienes to deliver the branched products. We hypothesized that merging visible light photoredox and nickel catalysis[14] may achieve this goal. A key Ni−H species could be generated by oxidation of low valent nickel catalyst with hydrogen radical under photoredox catalysis.[15] Then, branch-selective allylation may be realized via addition of ketyl radical to π-allylnickel intermediate generated via Ni−H insertion of 1,3-diene followed by reductive elimination (Scheme 1b, path a). Alternatively, allylation of aldehyde with π-allylnickel intermediate through Zimmerman-Traxler transition state[16] may also lead to branched homoallylic alcohols (Scheme 1b, path b). Herein, we report our preliminary results on the branch-selective reductive coupling of aldehyde with 1,3-dienes under visible light photoredox nickel dual catalysis (Scheme 1c).

We began the research by studying allylation of benzaldehyde **1** with 1,3-butadiene (**2**) under visible light photoredox Ni dual catalysis. With Hantzsch ester (HE) as a reductant, initial investigation found that homoallylic alcohol **3** was obtained in moderate yield with complete branch regioselectivity using $NiCl_2$ as a catalyst, 4,4'-di(*t*-Bu)-2,2'-bipyridine (**L1**) as a ligand, and $Ir(ppy)_3$ as a photocatalyst (Table 1, entry 1). Further examination of photocatalysts showed that product **3** was obtained in 50% yield with 1.9:1 d.r. ratio with $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (**I**) (Table 1, entry 2). Subsequent screening of the nickel catalysts demonstrated that $NiCl_2{\cdot}6H_2O$ gave better result with improved yield (Table 1, entry 6, also see Table S2 in Supporting Information). The ligand played an important role in the reaction (Table 1, entries 7-12, and Table S3 in Supporting Information). Electron-rich 5,5'-dimethyl-2,2'-bipyridine (**L2**) gave better yield and similar d.r. ratio (Table 1, entry 8). No reaction occurred with *ortho*-disubstituted 6,6'-dimethyl-2,2'-bipyridine (**L4**) (Table 1, entry 10). Lower yields of **3** were obtained with 1,10-phenanthroline (**L5**) and 2-(pyridin-2-yl)-4,5-dihydrooxazole (**L6**) (Table 1, entries 11 and 12). Further inspection of the solvents indicated that easily handled THF was a better choice with similar yield as DMF but improved d.r. ratio (Table 1, entry 15). When reducing the catalyst loading of nickel and ligand from 10 mol % to 5 mol %, the catalytic efficiency can also be maintained (Table 1, entry 18). Finally, we were glad to find that the reaction ran smoothly with a catalytic amount of Hünig's base ($^iPr_2NEt$, 12 mol %) (standard conditions, Table 1, entry 19).

Table 1. Reaction Development[a]



Entry	Photocatalyst	Ni catalyst	Ligand	Solvent	Yield^b (%)	d.r.^{b}
1	$Ir(ppy)_3$	$NiCl_2$	**L1**	DMF	39	1.1:1
2	**I**	$NiCl_2$	**L1**	DMF	50	1.9:1
3	**II**	$NiCl_2$	**L1**	DMF	54	1.2:1
4	**III**	$NiCl_2$	**L1**	DMF	39	1.4:1
5	**I**	$NiBr_2$	**L1**	DMF	33	0.8:1
6	**I**	$NiCl_2{\cdot}6H_2O$	**L1**	DMF	67	1.7:1
7	**I**	$NiCl_2{\cdot}6H_2O$	BiPy	DMF	78	1.5:1
8	**I**	$NiCl_2{\cdot}6H_2O$	**L2**	DMF	88	1.6:1
9	**I**	$NiCl_2{\cdot}6H_2O$	**L3**	DMF	72	1.6:1
10	**I**	$NiCl_2{\cdot}6H_2O$	**L4**	DMF	0	-
11	**I**	$NiCl_2{\cdot}6H_2O$	**L5**	DMF	8	1:1
12	**I**	$NiCl_2{\cdot}6H_2O$	**L6**	DMF	23	1.8:1
13	**I**	$NiCl_2{\cdot}6H_2O$	**L2**	DMSO	71	1.5:1
14	**I**	$NiCl_2{\cdot}6H_2O$	**L2**	MeOH	58	2.1:1
15	**I**	$NiCl_2{\cdot}6H_2O$	**L2**	THF	85	1.9:1
16	**I**	$NiCl_2{\cdot}6H_2O$	**L2**	Toluene	0	-
17	**I**	$NiCl_2{\cdot}6H_2O$	**L2**	Et_2O	0	-
18^c	**I**	$NiCl_2{\cdot}6H_2O$	**L2**	THF	81	1.6:1
19^{c,d}	**I**	**$NiCl_2{\cdot}6H_2O$**	**L2**	**THF**	**86**	**1.9:1**



