Ligand-Based Control of Nickel Catalysts: Switching Chemoselectivity from One-Electron to Two-Electron Pathways in Competing Reactions of 4-Halotetrahydropyrans

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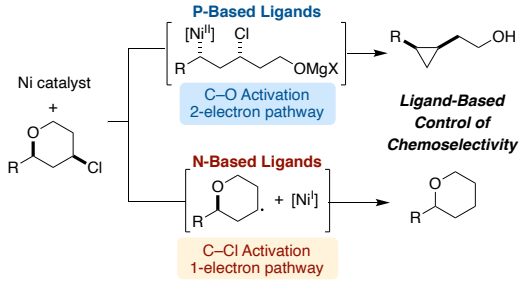
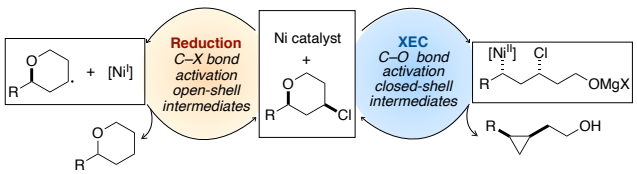
Supporting Information Placeholder



ABSTRACT: Development of nickel-catalyzed transformations would be facilitated by an improved ability to predict which ligands promote and suppress competing mechanisms. We evaluate ligand-based modulation of catalyst preference for one- or two-electron pathways employing 4-halotetrahydropyrans as model substrates that can undergo divergent reaction pathways. Chemoselectivity for one- or two-electron oxidative addition is predicted by ligand class. Phosphine-ligated nickel catalysts favor closed-shell oxidative addition. In contrast, nitrogen-ligated nickel catalysts prefer the one-electron pathway, initiating with halogen atom transfer.

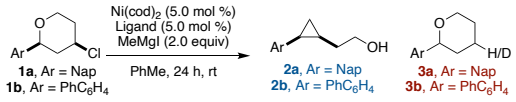
Experimental evidence that provides the basis for a broad-strokes understanding of ligand effects is critical for implementation of new catalytic methods by a broad range of synthetic chemists and can accelerate development of new catalytic transformations. Such experimentally determined design principles have driven powerful advances in palladium-catalyzed coupling reactions.[1,2] Guiding principles for the selection of nickel catalysts are still being identified.[3,4,5] Chemoselectivity for one- or two-electron oxidative addition is a critical feature of many reactions of alkyl electrophiles and can be controlled by identity of the substrate.[6,7,8] However, there is little empirical evidence that this selectivity can also be perturbed by the ligand. Many stereoablative reactions employ pyridyl- or imine-based ligands, while stereospecific transformations often employ phosphine ligands. In any given publication, typically either nitrogen- or phosphine-based ligands are evaluated. However, a direct contrast between the two classes is rarely provided. In this manuscript, we report experiments that provide, to our knowledge, the first data set that directly compares stereospecific and stereoablative reaction manifolds under the same reaction conditions.[9,10] As such, we directly interrogate the ligands' control of catalyst propensity for closed-shell and open-shell reactivity. These experiments complement detailed parameterization that has been employed to compare closely related ligands for single reaction pathways.[11,12] This work will impact the development of new base-metal-catalyzed reactions of alkyl electrophiles.

A major challenge is identifying a suitable control reaction, where a single variable can be changed to systematically compare catalyst systems, and where the reaction mechanisms are well-understood. We hypothesized that reactions of 4-halotetrahydropyrans fit these criteria (Scheme 1). These substrates undergo divergent reaction pathways and therefore provide a competition experiment where product outcome is determined by the chemoselectivity of the first elementary step, oxidative addition. One potential reaction product is the cyclopropane, formed by intramolecular cross-electrophile coupling (XEC).[8b] This product forms if the reaction initiates by oxidative addition at the ether. Our laboratory has reported mechanistic details for this XEC reaction and has determined that it proceeds through a robust two-electron pathway, where oxidative addition occurs via an S_N2-type transition state.[13] Radical intermediates are not formed. Alternatively, the tetrahydropyran can be formed as the product if the reaction initiates by halogen atom transfer (XAT) of the alkyl halide.[14] This pathway proceeds through the alkyl radical. Therefore, we hypothesized that correlating the product distribution to ligand identity would allow identification of the key features of the nickel catalyst that promote oxidative addition by one- or two-electron manifolds.



Scheme 1. Ligand-Based Control of Nickel Catalysis: Competition Between One- and Two-Electron Pathways.

