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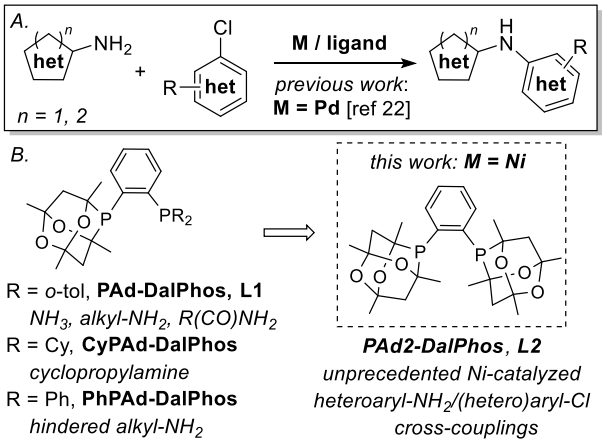
PAd2-DalPhos Enables the Nickel-Catalyzed C-N Cross-Coupling of Primary Heteroarylamines and (Hetero)aryl Chlorides

Jillian S. K. Clark,[a] Michael J. Ferguson,[b] Robert McDonald,[b] and Mark Stradiotto*,[a]

Abstract: *Base-metal catalysts capable of enabling the assembly of heteroatom-dense molecules via cross-coupling of primary heteroarylamines and (hetero)aryl chlorides, while sought-after given the ubiquity of unsymmetrical di(hetero)arylamino fragments in pharmacophores, are unknown. Herein, we disclose the new 'double cage' bisphosphine PAd2-DalPhos (**L2**). The derived air-stable Ni(II) pre-catalyst **C2** functions well at low loadings in challenging test C-N cross-couplings with established substrates, and facilitates the first Ni-catalyzed C-N cross-couplings of primary five- or six-membered ring heteroarylamines and activated (hetero)aryl chlorides, with synthetically useful scope that is competitive with Pd catalysis.*

Over the past 20 years, the Pd-catalyzed cross-coupling of NH nucleophiles with (hetero)aryl (pseudo)halide electrophiles (i.e., Buchwald Hartwig Amination, BHA) has evolved into a first-choice synthetic protocol for the synthesis of (hetero)anilines.[1] The development of such protocols can be attributed in part to the use of sophisticated ancillary ligands[2] (e.g., Buchwald biaryl monophosphines[3] and others[4]) designed to accommodate challenging reaction partners, including those featuring extensive heteroatom substitution, thereby providing access to target (hetero)anilines possessing useful biological activity (Scheme 1A).[1]



Scheme 1. *A*. Metal-catalyzed C-N cross-coupling of primary heteroarylamines and (hetero)aryl chlorides. *B*. Previously reported DalPhos ligands for Ni-catalyzed C-N cross-coupling, and the new 'double cage' ligand PAd2-DalPhos (**L2**) reported in this work.

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However, there is growing interest in the use of Ni-based catalysts in place of Pd for C-N cross-coupling,[5] not only from an environmental and economic standpoint (although costing of Pd vs Ni catalysts varies based on the precursor and ligands involved),[6] but also given the innate propensity of Ni species to engage electrophilic reaction partners where C-X oxidative addition is typically challenging (e.g., C-Cl in (hetero)aryl chlorides[7]). The repurposing of ligands from the early days of BHA, including bisphosphines[8] such as DPPF[9] and BINAP,[10] is a commonly employed approach that has enabled the Ni-catalyzed C-N cross-coupling of some substrate classes. However, this strategy has proven insufficient in the quest to match or exceed the performance of state-of-the-art BHA catalysts. Furthermore, the use of superlative BHA ligands, including decorated biaryl monophosphines,[3] has in general proven unsuccessful in facilitating Ni-catalyzed C-N cross-coupling chemistry.[8]