[a] All reaction were performed with 2 mol % photocatalyst, 10 mol % Ni catalyst, 10 mol % Ligand, 1.5 equiv Hantzsch ester, 2 equiv $^iPr_2NEt$, and 5 W blue LEDs if otherwise noted. [b] Determined by crude ^1H NMR with 1,1,2,2-tetrachloroethane as an internal standard. [c] With 5 mol % $NiCl_2{\cdot}6H_2O$ and 5 mol % **L2**. [d] With 12 mol % $^iPr_2NEt$.

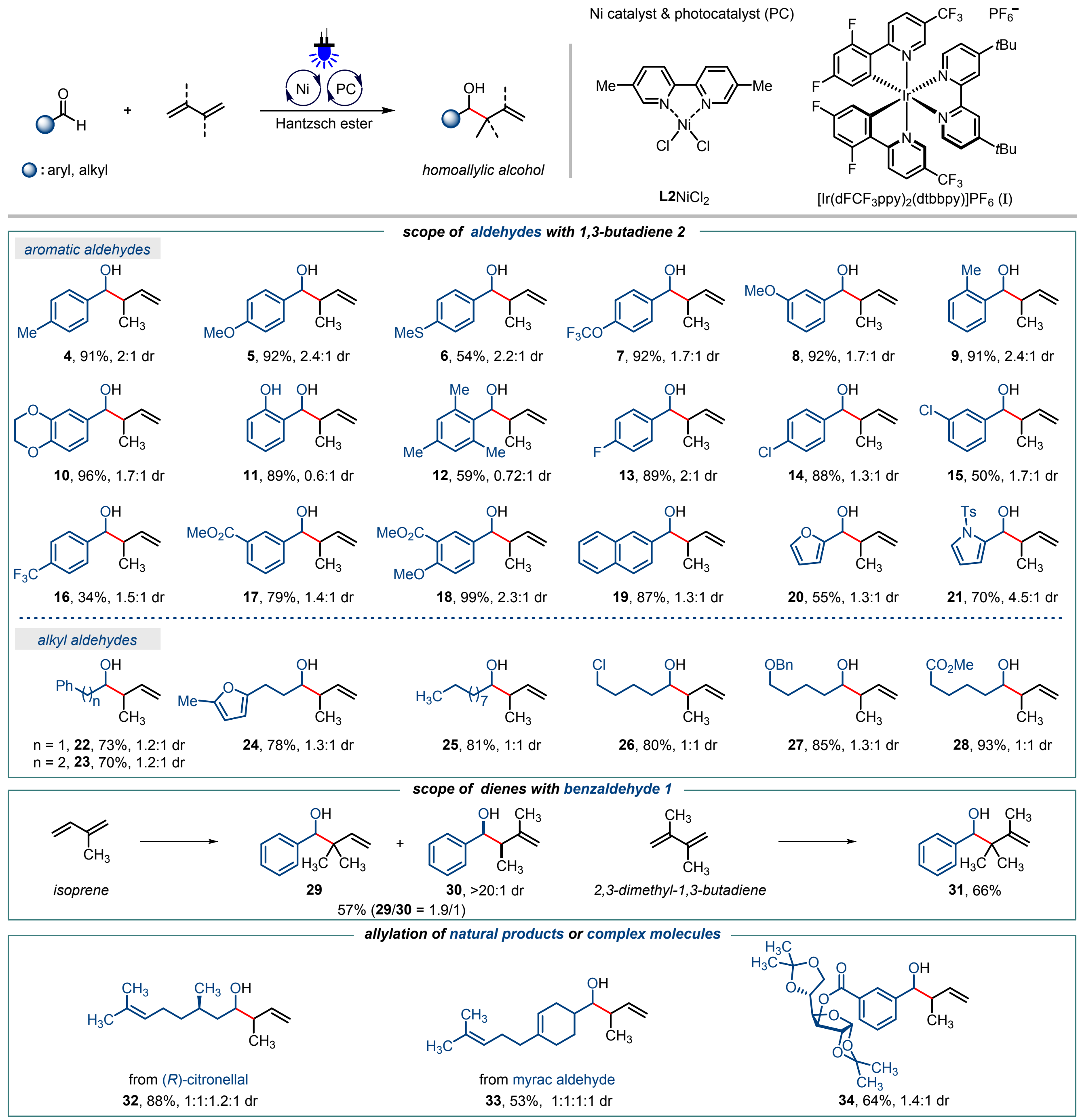
With the optimal reaction conditions in hand, we then examined the generality of this transformation (Table 2). Both aromatic and aliphatic aldehydes were found efficient coupling components affording the *syn*-homoallylic alcohols as the major products (up to 99% yield). The mild reaction conditions are compatible with a wide range of functional groups including OMe (**5**), SMe (**6**), OCF_3 (**7**), ether (**10**, **27**), phenol (**11**), CF_3 (**16**), and ester (**17**, **18**, **28**). It is noteworthy that the *ortho*, *meta*, and *para*-substituents on aromatic aldehydes show little influence on the reaction yield (**4**, **5**, **8**, and **9**). Moreover, sterically hindered 2,4,6-trimethylbenzaldehyde also gave the corresponding product **12** in moderate yield. In addition, the halogen functionalities remain intact after the coupling, furnishing additional reaction cite for further synthetic elaborations (**13**, **14**, **15**, **26**). Considering the wide presence of heterocyclic structures in the biologically important molecules, heteroaryl aldehydes (**20**, **21**) and alkyl aldehyde bearing heteroarene group (furan, **24**) are found suitable substrates in this reductive coupling reaction.