As a first step to validate our approach, we set out to confirm that the reduction products are indeed formed via open-shell intermediates (Table 1).[15] We proposed that the nickel catalyst undergoes halogen atom abstraction with the alkyl halide to form a secondary radical.[14,16] Substrates **1a** and **1b** were chosen for these experiments due to the resolution of the characteristic peaks in ^{1}H NMR. Experiments were performed employing $Ni(cod)_2$ in the presence of IndaBox and Biox ligands since these catalyst-substrate combinations facilitated the reduction pathway (vide infra). Addition of TEMPO to the standard reaction conditions suppressed formation of tetrahydropyrans **3a** and **3b** (entries 2 and 5). These results are consistent with formation of open-shell intermediates over the course of the reduction pathway. In contrast, the XEC reaction, employing *rac*-BINAP as the ligand, was not significantly inhibited by addition of TEMPO, consistent with closed-shell intermediates for the XEC pathway (entry 8).



Entry	Ar	Ligand	Deviation from standard conditions	Recovered 1 (%)	2 (%)	3 (%)	D incorporation (%)
1	Nap	IndaBox	none	30	<5	55	-
2	Nap	IndaBox	1 equiv TEMPO added	87	<5	10	-
3	Nap	IndaBox	D_8-PhMe as solvent	32	<5	16	21
4	PhC_6H_4	Biox	none	<5	<5	63	-
5	PhC_6H_4	Biox	1 equiv TEMPO added	54	<5	35	-
6	PhC_6H_4	Biox	D_8-PhMe as solvent	44	<5	33	41
7	Nap	*rac*-BINAP	none	<5	92	<5	-
8	Nap	*rac*-BINAP	1 equiv TEMPO added	9	83	<5	-

Table 1. TEMPO Trapping and Deuterium Incorporation Studies Provide Evidence of a Radical Mechanism for Reduction.

To provide additional evidence that the reduction pathway proceeds by initial XAT and an alkyl radical intermediate, we performed deuterium-incorporation experiments to determine the source of the hydrogen atom. Performing the reaction of substrates **1a** and **1b** in D8-toluene provided the reduction product with deuterium incorporation, consistent with formation of an alkyl radical by XAT and subsequent HAT from toluene (entries 3 and 6). Importantly, the reaction was stereoablative: product **3b** was formed as a 1:1 mixture of diastereomers. Taken together, these experiments are consistent with initiation of reduction by XAT of the alkyl halide with the nickel catalyst.

With robust mechanistic understanding of competing reaction pathways, we designed and evaluated a matrix of cross-electrophile coupling reactions with six racemic 4-halotetrahydropyrans and 11 ligands. Ligands were selected based on their success in previously developed cross-coupling (XC) and XEC reactions, and to span a range of ligand properties including ligand field, bite angle and redox activity (Figure 1). Bidentate phosphines were selected based on their success in our previously developed ring contractions.[8b,16] A variety of subclasses of nitrogen-based ligands that have been employed in XC and XEC reactions were examined, including bipyridine-, oxazoline-, and diamine-based ligands.[7e,17, 18, 19, 20, 21, 22]

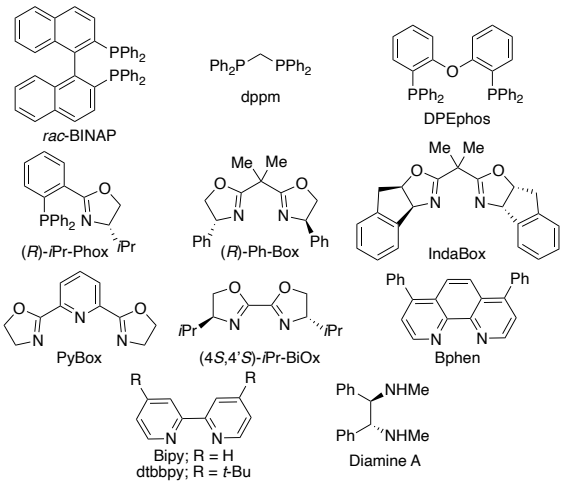


Figure 1: Ligands Selected for Initial Evaluation for XEC or reduction of 4-halotetrahydropyrans.

Analysis of the data trends supports a working hypothesis that two factors work in concert to predict selectivity: the identity of the electrophile and the identity of the ligand. Allylic ethers (in **4** and **5**) out-compete alkyl chloride and alkyl bromide moieties, resulting in XEC regardless of ligand structure. Conversely, simple benzylic ethers (in **1b** and **7**) are sluggish oxidative addition partners, resulting in no XEC. In this series, catalysts with nitrogen-based ligands support XAT of the alkyl chloride moiety, and many catalysts (nitrogen- and phosphine-based) promote XAT of the alkyl bromide.

