Ligand-Controlled Regiodivergence in Nickel-Catalyzed Hydroarylation and Hydroalkenylation of Alkenyl Carboxylic Acids

Zi-Qi Li†, Yue Fu‡, Ruohan Deng†, Van T. Tran†, Yang Gao†, Peng Liu‡, and Keary M. Engle†

† Department of Chemistry, Scripps Research, 10550 North Torrey Pines Road, La Jolla, California 92037, United States
‡ Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States

Supporting Information Placeholder

ABSTRACT: A nickel-catalyzed regiodivergent hydroarylation and hydroalkenylation of unactivated alkenyl carboxylic acids is reported, whereby the ligand environment around the metal center dictates the regiochemical outcome. Markovnikov hydrofunctionalization products are obtained under mild ligand-free conditions, with up to 99% yield and >20:1 selectivity. Alternatively, anti-Markovnikov products can be accessed with a novel 4,4-disubstituted Pyrox ligand in excellent yield and >20:1 selectivity. Both electronic and steric effects on the ligand contribute to the high yield and selectivity. Mechanistic studies suggest a change in the turnover-limiting and selectivity-determining step induced by the optimal ligand. DFT calculations reveal that in the anti-Markovnikov pathway, repulsion between the ligand and the alkyl group is minimized (by virtue of it being 1° versus 2°) in the rate- and regioselectivity-determining transmetalation transition state.

Catalytic, regioselective alkenes functionalization are valuable in organic synthesis owing to the widespread accessibility of alkenes starting materials and the growing arsenal of transformations that have been developed. In this context, systems that offer reliable and predictable access to either regioisomer from common reagents are highly desirable. Within the expansive alkenes functionalization toolkit, hydroarylation is a rapidly evolving area of synthetic methodology. In these reactions, simple arenes (ArH) or pre-functionalized arenes (ArX or ArM) can be activated through a variety of mechanistic pathways to furnish the corresponding hydroarylated product.

Recently, nickel catalysis has emerged as a powerful means of effecting alkenes hydroarylation. In particular, redox-neutral coupling of aryloboronic acids and alkenes is attractive in that it combines programmed reactivity at the Ar–B bond with operationally simple reaction conditions and does not require stoichiometric silane reductants (as in R–X/R,Sl–H systems). Originally pioneered by Zhou and co-workers, such reaction systems have been largely limited to conjugated alkenes, such as styrenes and 1,3-dienes, where regioselectivity is dictated by the stability of the corresponding n-benzyl/allyl intermediate. Zhao has developed a method using bidentate directing auxiliaries to enable ψ-hydroarylation of non-conjugated alkenyl carbonyl compounds without competitive chain-walking though this method has disadvantages in terms of requiring directing group installation and removal steps. Hence, developing a ligand-controlled regiodivergent version of this catalytic paradigm that is compatible with non-conjugated alkenes bearing only native functionality would be synthetically enabling and would complement other regioselective/ divergent catalytic hydroarylation methodology involving ArH or ArX coupling partners.

Previously, our lab has described a single example of regio-switchable hydroarylation under Pd(II) catalysis, where regioselectivity is hypothesized to stem from a difference in palladacycle stability with a tridentate versus bidentate directing group. In the absence of a polydentate directing auxiliary, we reasoned that regioselectivity control could alternatively arise from the combination of a weakly coordinating directing group and an appropriate ancillary ligand.

Scheme 1. Background and Synopsis of Current Work

A. Regiodivergent alkene functionalization

B. Previous work: Redox-neutral alkene hydroarylation under Ni catalysis

C. Directing-group-controlled regio-switchable hydrofunctionalization

D. This work: Regiodivergent hydrofunctionalization through ligand design

Supporting Information Placeholder

To initiate our investigation, we selected vinyl acetic acid (1a) and p-tolylboronic acid as the pilot substrates. Using Ni(cod)2 as the pre-catalyst, KO-Bu as the base, and 4-hydroxycurcumarin as the solvent at 60 °C, we evaluated a series of different ligands with the goal of identifying conditions for both Markovnikov (M) and anti-Markovnikov (a-M) hydroarylation (Table 1).
Interestingly, highly Markovnikov-selective hydroarylation took place under ligand-free conditions, giving 3aa as the major product. A control experiment ruled out an isomerization/1,4-addition sequence (vide infra); hence, we reasoned that the high selectivity could reflect the preference for forming a 5-membered metallacycle intermediate. \(^{[11]}\) Phosphine ligands (L1–L3) gave 3aa as major product. Individually using oxazoline (L4) or pyridine (L5) ligands did not change the innate reactivity, giving 3aa in high yield and selectivity. However, bisoxazoline ligand L8 gave a 1:1 ratio of 2aa and 3aa.

