

Regioselective Cross-Electrophile Coupling of Epoxides and (Hetero)aryl Iodides via Ni/Ti/Photoredox Catalysis

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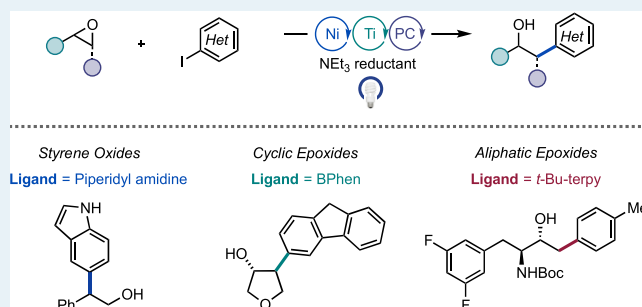
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ABSTRACT: A cross-electrophile coupling reaction of epoxides and (hetero)aryl iodides that operates via the merger of three catalytic cycles involving a Ni-, Ti-, and organic photoredox catalyst has been developed. Three distinct classes of epoxides, styrene oxides, cyclic epoxides, and terminal aliphatic epoxides, all undergo coupling in moderate to good yield and high regioselectivity with the use of three different nitrogen-based ligands for Ni under otherwise identical reaction conditions. The mild reaction conditions accommodate a broad scope of abundant and complex coupling partners. Mechanistic studies suggest that when styrene oxides are employed radical intermediates are involved via Ti-radical ring-opening of the epoxide. Conversely, for terminal aliphatic epoxides, involvement of an iodohydrin intermediate enables the formation of the unexpected linear product.

KEYWORDS: epoxides, arylation, cross-electrophile coupling, photoredox catalysis, nickel catalysis, titanium catalysis, radical chemistry, photochemistry



In recent years, Ni-photoredox catalysis has emerged as a powerful approach for forging C(sp²)–C(sp³) bonds that are otherwise challenging to prepare via traditional cross-coupling strategies.¹ Recently, researchers have applied Ni-photoredox catalysis to the area of cross-electrophile reactions, enabling the coupling of organohalides in the absence of a stoichiometric metal reductant (Scheme 1A).^{2,3} Most of the photoredox-assisted reductive cross-coupling (PARC) reactions rely on the coupling of aryl and alkyl halide electrophiles, with the exception of reports from the Amgouné lab using amides as the C(sp²)-component³¹ and from the Molander lab using Katritzky salts as the C(sp³)-component.^{3g} Notably, the use of distinct and abundant aliphatic electrophile classes could afford new PARC reactions and potentially broaden the scope of cross-electrophile couplings. Epoxides, in particular, are important and versatile building blocks in organic synthesis,⁴ but have seen limited application as partners in traditional cross-coupling reactions.⁵ For these reasons, and based on our interest in cross-coupling reactions with 3-membered ring heterocycles,⁶ we questioned whether a photoredox-assisted coupling approach could be utilized to develop a general, mild, and selective cross-electrophile coupling of epoxides.

Weix and co-workers have previously described a Ni-catalyzed cross-electrophile coupling reaction of epoxides and aryl halides using Mn as a stoichiometric reductant (Scheme 1B).⁷ In combination with a Ti co-catalyst to assist with ring-opening, the reaction proceeds efficiently for cyclic epoxides. The use of terminal aliphatic epoxides resulted in mixtures of regioisomers favoring the branched isomer in low to moderate

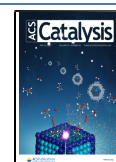
yield. These results prompted their identification of an alternative strategy featuring distinct reaction conditions for the coupling of terminal aliphatic epoxides via the intermediacy of an iodohydrin, which delivers the linear isomer selectively. For both activation strategies, styrene oxides were challenging substrates as they afforded low yield and low regioselectivity. Subsequently, Yamamoto and co-workers developed an asymmetric cross-electrophile coupling of styrene oxide derivatives possessing an ethyl alcohol-directing group; however, reactions of unsubstituted styrene oxides resulted in low yield and low regioselectivity.⁸ Hence, the development of an approach for the selective cross-coupling of styrene oxides is an unmet need.

