Nickel-Catalyzed Regiodivergent Opening of Epoxides with Aryl Halides: Co-Catalysis Controls Regioselectivity

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S *Supporting Information*

ABSTRACT: Epoxides are versatile intermediates in organic synthesis, but have rarely been employed in cross-coupling reactions. We report that bipyridine-ligated nickel can mediate the addition of functionalized aryl halides, a vinyl halide, and a vinyl triflate to epoxides under reducing conditions. For terminal epoxides, the regioselectivity of the reaction depends upon the cocatalyst employed. Iodide cocatalysis results in opening at the less hindered position via an iodohydrin intermediate. Titanocene cocatalysis results in opening at the more hindered position, presumably via Ti[III]-mediated radical generation. 1,2-Disubstituted epoxides are opened under both conditions to form predominantly the trans product.

The formation of carbon–carbon bonds by the opening of epoxides with aryl nucleophiles has long played an important role in organic synthesis.[1,2] Three major addition products are commonly observed (eq 1). Although the opening

of epoxides with heteroatom nucleophiles and stabilized or unstabilized carbon nucleophiles (most often cuprates) is well-known,[1–3] transition-metal catalyzed coupling of epoxides with less reactive nucleophiles or carbon electrophiles is rare, despite the obvious synthetic utility.[4]

The transition-metal-catalyzed coupling of epoxides with π-systems, such as alkenes,[5] alkynes,[6] aldehydes,[7] and CO,[8] have been developed recently, but few such reactions that couple simple aryl groups to epoxides are known.[9] Doyle reported a nickel-catalyzed coupling with arylboronic acids that formed rearranged products 4,[10] similar to related reactions with allylmetal reagents.[11] While Flowers and Gansäuer recently extended Ti(III)-epoxide chemistry[12] to the intramolecular internal arylation of epoxides,[13] the intermolecular arylation of epoxides to form products 2 and 3 remains limited to traditional methods.

In order to bypass the difficulties associated with the reaction of epoxides with nucleophiles, we sought out an alternative cross-electrophile approach[14]—the coupling of organic halides with epoxides. Initial attempts provided low conversion, and primarily biaryl and arene were formed (Table 1, entry 1). In analogy to our proposed mechanism for the cross-electrophile coupling of aryl halides with alkyl halides,[15,16] it was evident that conversion of the epoxide into a radical was inefficient

Table 1. Regiodivergent Opening of Epoxides[a]

entry	additives	yield (%)	2:3
1	none	9	ND
2	50 mol % NaI, 20 mol % py	50	91:9
3	10 mol % Cp$_2$TiCl$_2$	40	1:4

[a]See Tables 2 and 4 for conditions. Yield and ratio of **2:3** determined by GC analysis vs internal standard, uncorrected.

(Table 1C). Decomposition of the arylnickel intermediate forms biphenyl and benzene. Co-catalysis by iodide (Table 1A and entry 2) or titanium (Table 1B and entry 3) could enable the regioselective opening of epoxides by forming **2** via an iodohydrin[17,18] or **3** via a secondary radical.[12,19]

The iodide-cocatalyzed reactions produced the highest yields when NiI$_2$ was combined with a small amount of additional NaI (Table 2, entry 1). A suitable protic acid is also essential for high turnover number and frequency (entry 2), presumably because it assists in halohydrin formation.[18] A number of acids were examined and only acids with a pK_a around 9 in DMSO were effective (TEA·HX, DABCO·HCl, Me$_3$N·HCl, i-Pr$_2$NEt·HCl). Stronger acids (DABCO·2HCl, 2,4,6-collidine·HCl) and weaker acids (DBU·HCl) provided no cross product.[20] Even though nickel is known to isomerize epoxides to aldehydes,[10,21] no rearranged products (**4**) were observed.

The iodide source was optimally sodium iodide or Bu$_4$NI (entry 1 and entry 4). Reactions run with zinc or manganese iodide were notably slower. Reactions conducted with a smaller amount (entry 3) or no sodium iodide (entry 7) were slower,

Table 2. Nickel/Iodide Co-catalyzed Epoxide Ring-Opening with Aryl Halides[a]

entry	deviation from above	yield (%)[b]	2:3
1	none	81	>95:5
2	no TEA·HCl	32	89:11
3	15 mol % NaI	67	>95:5
4	25 mol % Bu$_4$NI in place of NaI	79	95:5
5	12.5 mol % ZnI$_2$ in place of NaI	46	88:12
6	12.5 mol % MnI$_2$ in place of NaI	61	95:5
7	no NaI, 12 h	68	>95:5
8	no NaI, 24 h	75	>95:5
9	25 mol % NaBr in place of NaI	52	>95:5
12	NiI$_2$ in place of NiI$_2$·xH$_2$O	86	>95:5
13	2 equiv of Mn in place of Zn	59	95:5
14[c]	2 equiv of TDAE in place of Zn	48[d]	>95:5
15	heated to 60 °C for 12 h	50	93:7
16	I-Ph in place of Br-Ph	51	91:9
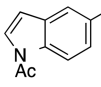
[a]Reactions were run with 1 equiv of Et$_3$N·HCl and 2 equiv of zinc dust; 0.1 equiv nickel catalyst, ligand; 0.2 equiv pyridine, 0.25 equiv sodium iodide, and 1.34 equiv of **1a** in 3 mL DMPU. [b]Uncorrected GC yield of **2aa**. [c]TDAE = tetrakis(dimethylamino)ethylene. [d]Bromobenzene (52%) remained, but no biaryl or benzene was formed.