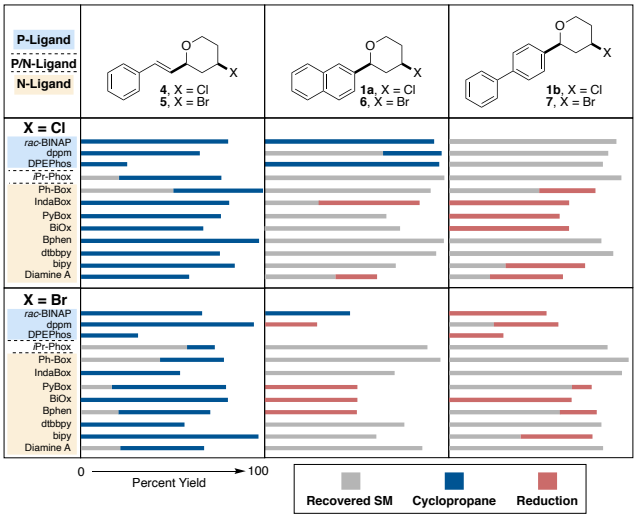
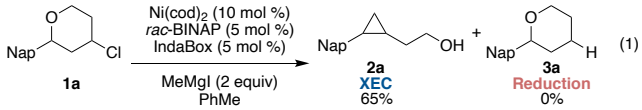


Figure 2: Results from the THPxLigand Matrix.[23]

Most illustrative are reactions of naphthyl-substituted tetrahydropyrans **1a** and **6**, where product selectivity is dictated by the ligand. The C–O bond of these substrates is moderately activated and, with the correct ligand structure, competes with the alkyl halide for the nickel catalyst. Particularly illustrative are reactions of 4-chlorotetrahydropyran **1a**. For this substrate, phosphine-based ligands promote two-electron oxidative addition and nitrogen-based ligands promote one-electron XAT. Therefore, we hypothesize that stronger field phosphine-based ligands favor two-electron oxidative addition, by providing an electron-rich, nucleophilic catalyst.[24] Conversely, weaker field nitrogen-based ligands that can support open-shell nickel complexes favor XAT.[25] In addition to ligand field effects, it is important to note that certain nitrogen-based ligands such as

bipyridine are known to be redox active and support Ni(I) intermediates by accommodating ligand-centered radicals.[26] However, this factor does not appear to be a key determinant for this data set, since some ligands that favor XAT, such as oxazoline-based ligands, have been shown to provide nickel(I) complexes with metal-centered radicals.[27]

To evaluate which reaction pathway is dominant, we performed a competition experiment, where substrate **1a** was exposed to both catalysts (eq 1). Subjecting **1a** to the reaction conditions with equivalent loadings of both *rac*-BINAP and IndaBox provided cyclopropane **2a** as the exclusive product. This result is consistent with the *rac*-BINAP-ligated nickel catalyst undergoing oxidative addition at the benzylic C–O bond faster than the IndaBox-ligated nickel catalyst can react with the secondary chloride by XAT. This follows our expectation that phosphine-ligated nickel catalysts have a high nucleophilicity, likely in part due to the strong sigma-donor properties of the ligand, which favors the S_N2-type oxidative addition. The nucleophilicity of the nickel catalyst with *rac*-BINAP coordination drives chemoselectivity towards the two-electron paradigm.



(1)

To further to evaluate whether this ligand dependency is a predictable trend, we examined a larger sample of a range of ligands in reaction of 4-chlorotetrahydropyran **1a** (Figure 3). We evaluated >40 ligands, including monodentate phosphines, phosphoramidites, bidentate phosphines, tridentate phosphines, N-heterocyclic carbenes, diamines and pyridines.[28,29] The overall data trends are clear, with nitrogen-based ligands, including diamines and pyridine-based ligands, providing the reduced THP **3a** via XAT. In contrast, only phosphine ligands provided significant yields of cyclopropane **2a**, by polar oxidative addition of the benzylic ether. There are clearly additional factors, including steric parameters, that control whether a ligand provides a reactive catalyst, since many ligands provided recovered starting material.[30] However, as a general design principle, the premise that phosphine ligands favor two-electron pathways and nitrogen-based ligands promote one-electron reactions appears to hold. These results are consistent with the prevalence of phosphine ligands in stereoselective XC and XEC reactions of benzylic and alkyl ethers. These results are also consistent with the prevalence of nitrogen-based ligands in stereoablative XC and XEC reactions of alkyl halides, and, within this series, accommodation of ligand-centered radicals does not appear to be a critical feature.[25, 26]