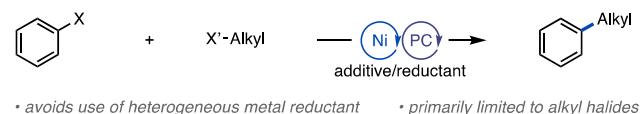
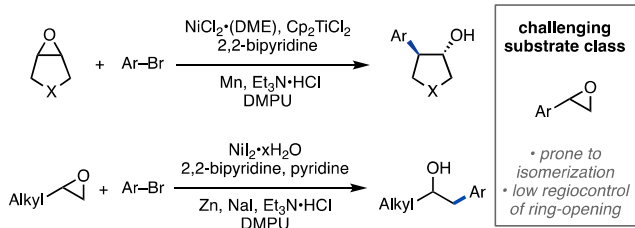
Here, we demonstrate that the combination of a Ni-, Ti-, and organic photoredox catalyst promotes highly regioselective and high-yielding cross-coupling of three distinct classes of epoxides: styrenyl-, cyclic-, and terminal aliphatic epoxides (Scheme 1C). Key to this generality is the identification of distinct ligands (holding the reaction conditions otherwise identical) that suppress undesired homocoupling and epoxide rearrangement pathways for each class of epoxides.^{6b,9} While

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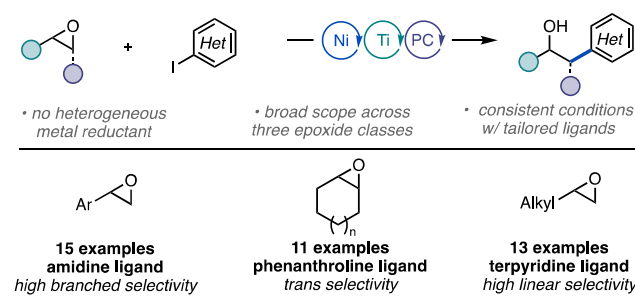
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Scheme 1. Cross-Electrophile Coupling^{3,7}A. Photoredox-assisted cross-electrophile coupling³B. Prior art: Cross-electrophile coupling with epoxides⁷

C. This work: Photoredox-assisted cross-electrophile coupling with epoxides



most Ni-photoredox reactions have been restricted to a single ligand, 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbbpy), thereby limiting opportunities for reaction optimization and translation to enantioselective reactions, this study represents a relatively rare example of a Ni-photoredox reaction that shows broad ligand response.^{3f,10} Notably, under otherwise similar conditions, opposite regiochemical outcomes were observed for the cases of styrenyl and terminal aliphatic epoxides. Mechanistic studies are presented to explain these observations.

Our investigation began by examining the Ni-photoredox coupling of 4-iodotoluene with three representatives of distinct epoxide classes: styrene oxide **1a**, cyclohexene oxide **2a**, and 1-dodecene oxide **3a** (Table 1). Gansäuer and Shi have recently reported Ti-catalyzed reductive reactions of aliphatic epoxides in the presence of an Ir(dF-CF₃-ppy)₂(dtbbpy)PF₆ and 4CzIPN photocatalyst, respectively.¹¹ Photophysical studies by both groups have shown that the active Ti(III)-complex can be formed via single electron transfer (SET) from a photoredox catalyst, thereby obviating the use of stoichiometric heterogeneous reductants. On the basis of these results and the precedent from Weix, we selected a starting set of reaction conditions: 5 mol % 4CzIPN as a photocatalyst, 10 mol % NiBr₂-diglyme as a precatalyst, 20 mol % dtbbpy as a ligand, 5 equiv Et₃N as a soluble reductant, and 25 mol % Cp₂TiCl₂¹² as a co-catalyst. For styrene oxide **1a**, the branched coupling product (**4a**) was formed as the sole regioisomer in 33% yield (entry 1). Conversely, the linear coupling product (**6a**) was formed selectively from **3a** in 38% yield under the same conditions (entry 3). Use of cyclohexene oxide **2a** resulted in the formation of 24% yield of the *trans* coupling product **5a** (entry 2). However, the formation of various side products was observed under these reaction conditions. Biaryl