Next, isoprene, another important industrial raw material with annual production scale of about 1 milllion tons,[17] was tested in this transformation. Benzaldehyde coupled with isoprene to furnish **29** and **30** at C2 and C3 position in moderate yield with branch selectivity. Notably, allylic alcohol **30** was obtained in excellent d.r. ratio. Furthermore, coupling of 2,3-dimethyl-1,3-butadiene with benzaldehyde occurred smoothly producing **31** in 66% yield. Unfortunately, no reaction occurred with 1-phenyl substituted 1,3-butadiene and cyclohexa-1,3-diene.

To further demonstrate the synthetic utility of the reaction, we tested the natural products and complex molecules containing aldehyde functionality. For example, coupling of 1,3-butadiene with natural citronellal or myrac aldehyde afforded the desired product **32** and **33** as diastereomeric mixtures in moderate to good yields. The sugar group, diacetone-D-glucose, could also be tolerated in this reductive coupling reaction (**34**).

We next explored the mechanism of this reductive diene-aldehyde coupling reaction. First, control experiments showed

Table 2. Scope of Photoredox Ni-catalyzed Branch-Selective Reductive Coupling of Aldehydes with 1,3-Dienes[a]



scope of aldehydes with 1,3-butadiene 2

aromatic aldehydes

4, 91%, 2:1 dr
5, 92%, 2.4:1 dr
6, 54%, 2.2:1 dr
7, 92%, 1.7:1 dr
8, 92%, 1.7:1 dr
9, 91%, 2.4:1 dr
10, 96%, 1.7:1 dr
11, 89%, 0.6:1 dr
12, 59%, 0.72:1 dr
13, 89%, 2:1 dr
14, 88%, 1.3:1 dr
15, 50%, 1.7:1 dr
16, 34%, 1.5:1 dr
17, 79%, 1.4:1 dr
18, 99%, 2.3:1 dr
19, 87%, 1.3:1 dr
20, 55%, 1.3:1 dr
21, 70%, 4.5:1 dr

alkyl aldehydes

n = 1, **22**, 73%, 1.2:1 dr
n = 2, **23**, 70%, 1.2:1 dr
24, 78%, 1.3:1 dr
25, 81%, 1:1 dr
26, 80%, 1:1 dr
27, 85%, 1.3:1 dr
28, 93%, 1:1 dr

scope of dienes with benzaldehyde 1

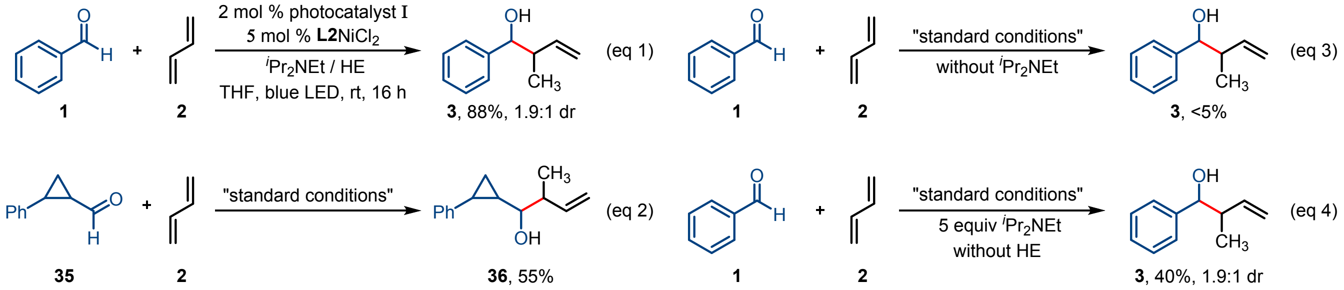
isoprene
29
30, >20:1 dr
57% (**29**/**30** = 1.9/1)
2,3-dimethyl-1,3-butadiene
31, 66%

allylation of natural products or complex molecules

from (*R*)-citronellal
32, 88%, 1:1:1.2:1 dr
from myrac aldehyde
33, 53%, 1:1:1:1 dr
34, 64%, 1.4:1 dr