Given the absence of reports focusing on the rational development of new ancillary ligands specifically for use in Ni-catalyzed C-N and related cross-couplings, we envisioned that sterically demanding and moderately electron-donating bisphosphines[8] might prove useful in enabling presumptively challenging C-N reductive elimination within a putative Ni(0)/Ni(II) cycle.[11] In 2016 we disclosed the new ligand PAd-DalPhos (**L1**, Scheme 1B), featuring trioxaphosphaadamantane (PCg) and di(*o*-tolyl)phosphino donor fragments spanned by an *o*-phenylene bridge.[12] The derived Ni(II) pre-catalyst (**L1**)Ni(*o*-tol)Cl has proven effective in a diversity of C-N cross-coupling applications, including the monoarylation of ammonia,[12] unhindered primary alkylamines,[12] primary amides,[13] and lactams,[13] with a wide range of (hetero)aryl electrophiles. Variation of the PR_2 group in PAd-DalPhos has enabled other challenging C-N cross-couplings, including the *N*-arylation of cyclopropylamine[14] and hindered primary alkylamines[15] (Scheme 1B). We have also demonstrated that replacing the phenylene backbone of **L1** with a 3,4-thiophenylene linker (i.e., ThioPAd-DaPhos) affords Ni catalysts for the C-N cross-coupling of unhindered primary alkylamines that operate under mild conditions (25 ºC, <1 mol% Ni), in a manner that is competitive with BHA.[16]

Despite recent advances in Ni-catalyzed C-N cross-coupling, the identification of new ancillary ligands/catalysts that are capable of addressing unmet reactivity challenges remains an important goal. Encouraged by the success of our PCg-containing PAd-DalPhos ligands (*vide supra*), we became interested in exploring the utility of analogous chelating bisphosphines featuring two bulky and moderately electron-donating PCg donor groups. Herein we report on the synthesis and characterization of such new 'double cage' ancillary ligands, including PAd2-DalPhos (**L2**, Scheme 1B). Application of air-stable (**L2**)Ni(*o*-tol)Cl allows for previously unknown and sought-after Ni-catalyzed cross-couplings of primary five- and six-membered ring heteroarylamines and (hetero)aryl chlorides (Scheme 1A) to be achieved with synthetically useful scope.

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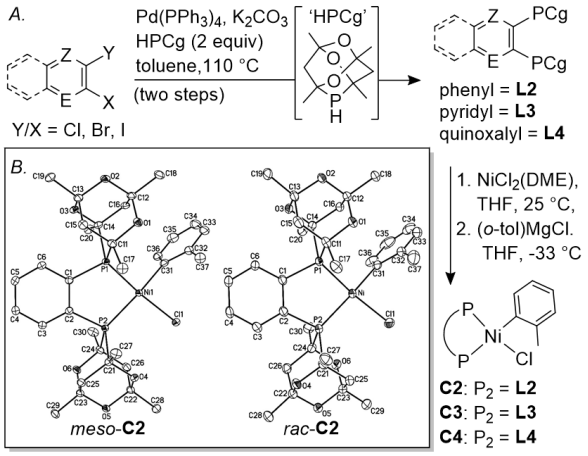
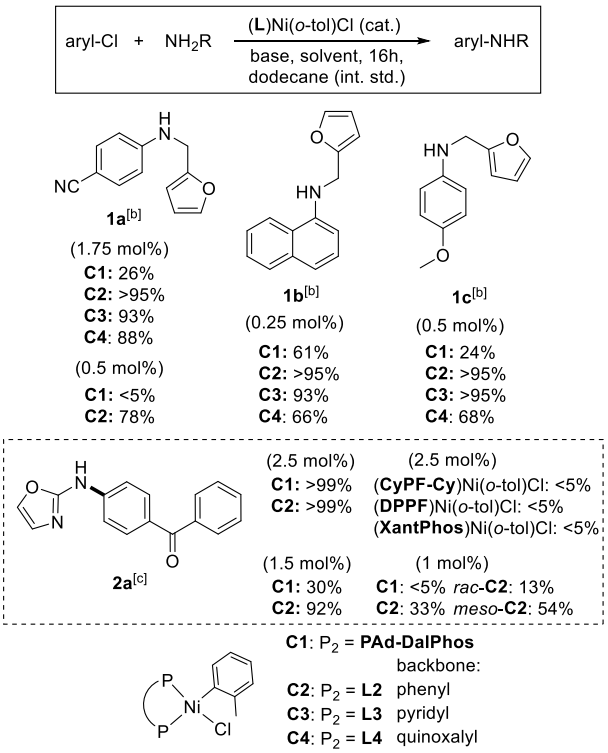
New double cage $(PCg)_2$(hetero)arene variants of **L1** based on phenyl (**L2**), pyridyl (**L3**), or quinoxalyl (**L4**) linking fragments were prepared in synthetically useful yield (Scheme 2A). Owing to the chiral (racemic) nature of the HPCg starting material, ~1:1 diastereomeric mixtures of air-stable *meso* (*RS*,*SR*) and *rac* (*RR*,*SS*) **L2**-**L4** were obtained when using the sequential P-C cross-coupling approach outlined in Scheme 2A; in the case of **L2** and **L3**, the *meso* and *rac* diastereomers could be separated in air by use of column chromatography.[17] The isolated diastereomers of **L2** and **L3**, and the *meso*/*rac* mixture of **L4**, were characterized on the basis of solution NMR spectroscopic data and high-resolution mass spectrometric analysis. Furthermore, single-crystal X-ray data were successfully obtained for each of the *meso* and *rac* isomers of **L2**-**L4** (see Figures S1-S6). The synthesis of variants of **L2**-**L4**, starting from 3,4-dibromothiophene under otherwise analogous conditions, proved to be low-yielding and thus unsuitable for further investigation.