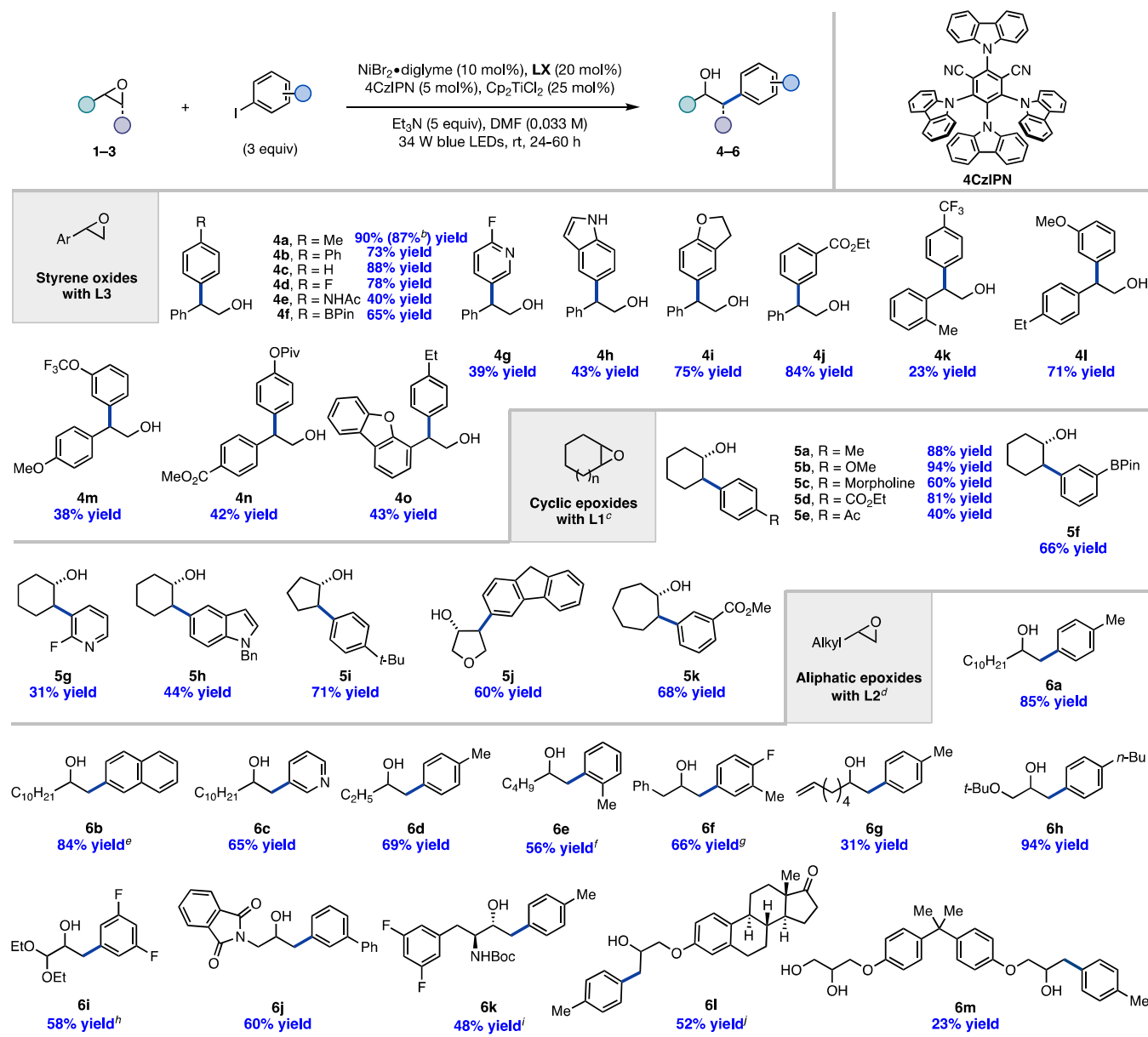
Table 1. Optimization of the Reaction Parameters^a

entry	epoxide ^b	deviation	b:l ^c	aldehyde % ^d	biaryl % ^e	yield % ^f
1	1a	none	20:1	20	14	33
2	2a	none	n/a	n/a	24	24
3	3a	none	1:20	12	40	38
4	1a	L1 instead of dtbbpy	20:1	19	26	42
5	2a	L1 instead of dtbbpy	n/a	n/a	17	85 (90 ^g)
6	3a	L1 instead of dtbbpy	1:20	12	44	44
7	1a	L2 instead of dtbbpy ^h	n/a	0	0	<2
8	2a	L2 instead of dtbbpy ^h	n/a	n/a	2	24
9	3a	L2 instead of dtbbpy ^h	1:20	5	3	85
10	1a	L3 instead of dtbbpy	20:1	2	17	90
11	2a	L3 instead of dtbbpy	n/a	n/a	2	24
12	3a	L3 instead of dtbbpy	1:20	15	55	11
13	1a	L3 w/ No PC or Ti or light	n/a	0	0	<2
14	2a	L1 w/ No PC or Ti or light	n/a	n/a	0	<2
15	3a	L2 w/ No PC or Ti or light	n/a	0	0	<2

