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

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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 co-catalyst employed. Iodide co-catalysis results in opening at the less hindered position via an iodohydrin intermediate. Titanocene co-catalysis 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,^{1,2, 3} transition-metal catalyzed coupling of epoxides with less reactive nucleophiles or carbon electrophiles is rare, despite the obvious synthetic utility.⁴

(1)

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 chemistry¹² to the intra-molecular, 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 approach¹⁴ – 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

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ASSOCIATED CONTENT

Supporting Information. Supplementary figures, detailed experimental procedures, characterization data, and copies of 1H , ^{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>.

coupling of aryl halides with alkyl halides,^{15, 16} it was evident that conversion of the epoxide into a radical was inefficient (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 co-catalyzed reactions produced the highest yields when NiI₂ 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, Me₃N•HCl, *i*-Pr₂NEt•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 Bu₄NI (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, 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). 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) demonstrates 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 like 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 (data not shown). As expected, the opening of enantioenriched (*R*)-propylene oxide with bromobenzene afforded product **2aj** with high enantiospecificity (99% *es*). Finally, a pre-formed iodohydrin substrate reacted to form product with regioselectivity (>95:5) and yield (64%) similar catalytic reactions (Scheme S1).

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, $\{\text{Cp}_2\text{Ti}(\text{Cl})\text{-O-(Cl)TiCp}_2\}$.^{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), but the addition of another 4 mol% of titanium after two hours resulted in a 9% improvement in yield for cyclohexene oxide (eq 2). Note that cyclohexene oxide reacts with titanium co-catalysis to provide arylated product in higher selectivity (99:1 vs. 86:14) and yield (75% vs. 61%) than with iodide co-catalysis. The improved selectivity is likely the result of the steric bulk of $\text{-O}(\text{Cl})\text{TiCp}_2$ shielding one face of the intermediate radical better than a simple -OH group.

(2)

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 $(\text{L})\text{Ni}_{\text{II}}(\text{Ar})\text{Br}$ (Table 1 and Table 4, entry 2), but the different regioselectivity 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 6 steps.²⁵ Consistent with a titanium(III)-mediated radical process, 4-bromobenzaldehyde did not couple in high yield due to competing pinacol coupling²⁶ and reaction of (*R*)-propylene oxide produced ($\pm$)-**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 co-catalyst. 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 enantio-selective variants^{12f-g} and longer-lived titanium catalysts, is currently underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

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 2Nickel/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_4NI 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 hours	68	> 95:5
8	No NaI, 24 hours	75	> 95:5
9	25 mol % NaBr in place of NaI	52	> 95:5
12	NiI_2 in place of $\text{NiI}_2 \cdot x\text{H}_2\text{O}$	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

^aReactions were run with 1 equiv of $\text{Et}_3\text{N} \cdot \text{HCl}$ 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.

^bUncorrected GC yield of 2aa.

^cTDAE = tetrakis(dimethylamino)ethylene.

^dBromobenzene (52%) remained, but no biaryl or benzene was formed.

Table 3

Scope of organic halides^a

entry	R-X	product ^c	yield (%) ^b	
1	PhBr 4a	2aa	87	
^{2d}	<i>p</i> -MeO-C ₆ H ₄ Br 4b	2ba	83	
^{3d}	<i>p</i> -TsNH-C ₆ H ₄ Br 4c	2ca	84	
^{4d}	<i>p</i> - <i>tert</i> -butyl-C ₆ H ₄ Br 4d	2da	72	
5	<i>p</i> -CF ₃ -C ₆ H ₄ Br 4e	2ea	79	
6	<i>p</i> -CH ₃ C(O)-C ₆ H ₄ Br 4f	2fa	84	
7	<i>p</i> -NC-C ₆ H ₄ Br 4g	2ga	55	
8	<i>p</i> -CHO-C ₆ H ₄ Br 4h	2ha	62 ^e	
^{9d}	<i>p</i> -HO-C ₆ H ₄ Br 4i	2ia	58 ^f	
10	<i>o</i> -CH ₃ -C ₆ H ₄ Br 4j	2ja	99	
11d	4k	4k	2ka 99	
12	4l X = OTf	4l X = OTf	2la 93	
13	4m X = Br	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%).

Table 4Formation 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	<i>p</i> -MeO-C ₆ H ₄ Br 4b	4:1	63 (3ba)
5	1a	<i>p</i> -MeO ₂ C-C ₆ H ₄ Br 4n	3.5:1	62 (3na)

^a Conditions: 2 equiv of Et₃N·HCl and 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 Cp₂TiCl₂ was added after 2 h. Ratios of **3**:**2** were determined by GC analysis. Yield is an isolated mixture of **2** and **3**.