We eventually identified Prox ligands as uniquely effective in favoring formation of the anti-Markovnikov hydroarylation to produce 2aa as major product. Brief optimization of the solvent and reaction temperature (see SI), led to slight improvements in yield and selectivity. We investigated the effects of steric and electronic modifications to the ligand on reactivity and selectivity. Adding steric repulsion on the pyridine ring (L9, L10) led to low yield and favored the formation of 3aa. To our delight, varying substituents on the oxazoline ring offered a pathway towards high anti-Markovnikov-selectivity. A clear trend was observed with increased steric bulk on the 4-position, with L15 (R1 = "Bu") giving a 99% yield and 79:21 selectivity. 4,4-Dimethyl-substituted ligand L17 gave a slightly higher selectivity of 82:18. Spirocyclic ligand L20 gave 92% yield, and increased the selectivity to 92:8. \(^{[13]}\) The highest selectivity (95:5) with 99% yield was obtained with the previously unknown 4,4-dibenzyl-substituted ligand L19. Tuning the electronic effect on the pyridine ring using L15 as the benchmark did not achieve further improvement. A ligand containing an electron-donating group on the pyridine ring (L22) gave similar selectivity to L15. However, introduction of an electron-withdrawing substituent completely shut down the reaction.

When Ni(cod)₂ was replaced with air-stable Ni(cod)[DQ] and the reaction was set up outside of the glovebox, 76% yield (2aa) and 16% yield (3aa) were obtained using L19 and no ligand, respectively (see SI for details). \(^{[14]}\)

**Table 1. Optimization of Reaction Conditions**

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Screening</th>
<th>Ar= p-Tol</th>
<th>[C]= B(OH)₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>3aa</td>
<td>2aa</td>
<td>3aa</td>
<td>2aa</td>
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**Table 2. anti-Markovnikov Hydrofunctionalization Scope**

![Table 2. anti-Markovnikov Hydrofunctionalization Scope](image)

\[^{[a]}\]Reaction conditions: Ni(cod)/ligand/1a/boronic acid/KOtBu = 0.05/5/0.06/0.1/2/0.2 (mmol). All percentages represent ‘H NMR yields with CH₂Br₂ as internal standard. After a brief optimization, 3aa was obtained in 99% yield (see SI for details). Selectivities (a-M) are shown in parentheses.

After identifying conditions for both Markovnikov and anti-Markovnikov selectivity, we next examined the scope and limitations of both protocols. We first explored the anti-Markovnikov-selective protocol with ligand L19. In terms of arylboronic acids, the presence of electron-donating and -withdrawing groups at the para and meta position did not affect the yield and selectivity (2aa–2ae, 2aj–2ao). Notably, potentially reactive groups, such as –Cl and –CHO (2af, 2ah), and coordinating substituents, such as –NHBOc and –CN (2ag, 2as), were also tolerated. With an electron-deficient arylboronic acid bearing 3,5-difluoromethyl substituents, the reaction benefited from a less sterically hindered ligand L18, giving 2av in 90% yield. ortho-Substituted arylboronic acids, which had previously proven to be recalcitrant coupling partners in related directed alkene functionalization reactions developed in our lab, can give 2ax in 80% yield. \(^{[14]}\)

Hydroalkenylation reactions were achieved with vinylboronic acids, giving alkene homologation products (from β-γ unsaturated alkene to δ-γ unsaturated alkene) in good to excellent yields (2ba–2bd). We then evaluated a few α-substituted 3-butenioic acid substrates. The method was found to be sensitive to steric hindrance at the α-position. With an α-methyl substrate, less than 10% of the product 2ca was obtained under the standard reaction conditions, presumably due to steric clashing between the methyl group of the substrate and the bulky benzyl substituents on the oxazoline. Consistent with this hypothesis, using a less encumbered ligand, L18, in which one benzyl group is replaced with a methyl group allowed the desired product 2ca to be obtained in 60% yield as a single regiosomer. Larger substituents on the α-position required higher catalyst loading and even still furnished diminished yield (2cc and 2cd).
we found that using °BuOH instead of °PrOH could provide slightly better yield and selectivity at 40 °C. Similar to what we observed with the anti-Markovnikov selective hydrofunctionalizations, substrates on the para and meta position of the arylboronic acid coupling partner had little effect on the reactivity, with products (3aa–3am) obtained in good to excellent yields. Arylboronic acids containing reactive electrophilic or coordinative moieties such as −Cl, −CHO or −CN were incompatible. The ortho-fluoro coupling partner furnished a diminished yield of 49% (3an) and attenuated selectivity of 17:83 (a:M:M), as compared to 2za. Satisfying results were observed with alkylbenzonic acids, giving 3ba–3bd in good to excellent yield. With α-substituted substrates, the Markovnikov selective products were formed in approximately 4:1 regioisomeric ratio and 1:7:1 dr favoring the C(sp²)−Ar bond formation on the alkene face opposite to the α-substituent (3ca–3cb). However, when sterically hindered substrate 2-[cyclopentymethyl]but-3-enoic acid was tested, the hydrogenated product was observed as major byproduct. It is worth mentioning that using 2-vinyl benzoic acid as substrate gave the same product 3cd in good yield with or without ligand. Previous reports have shown that phosphine ligands or bisoxazoline ligands were required for the same type of reactivity,[10] demonstrating the importance of the carbonyl directing group in this system.