^aReactions were conducted on a 0.05 mmol scale. n/a = not applicable. ^bReaction time with **1a** = 24 h; with **2a** = 36 h; and with **3a** = 60 h. ^cBranched (b):linear (l) as determined by gas chromatography (GC). ^dAldehyde was formed via isomerization of the epoxide. ^e4,4'-Dimethyl-1,1'-biphenyl. ^fGC yields were calibrated using pentadecane as an internal standard. GC yield of the major isomer is shown. ^gMeCN was used as solvent. ^h10 mol % of L2 was used.

(4,4'-dimethyl-1,1'-biphenyl) was detected in 14%, 24%, and 40% yield for the reaction of epoxides **1a**–**3a**, respectively. The formation of biaryl is a common side reaction in cross-electrophile coupling reactions. For **1a** and **3a**, the corresponding aldehydes, formed via Ti/Ni-catalyzed isomerization, were also detected in 20% and 12% yield, respectively.

We sought to evaluate whether the use of an alternate ligand could be used to suppress these side pathways to improve the efficiency of the epoxide coupling. From our screening studies, three ligands emerged as successful: with phenanthroline

Table 2. Scope of the Cross-Electrophile Coupling of Epoxides^a

^aIsolated yields are reported based on an average of two runs (0.2 mmol scale). b:l = branched:linear ratio. Unless otherwise noted, the regioselectivity is $\geq 20:1$. Reaction time with 1 = 24 h; with 2 = 36 h; and with 3 = 60 h. ^b1 mmol scale. ^cMeCN was used instead of DMF. ^d10 mol % of L3 was used. ^eb:l = 1:17. ^fdtbbpy was used instead of L2. ^gb:l = 1:11.4. ^hb:l = 1:15. ⁱSingle diastereomer. ^jb:l = 1:7.3; regioisomers are separable.

ligand BPhen (L1), reactions of 1a and 3a resulted in low reaction yield with significant generation of biaryl and isomerization byproducts (entries 4 and 6). However, reaction of 2a with L1 generated the desired coupling product 5a in 90% yield with minor side product formation (entry 5). With tridentate ligand *t*-Bu-terpy (L2), 3a afforded the linear coupling product 6a in 85% yield with trace amounts of the reaction byproducts (entry 9). The reactions of 1a and 2a, however, resulted in low yields under the reaction conditions with L2 (entries 7 and 8). Finally, using amidine ligand L3, the branched coupling product 4a was obtained in high yield and selectivity from epoxide 1a (entry 10). Interestingly, 2a and 3a were poor-performing substrates under the reaction conditions with L3 (entries 11 and 12). Control studies for each class of

epoxides, with their respective ligand, indicated that all of the reaction parameters were necessary (entries 13–15 and Supporting Information (SI)).

A few general considerations emerge from these optimization studies. First, linear isomeric product 6a was obtained from aliphatic epoxide 3a independent of the ligand identity, whereas the branched isomeric product 4a was formed from styrene oxide 1a, suggestive of a change in mechanism (*vide infra*). Second, dtbbpy was not optimal for any epoxide class but showed intermediate reactivity in each case, an illustration of how it may have emerged as the most general ligand in Ni-photoredox catalysis (entries 1–3). While our future efforts will be directed at gaining a detailed understanding of the origin of ligand specificity in these reactions, it is clear from the