but would produce the product in nearly the same yield after an extended reaction time (entry 8). The source of iodide was presumably the nickel source in the latter reaction. The addition of sodium bromide in place of sodium iodide decreased the yield and selectivity for cross product (entry 9 and Figure S1 in Supporting Information [SI]). Dimethylpropylene urea (DMPU) was found to be the optimal solvent, and reactions in impure DMPU provided lower yields. Finally, zinc could be replaced by manganese or the organic reductant tetrakis(dimethylamino)-ethylene (entries 13 and 14).[22] The latter result argues against organozinc intermediates.

Examination of the scope for aryl and vinyl halides (Table 3) and for epoxides (Scheme 1) reveals the generality of the method. Not only electron-rich and electron-poor bromoarenes (Table 3, entries 2 and 5−6) but also bromoarenes with a variety of functional groups provided good yields of product. This synthesis of **2ea** is four steps shorter than the only literature report.[23] Bromoarenes bearing acidic functional groups (TsNHAr, entry 3; -OH, entry 9) were well tolerated. Reactions with phenols under basic conditions could result in ring-opening of the epoxide by the phenolate nucleophile, but none of this product was observed. Unprotected ketone, nitrile, and aldehyde groups were well tolerated (entries 6−8). Finally, a vinyl bromide and a vinyl triflate both coupled in high yield under our standard conditions (entries 12−13).

Besides simple terminal epoxides such as hexene oxide and octene oxide, terminal epoxides with protected alcohol or protected nitrogen functional groups were also good substrates (**2ad**, **2ag**, **2ah**, **2ak**). Styrene oxide provided a mixture of products **2ae** and **3ae**, favoring the product of internal attack (**3ae**), consistent with the reported regioselectivity for halohydrin formation.[18a] More substituted 1,2- and 1,1-disubstituted epoxides form ring-opened products in good yield (**2af**, **2ai**, **2al**), but a 1,1,2-trisubstituted epoxide did not form product

Table 3. Scope of Organic Halides[a]

entry	R–X	product[c]	yield (%)[b]
1	PhBr **4a**	**2aa**	87
2[d]	p-MeO-C$_6$H$_4$Br **4b**	**2ba**	83
3[d]	p-TsNH-C$_6$H$_4$Br **4c**	**2ca**	84
4[d]	p-tert-butyl-C$_6$H$_4$Br **4d**	**2da**	72
5	p-CF$_3$-C$_6$H$_4$Br **4e**	**2ea**	79
6	p-CH$_3$C(O)-C$_6$H$_4$Br **4f**	**2fa**	84
7	p-NC-C$_6$H$_4$Br **4g**	**2ga**	55
8	p-CHO-C$_6$H$_4$Br **4h**	**2ha**	62[e]
9[d]	p-HO-C$_6$H$_4$Br **4i**	**2ia**	58[f]
10	o-CH$_3$-C$_6$H$_4$Br **4j**	**2ja**	99
11[d]	[indole structure] **4k**	**2ka**	99
12	[cyclohexenyl] **4l** X = OTf	**2la**	93
13	[cyclohexenyl] **4m** X = Br	**2ma**	86

[a]As in Table 2, footnote a. [b]Isolated yield of purified product. [c]Numbering scheme: **2xy** is the product of **4x** and **1y**. [d]Longer reaction time (24 h) was required. [e]Mixture of **2ha** (55%) and **3ha** (7%). [f]Mixture of **2ia** (53%) and **3ia** (5%).

Scheme 1. Scope of Epoxides[a]
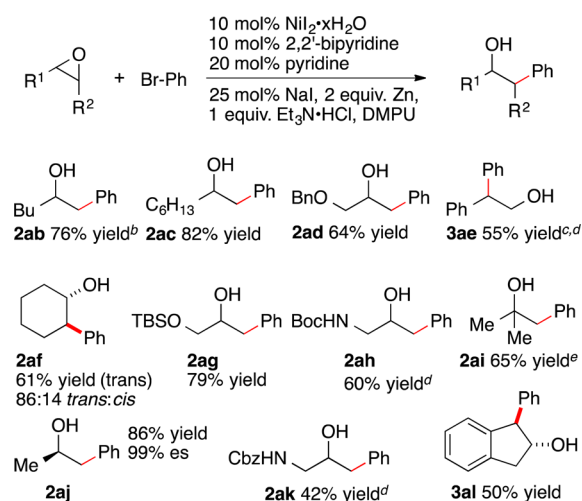
[a]As in Table 2, footnote a, but with 1 equiv of epoxide. Yield is the isolated yield of the product shown. [b]Mixture of **2ab** (66%) and **3ab** (10%). [c]Product of internal attack. **2ae** was also isolated in 14% yield. [d]Longer reaction time (24 h) was required. [e]From 0.56 mmol of isobutene oxide.