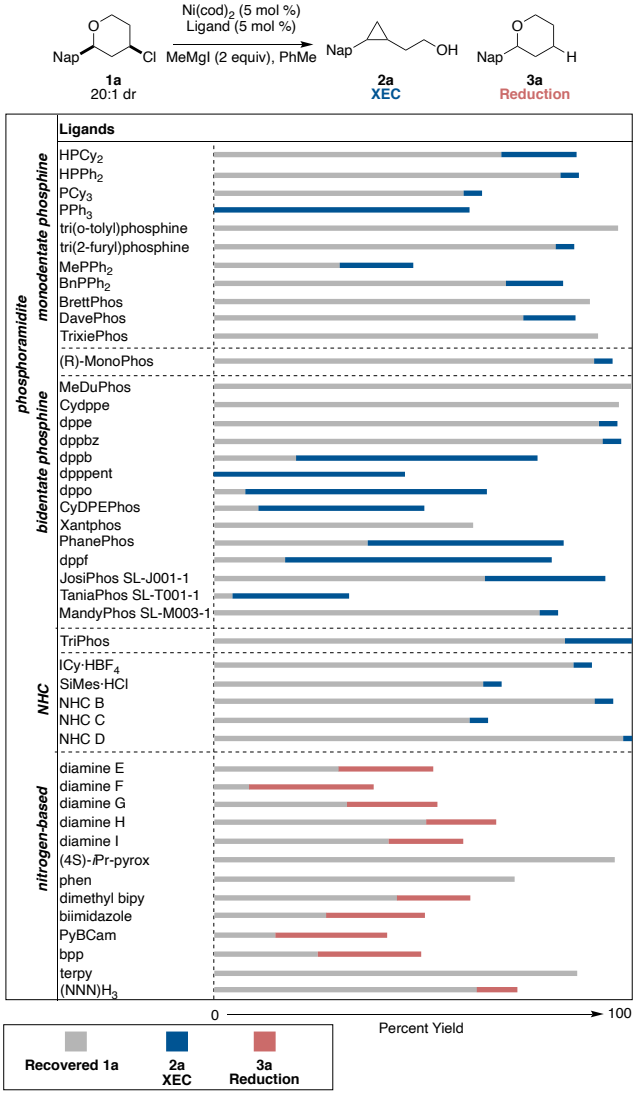


Figure 3: Results from Expanded Ligand Set.[31]

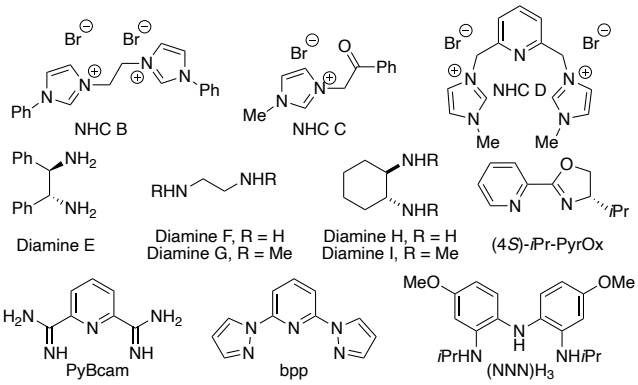


Figure 4. Ligand Key for the Expanded Reaction Matrix.

In conclusion, we provide experimental evidence for a ligand-based switch in selectivity for one- and two-electron pathways in a nickel catalyzed reaction, by examining competitive XEC and reduction of 4-halotetrahydropyrans. Both phosphorous- and nitrogen-based ligands were examined to determine the preference of the catalysts for activation of C–O or C–X bonds. In general, two factors work in concert to control the preferred pathway: identity of electrophile and the identity of the ligand. These results will inform the development of new

coupling reactions by providing insight into the synergistic effect of the ligand and oxidative addition mechanism evoked. Current investigations include more detailed analysis of these trends and establishing related structure-activity relationships for a broad range stereospecific and stereoablative reactions.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge on the ACS Publications website. Full experimental procedures and characterization data for all new compounds.

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[31] See SI Tables S-7 and S-8 for exact numbers and byproducts .