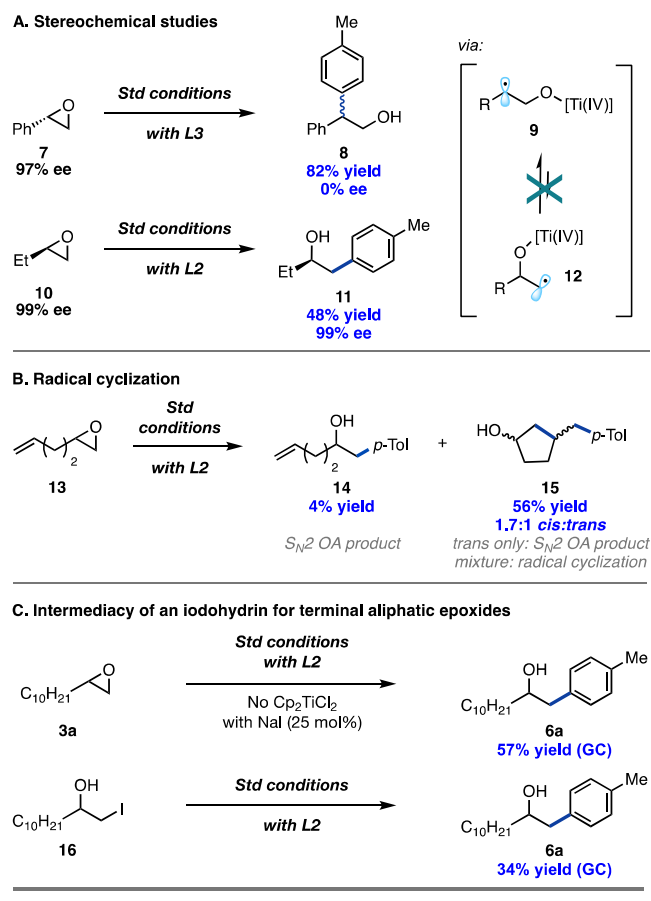
data that use of a tridentate ligand suppresses biaryl formation, consistent with literature reports on Ni cross-electrophile coupling reactions.¹³ However, *t*-Bu-terpy is only effective for coupling with epoxide **3a**, presumably because the ligand is too hindered to facilitate productive bond formation in the cases of epoxides **1a** and **2a**, which both afford secondary as compared to primary C(sp³)-C(sp²) bonds. In the case of styrene oxide **1a**, amidine ligand **L3** is optimal instead. While amidine ligands have been employed for Ni-catalyzed reductive coupling reactions,¹⁴ to the best of our knowledge, they have not been used in Ni-photoredox catalysis. We propose that amidine ligand **L3** is effective because it affords an electron-rich Ni-complex that suppresses Ni-mediated isomerization of **1a**. Among the three epoxide classes, cyclohexene oxide **2a** represents the most challenging from the perspective of C-C reductive elimination. As such, we expect that the enhanced π -acidity of BPhen could accelerate reduction steps at Ni such as reductive elimination, which may be responsible for its role in this coupling reaction.¹⁵

Next, the scope of the transformation was investigated (Table 2), beginning with an examination of different styrene oxides (**1**). Under the standard reaction conditions using **L3**, both electron-rich and electron-deficient aryl iodides were well tolerated, affording branched products **4a–e** in good yields. Employment of an aryl iodide possessing a BPin substituent that can be further functionalized by traditional cross-coupling methods produced **4f** in 65% yield. Heteroaryl iodides, such as 2-fluoro-5-iodopyridine and 5-iodoindole, afforded the corresponding alcohols **4g** and **4h** in moderate yield. In varying the styrene oxide framework, we found that sterically hindered 2-(*o*-tolyl)oxirane **1k** underwent coupling regioselectively, albeit in 23% yield (**4k**). Coupling of electronically diverse styrene oxides (**1l–1n**) with a range of aryl iodides generated the corresponding branched products in moderate to good yields (**4l–n**). Finally, heterocyclic styrene oxide **1o** produced **4o** in 43% yield under the reaction conditions.

In exploring the scope of cyclic epoxides using ligand **L1**, we found that cyclohexene oxide reacted with electron-rich and electron-deficient aryl iodides, resulting in *trans* products **5a–e** in 40–94% yield. Of note are products **5d** and **5e**, since their synthesis via traditional ring-opening of cyclohexene oxide with Grignard reagents would lead to low chemoselectivity due to the pendant ester and ketone functionalities. In addition, 3-BPin-aryl iodide and heteroaryl iodides coupled well with cyclohexene oxide (**5f–h**). Notably, the 5-membered cyclic epoxides, such as cyclopentene oxide and epoxy tetrahydrofuran, were high-performing substrates (**5i–j**). A 7-membered cyclic epoxide **2k** was also amenable to this cross-coupling reaction (**5k**).