(data not shown). As expected, the opening of enantioenriched (*R*)-propylene oxide with bromobenzene afforded product **2aj** with high enantiospecificity (99% es). Finally, a preformed iodohydrin substrate reacted to form product with regioselectivity (>95:5) and yield (64%) in similar catalytic reactions (Scheme S1 in SI).

The refinement of titanium-mediated conditions required several small changes. Higher yields were obtained with manganese as the reductant. In many cases, significant amounts of epoxide remained at the end of the reaction due to inactivation of the titanium catalyst. In these reactions, we also observed that small amounts of the epoxide were converted to olefin. As reported by Gansäuer and Neese, the olefin likely arises from capture of the alkyl radical by another equivalent of titanium(III) and subsequent β-alkoxy elimination of an oxo-bridged titanium(IV) dimer, {Cp$_2$Ti(Cl)−O−(Cl)TiCp$_2$}.[12e] This titanium dimer is not easily reduced back to Ti(III), preventing further conversion of epoxide into product.

This side reaction was not eliminated by the use of additional titanium; at the beginning of the reaction 2:1 Ti:Ni provided similar yield to 1:1 Ti:Ni, see Table S1 in SI, but the addition of another 4 mol % of titanium after 2 h resulted in a 9% improvement in yield for cyclohexene oxide (eq 2). Note that

$$(2)$$
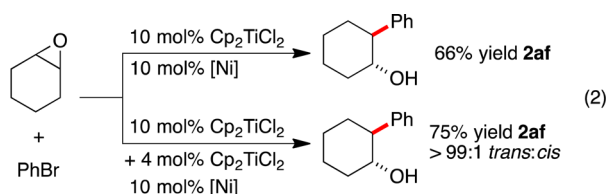
cyclohexene oxide reacts with titanium cocatalysis to provide arylated product in higher selectivity (99:1 vs 86:14) and yield (75% vs 61%) than with iodide cocatalysis. The improved selectivity is likely the result of the steric bulk of −O(Cl)TiCp$_2$ shielding one face of the intermediate radical better than a simple −OH group.

These conditions were applied to several terminal epoxides (Table 4). In line with Gansäuer's report,[12d] regioselectivity favored the internal product.[24] Selectivity and yield with **1b** was consistent with previous reports and calculations for irreversible radical formation followed by fast trapping by (L)Ni^{II}(Ar)Br (Table 1 and Table 4, entry 2), but the different regioselectivity

Table 4. Formation of Branched Products with Ni/Ti Catalysis[a]

entry	R	Ar−Br	3:2	yield (%)
1	Me **1a**	PhBr **4a**	3.3:1	70 (**3aa**)
2	C$_4$H$_9$ **1b**	**4a**	6:1	54 (**3ab**)
3	C$_6$H$_{13}$ **1c**	**4a**	99:1	41 (**3ac**)
4	**1a**	p-MeO-C$_6$H$_4$Br **4b**	4:1	63 (**3ba**)
5	**1a**	p-MeO$_2$C−C$_6$H$_4$Br **4n**	3.5:1	62 (**3na**)

[a]Conditions: 1 equiv of Et$_3$N·HCl and 2 equiv of Mn dust were combined with **4** (1 equiv), **1** (1.34 equiv), and catalysts (10 mol %) in DMPU (0.17 M) and stirred for 12 h at rt. An additional portion of Cp$_2$TiCl$_2$ was added after 2 h. Ratios of **3:2** were determined by GC analysis. Yield is an isolated mixture of **2** and **3**.

in reactions with **1a** and **1c** suggests that in some cases rapid reversible radical formation followed by slower trapping is operative (entries 1 and 3).[12d] Functional group compatibility is promising, and electronics of the aryl halide do not dramatically alter the selectivity or yield (entries 4 and 5). For comparison

with existing methods, a previous synthesis of **3na** was six steps.[25] Consistent with a titanium(III)-mediated radical process, 4-bromobenzaldehyde did not couple in high yield due to competing pinacol coupling,[26] and reaction of (R)-propylene oxide produced (±)-**3aj**.

In conclusion, mechanism-based reaction design has extended cross-electrophile coupling to epoxides for the first time. We have demonstrated that nickel/iodide and nickel/titanium catalyst systems can open epoxides with aryl bromides, vinyl bromides, and vinyl triflates and that the regioselectivity for reactions with terminal epoxides is governed by the cocatalyst. The results demonstrate the potential of new cross-coupling reactions based upon the interplay of radicals and transition-metal catalysis.[27] Further improvement of the selectivities, including the development of enantioselective variants[12f,g] and longer-lived titanium catalysts, is currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

ⓢ Supporting Information
Supplementary figures, detailed experimental procedures, characterization data, and copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra for new compounds. 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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