Scheme 2. *A*: Synthesis of **L2**-**L4** using sequential Pd-catalyzed P-C cross-coupling protocols, as well as **C2**-**C4**. *B*: Single-crystal X-ray structures of *meso*-**C2** and *rac*-**C2**, each represented with thermal ellipsoids at the 30% probability level, and with hydrogen atoms omitted for clarity. Selected interatomic distances (Å) and angles (°): for *meso*-**C2**: Ni-P1 2.1791(7), Ni-P2 2.2458(7), Ni-Cl1 2.2177(8), Ni-C31 1.925(3), P1-Ni-P2 87.99(2), P2-Ni-Cl1 96.33(3), P1-Ni-C31 92.77(8), Cl1-Ni-C31 85.44(8); for *rac*-**C2**: Ni-P1 2.1679(10), Ni-P2 2.2402(10), Ni-Cl1 2.1893(11), Ni-C31 1.923(3), P1-Ni-P2 87.34(4), P2-Ni-Cl1 96.22(4), P1-Ni-C31 93.96(11), Cl1-Ni-C31 84.94(11).

Pre-catalyst complexes of the type (**L**)Ni(*o*-tol)Cl often exhibit improved performance relative to catalytic mixtures formed *in situ* from the combination of a metal source (e.g. $Ni(COD)_2$) and ligand.[18] As such, complexes of this type featuring **L2**-**L4** were prepared via treatment with $NiCl_2$(DME), followed by transmetallation of the putative intermediates (**L**)$NiCl_2$ with (*o*-tol)MgCl, to afford **C2**-**C4** as analytically pure, air-stable solids (Scheme 2A). In addition to the solution NMR spectroscopic characterization of these complexes, single-crystal X-ray diffraction data were obtained for *meso*-**C2** and *rac*-**C2** (Scheme 2B), as well as *meso*-**C3** and *meso*-**C4** (see Figures S9 and S10). In each case, a distorted square planar geometry is observed at Ni, with the Ni-P distance *trans* to chloride being shorter than the Ni-P distance opposite to the more strongly *trans*-directing *o*-tolyl group.