Next, the scope of terminal aliphatic epoxides was examined with **L2**. The reaction of electronic rich, neutral, and heteroaryl iodides with 1-dodecene oxide provided linear products (**6a–c**) in high yield and regioselectivity. Coupling of sterically hindered 2-iodotoluene with 1-hexene oxide resulted in no reaction; however, using less sterically hindered dtbbpy in place of **L2** afforded product **6e** in 56% yield. Benzyl epoxide reacted well under the reaction conditions, producing **6f** in 66% yield, with slightly diminished regioselectivity (b:l = 1:11.4). Employment of aliphatic epoxide **3g**, possessing sensitive olefin functionality, generated coupling product **6g** in 31% yield. Epoxides possessing glycidyl ether, acetal, and phthalimide functional groups were well tolerated (**6h–j**),

Scheme 2. Mechanistic Studies



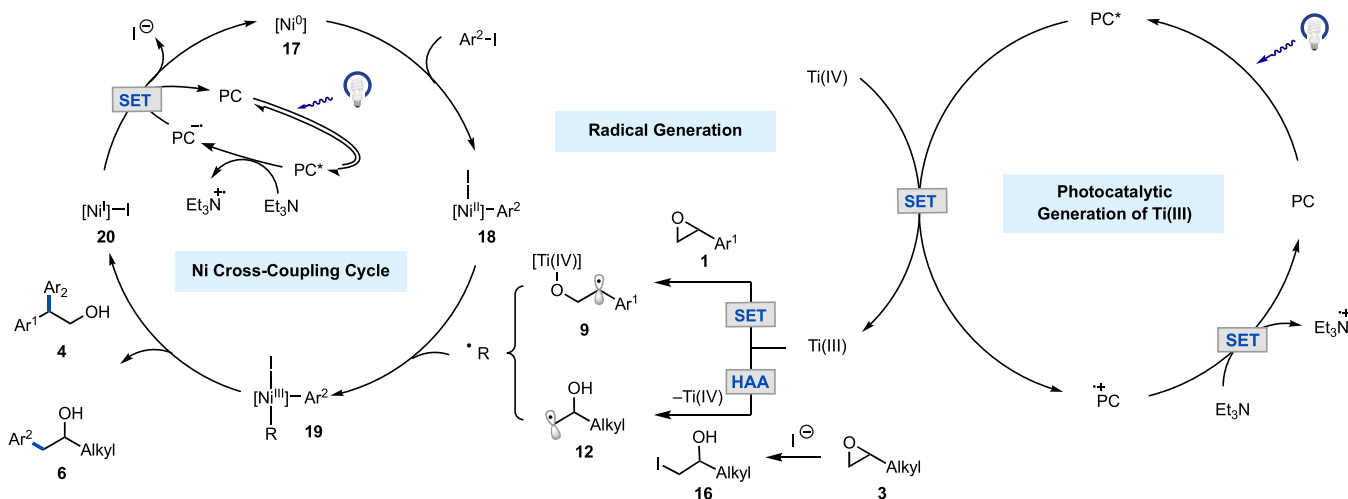
highlighting the broad functional group tolerance of the method.

Notably, this protocol was amenable to late-stage coupling as showcased by the following reactions. Protease inhibitor precursor **3k** produced amino alcohol **6k** in 48% yield as a single diastereomer under the reaction conditions. Glycidyl estrone ether **3l** reacted smoothly, producing **6l** in 52% yield and 1:7.3 b:l regioselectivity. Bisphenol A glycidyl ether, an industrial resin,¹⁸ was subjected to the reaction conditions, affording **6m** in 23% yield.

The mechanism of the reaction was interrogated next. Given the difference in regioselectivity for styrenyl and aliphatic epoxides, tandem mechanistic experiments were performed with these two substrate classes. Control experiments for all classes of epoxides revealed that the Ti-catalyst was an important parameter (Table 1, entries 13–15). Thus, we considered radical ring-opening of the epoxide via SET with the Ti-catalyst as a possible mechanistic pathway.¹² To probe this possibility further, stereochemical studies were conducted involving enantioenriched styrene oxide **7** and aliphatic epoxide **10** (Scheme 2A). Subjecting **7** to the reaction conditions resulted in coupling product **8** with erosion of the stereocenter, supporting the formation of radical intermediate **9**. Conversely, **10** generated product **11** with conservation of *ee* under the reaction conditions, suggesting that reversible Ti-mediated ring-opening, leading to the primary alkyl radical **12**, is highly unlikely (**9** → **12**).¹²

Since arylation occurs at the terminal end of the aliphatic epoxide, we considered that an S_N2 oxidative addition (OA)