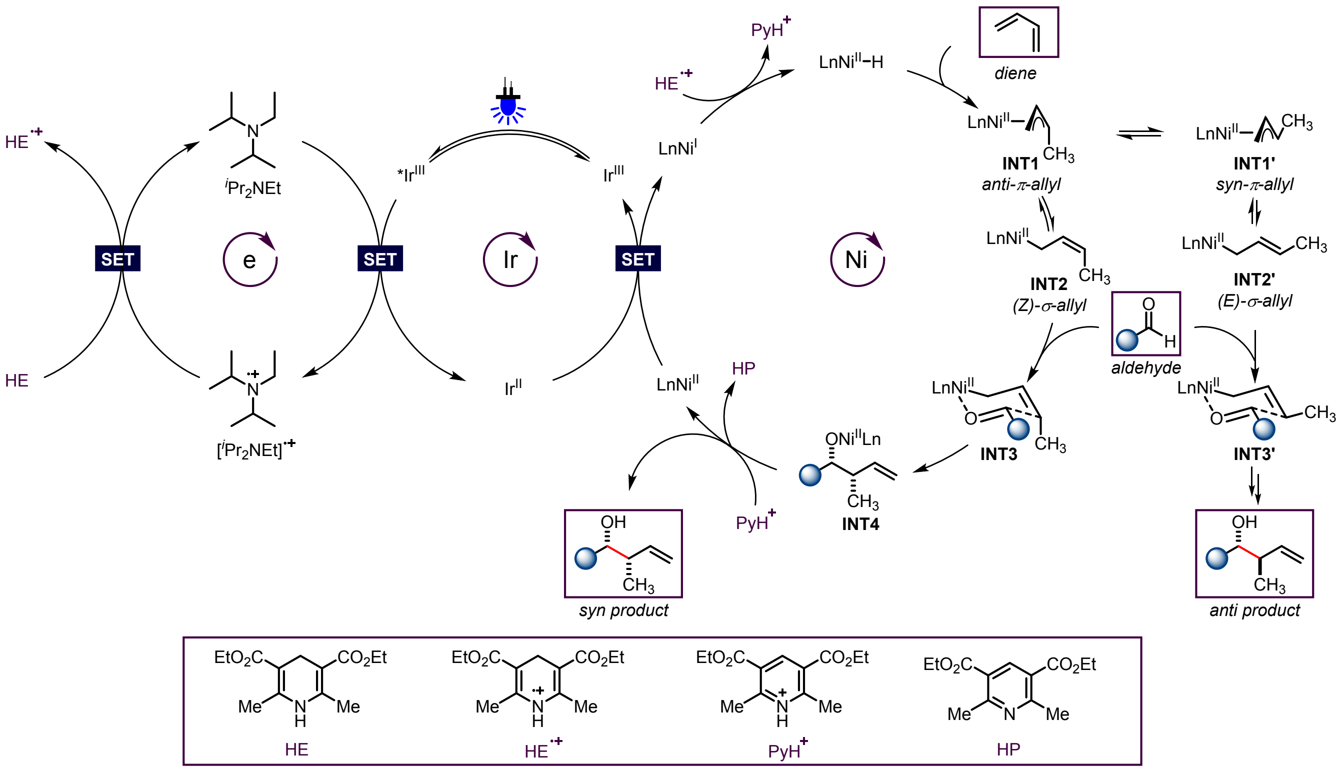
[a] All reactions performed with 0.2 mmol of aldehyde and 0.4 mmol 1,3-dienes. Isolated yield was provided. The d.r. value (*syn*:*anti*) was determined by ^{1}H NMR analysis. For standard conditions, see Table 1, entry 19. For details, see Supporting Information.