The catalytic competence of the new complexes **C2**-**C4**, versus **C1**, was assessed initially in challenging room temperature Ni-catalyzed C-N cross-couplings of the heteroaryl-containing substrate furfurylamine with aryl chlorides at low catalyst loadings, leading to the known products **1a-c**[16] (Scheme 3). Employing 1.75 mol% **C1**-**C4** with 4-chlorobenzonitrile to give **1a** revealed the superiority of **C2**-**C4** (>88% yield) versus **C1** (26% yield) in this reaction. In cross-couplings of 1-chloronaphthalene using 0.25 mol% Ni, the exceptionally high conversion to **1b** achieved when using **C2** or **C3** (>93% yield) was contrasted by the lower productivity of **C1** and **C4** (61% and 66% yield, respectively). These entries involving **C2** and **C3** represent the first examples of such high-yielding (> 90%), Ni-catalyzed C-N cross-couplings of aryl chlorides conducted at room temperature using only 0.25 mol% Ni. Similar trends were noted in cross-couplings involving 4-chloroanisole using 0.5 mol% catalyst, whereby **C2** and **C3** (>95% yield of **1c**) outperformed **C1** (24%). Having established **C2** and **C3** as offering comparably high catalytic efficiency, for simplicity we narrowed our subsequent examination of $(PCg)_2$(hetero)arene-based pre-catalysts to the use of **C2**. In examining further cross-couplings leading to **1a** using only 0.5 mol% **C1** or **C2**, excellent productivity was attained with **C2** (78% yield), whereas no turnover was achieved using **C1**. Collectively, this survey establishes **C2** (and **C3**) as having the potential to offer superior catalytic performance in these transformations versus otherwise best-in-class Ni pre-catalysts, such as **C1** and related variants.



Scheme 3. Pre-catalyst screening. [a] Estimated conversion to the target product after 16 h (unoptimized time) on the basis of calibrated GC data using dodecane and authentic samples of the known products **1a-c** as standards; mass balance corresponds to unreacted starting material; [b] NaO*t*Bu (2 equiv), toluene (0.12M ArCl), 25 °C; [c] NaOPh (1.2 equiv), 2-MeTHF (0.25M ArCl), 80 °C.

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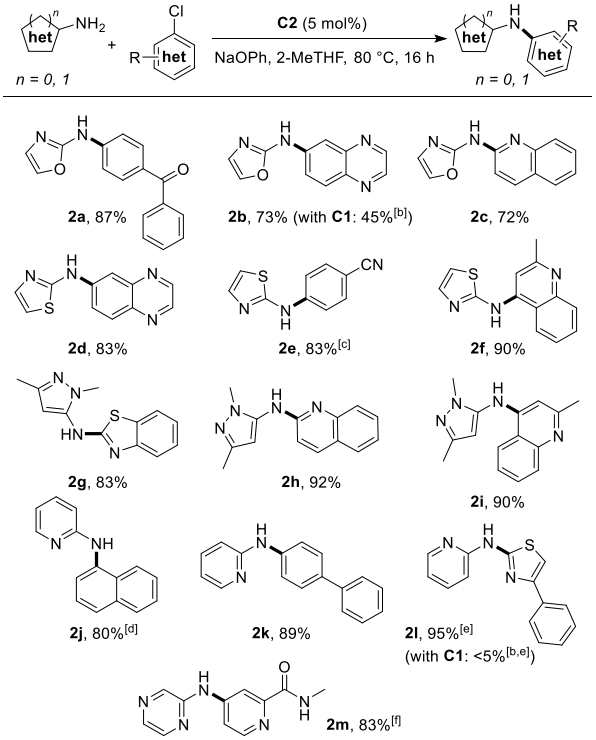
Encouraged by the outstanding catalytic performance of **C2** in known transformations leading to **1a-c**, we sought to apply this pre-catalyst in a desirable class of C-N cross-couplings for which no broadly effective base-metal catalyst is known. In this regard, the base-metal cross-coupling of primary five- or six-membered ring heteroarylamines with (hetero)aryl chlorides to afford unsymmetrical di(hetero)arylamines represents an attractive route to heteroatom-dense, biologically active compounds that exploit relatively inexpensive starting materials (Scheme 1).[19] Heteroaromatic rings are found commonly in active pharmaceutical ingredients, owing to their roles as bioisosteres[20] and enhanced binding affinity with polar functional groups of proteins. The di(hetero)arylamine motif in particular, formally derived from primary five-membered ring heteroarylamines, is featured in a number of commercialized pharmaceuticals, including dasatanib (leukemia). However, metal-catalyzed C-N cross-coupling involving such NH nucleophiles has proven to be significantly more challenging than transformations involving alkylamines or simple anilines, due in part to the increased acidity of the amine as a result of adjacent heteroatoms, which can lead to poor substrate binding and/or slow C-N reductive elimination.[21] Prior to our work herein, no base-metal catalyst capable of effecting the cross-coupling of primary five-membered ring heteroarylamines and (hetero)aryl chlorides with synthetically useful scope had been disclosed in the literature. In the context of Pd catalysis, a 2017 report from Buchwald and co-workers[22] describing the C-N cross-coupling of (hetero)aryl chlorides and bromides with 2-aminooxazole and 4-aminothiazole using a Pd/EPhos catalyst (2.0-7.5 mol% Pd; 100 °C) represents the state-of-the-art for this type of transformation. In light of these considerations, we compared the performance of **C1** and **C2**, as well as related pre-catalysts featuring JosiPhos CyPF-Cy,[23] DPPF,[9a] or XantPhos,[24] which have each been employed successfully in alternative C-N cross-coupling applications, in the cross-coupling of 2-aminooxazole and 4-chlorobenzophenone to give **2a** (2.5 mol% Ni, 80 °C; Scheme 3). Under these conditions, **C1** and **C2** afforded quantitative conversion to **2a**, whereas negligible catalytic turnover was achieved by use of the other Ni pre-catalysts. In lowering the loading to 1.5 mol% Ni, 92% yield of **2a** was achieved with **C2**, whereas use of **C1** afforded only 30% yield of **2a**. A significant drop-off in conversion was noted upon lowering the catalyst loading to 1 mol% Ni, whereby negligible conversion of the starting materials was achieved with **C1**, and 33% yield of **2a** was observed when using **C2**. Notably, further screening of this C-N cross-coupling reaction leading to **2a** employing diastereomerically pure *meso*-**C2** or *rac*-**C2** (1 mol% Ni) revealed the former to be more effective than the latter (with both being superior to **C1**) in this particular transformation.