Scheme 3. Proposed Mechanisms



mechanism of Ni(0) with the epoxide could instead be operative.⁵¹ To probe if epoxide ring-opening occurs via Ni-activation or a radical pathway, radical clock substrate **13** was tested (Scheme 2B).¹⁹ If an S_N2-type OA by Ni(0) were occurring, then **14** and/or the *trans* diastereomer of **15** would be expected as the major product(s).⁵¹ However, upon exposure of **13** to the reaction conditions, the cyclization product **15** was formed as a mixture of *cis/trans* isomers, providing evidence for the formation of a radical species at the terminal position of the epoxide. Next, a control study was conducted by replacing Cp₂TiCl₂ with a catalytic amount of NaI (Scheme 2C).^{7a} The reaction of **3a** under these modified conditions resulted in significant yield of **6a**, suggesting the intermediacy of an iodohydrin (**16**).⁷ Furthermore, submission of independently synthesized iodohydrin **16** to the standard reaction conditions generated linear product **6a** in 34% yield. Hence, for aliphatic epoxides, formation of an iodohydrin intermediate is highly probable.

Based on the above mechanistic studies, two distinct mechanisms are proposed for styrenyl and aliphatic epoxides (Scheme 3). In both cases, irradiation of 4CzIPN (PC) under blue light generates photoexcited 4CzIPN*,¹¹ which undergoes oxidative quenching with Ti(IV) to generate Ti(III) ($E_{1/2}$ PC^{•+}/PC^{•-} = −1.18 V vs SCE,²⁰ $E_{1/2}$ Ti(IV)/Ti(III) = −0.57 V vs SCE¹¹). This quenching pathway was supported by Stern–Volmer quenching studies (see SI) and recent literature reports. For styrene oxides, the formed Ti(III) species engages in a radical ring-opening event with **1** to form intermediate **9**. This intermediate reacts with the Ni(II) complex **18**²¹ to form branched Ni(III) intermediate **19**. Facile reductive elimination of **19** results in the branched coupling product **4** and Ni(I) intermediate **20**. Complex **20** undergoes reduction with 4CzIPN^{•-} ($E_{1/2}$ PC/PC^{•-} = −1.24 V vs SCE,²⁰ $E_{1/2}$ Ni(I)/Ni(0) = −1.17 V vs SCE²²), which was generated via reductive quenching with triethylamine (Et₃N) ($E_{1/2}$ PC^{•+}/PC^{•-} = +1.43 V vs SCE,²⁰ $E_{1/2}$ Et₃N^{•+}/Et₃N = +0.93 V vs SCE²³) to turn over the Ni-cycle and the photocatalytic cycle.²³ The mechanism for cyclic epoxides is speculated to be analogous to that of styrene oxides based on current (see SI) and previous mechanistic studies.^{7b}

For terminal aliphatic epoxides, formation of the iodohydrin intermediate **16** is proposed to occur via the nucleophilic addition of *in situ* generated iodide with the aliphatic epoxide

(**3**). Catalytic amounts of iodide are likely formed via reduction of Ni(I)–I intermediate **20** with 4CzIPN^{•-}. Next, the iodohydrin intermediate **16** participates in a halogen atom abstraction²⁴ (HAA) event with Ti(III) to generate primary alkyl radical **12**,²⁵ which undergoes radical addition to Ni(II) complex **18** to form linear Ni(III) species **19**. Subsequent reductive elimination of the latter generates the linear coupling product **6**. An alternative pathway, where the iodohydrin intermediate is formed via Lewis acid-mediated iodide ring-opening of the epoxide with Ti, cannot be ruled out (see SI).

In conclusion, we have developed a photocatalytic cross-electrophile coupling of three different classes of epoxides with (hetero)aryl iodides. The transformation exhibits interesting ligand effects, where a different amine-based ligand was required for the efficient coupling of a particular class of epoxide. The scope of the transformation was found to be general, as a range of electronically and sterically diverse epoxides and aryl iodides coupled efficiently. Notably, reaction of styrene epoxides led to the branched coupling products selectively, whereas terminal aliphatic epoxides generated the unexpected linear isomer under otherwise similar reaction conditions. Mechanistic studies revealed that linear selectivity from aliphatic epoxides arises due to the involvement of an iodohydrin intermediate. In contrast, for styrene epoxides, branched products are formed via Ti-mediated radical epoxide ring-opening. Based on the broad ligand response of this transformation, future efforts will be focused on understanding ligand effects for related Ni-photoredox reactions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.0c01199>.

Full optimization of the reaction parameters; experimental details; general procedures; isolated yields and characterization data; mechanistic studies; and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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