Scheme 2. Control Experiments



1 **2** → **3**, 88%, 1.9:1 dr (eq 1)
1 **2** → **3**, <5% (eq 3)
35 **2** → **36**, 55% (eq 2)
1 **2** → **3**, 40%, 1.9:1 dr (eq 4)

Scheme 3. Proposed Catalytic Pathway



that no reaction occurred without ligand **L2**. The reaction ran smoothly affording **2** in excellent yield with **L2**NiCl$_2$ as the catalyst, indicating that the ligand coordinated Ni complex is an active catalyst (Scheme 2, eq 1). Next, addition of radical scavengers into the reaction did not inhibit the reaction, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or ethene-1,1-diyldibenzene (See Supporting Information). Furthermore, the radical clock experiment[18] was conducted with cyclopropane-substituted aldehyde **35** as a substrate under standard conditions. The direct coupling product **36** was formed, but no ring opening product was observed (Scheme 2, eq 2). This result demonstrates that the reaction may not occur via ketyl radical intermediate generated through single electron transfer between photoexcited Hantzsch ester and aldehyde. Moreover, a trace amount of product was observed in the absence of Hünig's base (^{i}Pr$_2$NEt) (Scheme 2, eq 3). In addition, moderate yield of product was obtained in the presence of stoichiometric ^{i}Pr$_2$NEt without Hantzsch ester as the reducing reagent (Scheme 2, eq 4). These results indicate that ^{i}Pr$_2$NEt can function as a reductant albeit with low efficiency comparing with Hantzsch ester in this transformation. The ^{i}Pr$_2$NEt is considered to be an electron shuttle between Hantzsch ester and photocatalyst.[19]

Our proposed catalytic cycle for this transformation is described in Scheme 3. Initial excitation of Ir^{III} photocatalyst Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (**I**) generates the photoexcited *Ir^{III} intermediate. The *Ir^{III} catalyst ($E_{1/2}^{red}$ [*Ir^{III}/Ir^{II}] = +1.21 V *vs*. saturated calomel electrode (SCE) in CH$_3$CN)[20] is reduced by ^{i}Pr$_2$NEt (E^{ox} (^{i}Pr$_2$NEt) = +0.65 V)[21] via SET to produce a highly reducing Ir^{II} species and [^{i}Pr$_2$NEt]$^{•+}$, which accepts one electron from Hantzsch ester (HE) to regenerate ^{i}Pr$_2$NEt and the corresponding Hantzsch ester radical cation (HE$^{•+}$).[22] Reduction of ligand coordinated Ni^{II} complex (L$_n$Ni^{II}) by Ir^{II} ($E_{1/2}^{red}$[Ir^{III}/Ir^{II}] = −1.37 V *vs*. SCE in CH$_3$CN)[20] affords active Ni^{I} species ($E_{1/2}^{red}$[Ni^{II}/Ni^{I}] = -0.68 V *vs*. SCE in DMSO)[23] and Ir^{III} to close the iridium photoredox catalytic cycle. The following capture of the hydrogen radical from HE$^{•+}$ with Ni^{I} species would yield pivotal nickel hydride (Ni−H) species and pyridinium ion PyH$^+$. The kinetically preferred hydrometalation of the *s-cis* conformer of 1,3-diene with the nickel hydride generates the key *anti*-π-allyl-nickel intermediate **INT1**,[24] which can isomerize to *syn*-π-allyl-nickel intermediate **INT1'** rapidly. The corresponding *(Z)*- and *(E)*-*σ*-crotyl nickel intermediate **INT2** and **INT2'** would be formed subsequently. In our reaction, the unusual *syn*-diastereoselectivity is observed in most of the cases. The *syn*-product may be achieved via Zimmerman-Traxler transition state **INT3**, generating *syn*-homoallylic nickel alkoxide **INT4** through C−C bond formation. Finally, protonation of **INT4** by PyH$^+$ affords homoallylic alcohol product. The corresponding pyridine compound (HP) has been isolated as a byproduct. The crotyl methyl group placed pseudoaxially in transition state **INT3** may minimize gauche interactions between this group and the substituent of the aldehyde, which has been observed in certain reactions.[25] This may account for **INT3** more favorable than **INT3'** in this reaction, and the latter TS model results in *anti*-diastereoselectivity.

In summary, the first Ni-catalyzed branch-selective reductive coupling of aldehydes with 1,3-dienes has been developed under visible light photoredox catalysis. A novel strategy was realized to achieve the branch selectivity through the key π-allylnickel intermediate which was obtained via insertion of 1,3-dienes with a Ni−H intermediate derived from oxdative addition of low valent Ni salt with hydrogen radical. Coupling of widely available 1,3-dienes with (hetero)aryl, and alkyl aldehydes afforded homoallylic alcohols with broad scope and good functionality tolerance under the synergistic catalysis. Development of an enantioselective version of this novel transformation is currently ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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