Table 3. Markovnikov Hydrofunctionalization Scope

Next

With internal alkenes as substrates, the ligand-free conditions led to only trace product formation. With L19 as ligand, 5% mixture of β- and γ-arylated products (5b and 6b) were obtained with 2:1 ratio. The regiosomeric ratios are closely related to the size of distal alkyl group (see SI for detail). In these cases, both potential regioisomeric outcomes would proceed through 2° alkynickel intermediates, rather than the above cases, where there is competition between 1° and 2° alkynickel formation. Hence, the results with internal alkenes suggest that while L19 enhances reactivity, it is insufficient to overcome the innate proclivity of the system to proceed via a 5-membered metallacycle, which is why β-arylation is observed as the major product. Two other representative ligands (L14 and L18) gave low conversion and yield. These limitations notwithstanding, the results demonstrate that through proper ligand design, we were able to achieve functionalization of these inert substrates without utilizing strong directing groups.

Table 4. Reactivity with a Representative Internal Alkene Substrate

3/4-Arylbutanoic acids and derivatives are of pharmacological utility. To showcase the synthetic versatility of the carboxylic acid directing group, we conducted a series of diversifications on product 2ac and 3aa, which could be synthesized on large scale with excellent yield (Table 5). The classical 2e-logic could easily transform the products into ester, alcohol, amine etc.[11] Additionally, the 1e synthetic logic offered us a more divergent space to exert.[16] Decarboxylative borylation gave 7a and 7d in moderate yield, introducing the functional handle for future manipulation. Decarboxylative Giese reaction enabled a formal distal (6 or 8) functionalization of carbonyl compounds, giving the double homologation products 7b and 7e. Finally, decarboxylative cross-coupling with aryl boronic acids gave rise to the 1,2- or 1,3-diarylpropane motifs.

Table 5. Large-Scale and Derivatization Experiments

The pronounced effect of L19 on regioselectivity prompted us to consider its role in the reaction mechanism. Generally, nickel(0)-catalyzed hydroarylations with arylboronic acids are proposed to proceed via hydrometalation followed by transmetalation with the arylboronic acid and reductive elimination. Hence, we reasoned that the Markovnikov versus anti-Markovnikov selectivity would likely be determined in either the Ni-H migratory insertion step or downstream steps. To shed light on this point we turned to experimental and computational techniques.

First, to evaluate the possible role of alkene isomerization in the Markovnikov-selective protocol, we tested crotonic acid as substrate under optimized conditions, and in this case only trace amount (<5%) of the β-arylated product 3aa was formed. This result rules out a mechanism involving isomerization followed by 1,4-addition,[17] establishing that the reaction predominantly proceeds through reaction of the βγ-alkene. Next, we performed kinetic isotope effect experiments using either
ethanol or ethanol-d₆ as solvent. For the Markovnikov selective hydroarylation, we found νₓ/νₓ = 2.7, suggesting that a hydride transfer process is involved in the turnover-limiting step. For the anti-Markovnikov selective reactions, a smaller ratio (νₓ/νₓ = 1.3) was observed, suggesting that either transmetalation or reductive elimination is the turnover-limiting step, taking into consideration the possibility for a solvent kinetic isotope effect. To disambiguate between these two possibilities with L19, we examined substituent effects on initial rate with p-OMe and p-F substituted phenyl boronic acids; electron-donating substituents led to a higher initial rate, consistent with a scenario in which transmetalation is the turnover-limiting step.[18] Deuterium labeling experiments using ethanol-d₆ as solvent were conducted. In the anti-Markovnikov system, deuterium was mainly incorporated at the β-position, and in the Markovnikov system, deuterium was incorporated at the γ-position. In both cases, the presence of deuterium scrambling at the γ-position (2aα) or β-position (3aα) as well as the presence of doubly deuterated products suggests that the reaction involves a reversible hydride insertion step before the selectivity-determining step.