Encouraged by the utility of **C2** in the cross-coupling of 2-aminooxazole leading to **2a**, we turned our attention toward exploring the scope of reactivity with other heteroarylamines and (hetero)aryl chlorides (Scheme 4). To avoid substrate-specific optimization, the diastereomeric mixture of **C2** (*meso* and *rac*) was employed at 5 mol% (i.e., the mid-point loading of the Pd/EPhos catalyst employed by Buchwald and co-workers[22]). 2-Aminooxazole, 2-aminothiazole, 5-amino-1,3-dimethyl-1H-pyrazole, and 2-aminopyridine were each employed successfully as nucleophiles in combination with our **C2** pre-catalyst, affording products **2a**-**2l** in synthetically useful isolated yield. Aryl chlorides containing ketone (**2a**) and cyano (**2e**) functionality proved to be suitable reaction partners, as did electrophiles featuring extended or linked aromatic hydrocarbon groups (**2j**, **2k**). Heteroaryl chlorides based on quinoxaline (**2b**, **2d**), quinoline (**2c**, **2h**), benzothiazole (**2g**), and quinaldine (**2f**, **2i**) core structures proved to be suitable reaction partners, and the successful cross-coupling of 2-bromo-4-phenylthiazole leading to **2l** confirmed the compatibility of heteroaryl bromides in this chemistry. In keeping with the trends in Scheme 3, inferior catalytic performance was observed for **C1** versus **C2** under analogous conditions in cross-couplings leading to **2b** or **2l**. For convenience, the experimental setup employed in the cross-coupling reactions leading to **2a**-**2l** involved handling of the air-stable pre-catalyst **C2** on the benchtop, followed by reaction setup within an inert-atmosphere glovebox. To evaluate the chemoselectivity of **C2**, and to establish that glovebox/Schlenk methods are not required for the chemistry reported herein, the cross-coupling of 4-chloro-*N*-methylpicolinamide and aminopyrazine was conducted under nitrogen using benchtop-only protocols. The targeted unsymmetrical di(hetero)arylamino product **2m** was obtained in 83% isolated yield.



Scheme 4. Scope of the Ni-catalyzed C-N cross-coupling of primary heteroarylamines with (hetero)aryl electrophiles using C2. [a] Reaction conditions: **C2** (5 mol%), electrophile (1 equiv), amine (1.2 equiv), NaOPh (1.2 equiv), 2-MeTHF (0.25M ArX), 80 °C, 16 h (unoptimized time). Isolated yields are reported, unless otherwise indicated. [b] NMR integrated yield using ferrocene as an internal standard in DMSO-d_6. [c] THF used as solvent, mixture of NaO*t*Bu/PhOH (1.2 equiv each) used as base. [d] NMR integrated yield using dodecane as an internal standard in $CDCl_3$. [e] Starting from the corresponding heteroaryl bromide. [f] In THF.