On the basis of literature reports and the experimental mechanistic studies, three different pathways can be proposed for the hydrofunctionalization (Figure 1). A previously proposed mechanism[9-10][19] involves the O–H oxidative addition of the alcohol solvent to generate a nickel-hydride intermediate, which may undergo migratory insertion followed by transmetalation (Path I) or transmetalation followed by insertion (Path II) to form an Ni[Ⅰ](alkyl)[ary] species and yield the hydroarylation product after reductive elimination. We surmised that an alkenylnickel(Ⅱ) species could be formed via an alternative pathway that involves a concerted, carboxylic acid-assisted hydronickelation of the alkene (Path III), bypassing the discrete nickel–hydride. Following transmetalation and reductive elimination as above, this path would also generate the hydroarylation product. Previous computational studies on Pd-catalyzed reactions suggest that the concerted, carboxylic acid-assisted hydropalladation[19] and β-H elimination[20] is kinetically more favorable than alternative pathways involving palladium–hydride intermediates. To the best of our knowledge, the analogous concerted hydronickelation pathway has not been explored computationally.

We performed density functional theory (DFT) calculations to study the proposed mechanisms in the hydroarylation of 1a and the origin of the effects of ligand L19 on the anti-Markovnikov regioselectivity (Figure 2).[21] The O–H oxidative addition pathways using either alcohol or carboxylic acid as the hydride source both require relatively high barriers (TS3 and TS2, ΔG° = 36.3 and 32.1 kcal/mol, respectively). These pathways are disfavored due to the high ligand exchange energy to replace the alkene in the ɑ-alkene complex 8 with PrOH[22] and the distortion in the intramolecular carboxylic acid O–H oxidative addition, respectively. On the other hand, the concerted hydronickelation (TS1) requires a much lower barrier (11.3 kcal/mol with respect to 8) and directly leads to the primary alkenylnickel(Ⅱ) species 13-A. TS1 involves a fused bicyclic geometry, where the O–H cleavage and the Ni-C/H-C bond formation occur simultaneously. Although the Ni–H distance in TS1 is relatively short (1.7 Å), nickel–hydride species are not involved in this concerted process. These geometrical features are consistent with carboxylic acid-assisted alkene hydropalladation transition states.[19] Complex 13-A may undergo transmetalation/reductive elimination to form the anti-Markovnikov-selective hydroarylation product or isomerization to 13-M via relatively facile β-hydride elimination and alkene reinsertion (see SI for details), which would eventually lead to the Markovnikov isomer. Transmetalation from 13-A and 13-M occurs via four-coordinate square-planar transition states[23] (TS4-A and TS4-M) where the pyridine group on L19 dissociates from the nickel center.[24] Because the hydronickelation and the subsequent reductive elimination (TS5-A and TS5-M) are both facile, transmetalation is the rate-determining step of the catalytic cycle. The computed regioselectivity (ΔΔG° = 3.1 kcal/mol) is consistent with the high levels of anti-Markovnikov selectivity observed in reactions with the L19-supported Ni catalyst. The regioselectivity is mainly controlled by steric repulsions between the secondary alkyl group and the benzyl groups on the oxazoline ligand that destabilize the Markovnikov-selective transmetalation transition state (TS4-M). To shed more light onto the ligand steric effects on the regioselectivity, we computed the transmetalation transition states using a sterically less demanding oxazoline ligand L10. When L10 is employed, the Markovnikov-selective transmetalation transition state is 1.1 kcal/mol lower in energy than the anti-Markovnikov-selective isomer due to diminished steric repulsions with the ligand (see SI for detailed discussions). These results are consistent with

![Figure 1. Possible catalytic pathways.](image-url)
the reversed regioselectivity when L10 is used in place of L19.\[25\]

In conclusion, we developed a ligand-controlled regiodivergent nickel-catalyzed hydroarylation and alkynylation reaction of alkene carboxylic acids. Both Markovnikov and anti-Markovnikov selective hydrocarbofunctionalized products were prepared with excellent yield and selectivity. Mechanistic studies revealed that use of the 4,4-dibenzyl Pyrox ligand leads to a switch in the turnover-limiting step and results in reversal of regioselectivity compared to ligand-free conditions. DFT calculations indicated that the anti-Markovnikov selectivity is controlled by steric repulsions between the substrate and the sterically encumbered Pyrox ligand in the transmetalation step.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author
keary@scripps.edu
pengliu@pitt.edu

Notes
The authors declare no competing financial interest.

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REFERENCES


(21) DFT calculations were performed at the M06/6-311+G(d,p), SMD(1-propanol)//B3LYP-D3/6-31G(d) level of theory. See the Supporting Information for computational details.


(25) Due to the uncertainty regarding the actual ancillary ligand(s) under the “ligand-free” conditions, we did not computationally model the Markovnikov-selective hydroarylation in the absence of Pyrex ligand.
Markovnikov

- Ligand-free
- >25 examples
- DG controlled

anti-Markovnikov

- >30 examples
- >20:1 selectivity
- Ligand controlled