Some substrate scope limitations were encountered, including unsuccessful cross-couplings of 5-amino-3-methylisoxazole with 4-halobenzonitrile (X = Cl or Br), or 3-chloropyridine with 4-aminopyridine, under conditions outlined in

Scheme 4. Our efforts to accommodate more complex diamine substrates, including the cross-coupling of 2,3-diaminopyrazine or 3,4-diaminopyridine with 4,6-dichloro-2-methylaniline, as well as electrophiles lacking activating groups (i.e., 4-chlorobiphenyl or 4-chloroanisole with 2-aminothiazole), were similarly unsuccessful.

We independently confirmed via control experiments that the transformations reported herein proceed negligibly in the absence of **C2** under the conditions employed. For the reaction leading to **2g**, exclusion of **C2** resulted in the formation of substantial quantities of the C-O coupled product arising from reactivity with the phenoxide base. These results notwithstanding, our observation that ethyl 2-chlorooxazole carboxylate, 2-chlorobenzoxazole, 2-chlorobenzothiazole, 2-chloro-4,6-dimethoxypyrimidine, and 4-chloro-6,7-dimethoxyquinazoline afforded C-N coupled (and other) products in selected reactions with 2-aminothiazole, 2-aminooxazole, and 2-aminopyridine under the conditions in Scheme 4, but in the absence of **C2**, underscores the importance of conducting control experiments in developing metal-catalyzed cross-coupling methodologies.

In summary, a new class of double cage bisphosphine ligands, including PAd2-DalPhos (**L2**), have been developed for use in addressing outstanding challenges in Ni-catalyzed C-N cross-coupling. Building on our observation that **L2** systematically outperformed the state-of-the-art parent PAd-DalPhos (**L1**) in selected challenging test cross-couplings involving furfurylamine and 2-aminooxazole as nucleophiles, the **L2**-derived Ni pre-catalyst **C2** was employed successfully in establishing the first base-metal cross-coupling of (hetero)aryl chlorides and primary five- or six-membered ring heteroarylamines, with synthetically useful scope. Notably, the catalytic performance of the Ni pre-catalyst **C2** in enabling the assembly of sought-after heteroatom-dense, unsymmetrical di(hetero)arylamines is competitive with state-of-the-art Pd catalysis, in terms of catalyst loading and substrate scope, while operating effectively at more milder reaction temperatures. We are currently exploring the application of **L2** and related ancillary ligands in addressing other outstanding reactivity challenges in base-metal catalysis, and will disclose our progress in this regard in future reports.

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Keywords: amination • bisphosphines • cross-coupling • ligand design • nickel

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[17] We employ 'meso' (RS/SR) and 'rac' (RR/SS) in reference to the relative handedness of the PCg fragments within the ligands **L2**-**L4**. Complete experimental details and characterization data are provided in the Supporting Information, and CCDC 1883505-1883514 contain the supplementary data for the crystallographic characterization of *meso*-**L2**, *rac*-**L2**, *meso*-**L3**, *rac*-**L3**, *meso*-**L4**, *rac*-**L4**, *meso*-**C2**, *rac*-**C2**, *meso*-**C3**, and *meso*-**C4**.
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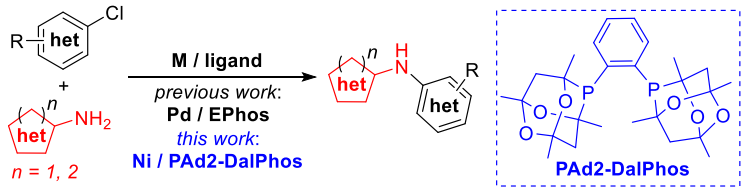

Cage match: A nickel(II) pre-catalyst featuring the new double cage PAd2-DalPhos ancillary ligand enables the first examples of Ni-catalyzed C-N cross-couplings of primary five- or six-membered ring heteroarylamines and (hetero)aryl chlorides with synthetically useful scope.

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