Branch-Selective, Iridium-Catalyzed Hydroarylation of
Monosubstituted Alkenes via a Cooperative Destabilization Strategy

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ABSTRACT: Highly branch-selective, carbonyl-directed hydroarylations of monosubstituted alkenes are described. The chemistry relies upon a cationic Ir(1) catalyst modified with an electron deficient, wide bite angle bisphosphine ligand. This work provides a regioisomeric alternative to the Murai hydroarylation protocol.

In 1993, Murai and co-workers demonstrated that Ru-catalyzed alkene hydroarylation can be achieved by carbonyl-directedaryl C−H activation (Scheme 1A). This protocol provides access to linear hydroarylation products and is considered a milestone in the development of atom-economical methodology. In the ensuing years, a wide range of related π-bond insertion protocols have emerged that use a variety of late transition metal catalysts. For intermolecular processes involving monosubstituted alkenes, linear selectivity dominates and branched products are not usually accessible. Branch selectivity has been achieved under Co- or Ru-catalyzed conditions but requires aniline, pyridine, or imine directing groups and is limited to styrenes as the olefinic partner. To date, a regioisomeric alternative to the original Murai protocol, which enables carbonyl-directed, branch-selective hydroarylation, remains elusive. This represents a surprising gap in synthetic technology, especially given that such a process would provide direct and potentially enantioselective access to products that are difficult to obtain using conventional cross-coupling chemistry. In this report, we detail the design of a catalyst system that achieves high branch selectivity for carbonyl-directed hydroarylation of aryl- and alkyl-substituted alkenes. The protocol has wide scope, is highly selective for mono-ortho-alkylation, and opens the door to the development of related processes, including enantioselective variants.

At the outset of our investigations, we were drawn to cationic BINAP-ligated Ir(1) catalysts that were reported by Shibata for ketone-directed hydroarylation of styrenes. These systems preferentially provide linear products but are less discriminating than Ru-based catalysts and deliver significant quantities of branched adducts (7:1 to 3:1 selectivity). The relatively low selectivities hinted that appropriate modifications could lead to a catalyst system that favors branched products. Related studies on directed hydroheteroarylation indicate that alkene coordination and hydrometalation are reversible and that these steps do not determine product regioselectivity. The predominance of linear products likely reflects a higher equilibrium preference for linear Ir(III) intermediate 1a over sterically disfavored isomer 1b (Scheme 1A). Access to a branch-selective manifold thus requires acceleration of reductive elimination Path b over Path a. Our reaction design was guided by two observations that are common in the organometallic literature. First, reductive elimination is accelerated by wide bite angle bisphosphine ligands in a range of transition-metal-catalyzed C−C bond formations. There is some debate on the origin of this effect, but an appealing explanation is that an increase in the P−M−P bond angle compresses the C−M−C bond angle and thus renders C−C bond formation more facile. Second, it has been observed that bulkier alkyl groups undergo faster reductive elimination, perhaps due to sterically induced destabilization. We considered whether these two effects could be combined to promote branch-selective alkene hydroarylation (Scheme 1B, cartoon representation). Specifically, wide bite angle ligand systems should compress bond angle xa/b, which may accentuate steric destabilization of adduct 1b (2° alkyl ligand) relative to 1a (1° alkyl ligand) such that reductive elimination via Path b is amplified. In this approach, the wide bite angle bisphosphine and the branched alkyl ligand of 1b provide "cooperative destabilization", thereby accelerating reductive elimination and, at the same time, controlling product regioselectivity.

Received: June 9, 2014
Published: July 14, 2014
selectivity. As such, branched products are potentially accessed by ligand-controlled exploitation of the Curtin—Hammert scenario.

As a benchmark reaction, hydroarylation of styrene with \( \text{N,N-diethylbenzamide (NDB)} \) was conducted using Shibata’s conditions using \( \text{rac-BINAP} \) as ligand (Table 1, entry 1). The process was chemically efficient but delivered a 29:71 mixture of branched to linear products (3a vs 4). To probe the idea that bite angle might be important, we systematically studied the effects of using dppm, dppe, dppp, or dppb as ligand (entries 2–5). As the size of the alkyl linker was increased, a gradual progression from linear to complete branch selectivity was observed. However, this selectivity came at the expense of decreased chemical efficiency (e.g., only 28% yield using dppb). Based upon the observation that commercial electron-deficient aryl phosphines increase reaction yields (cf. entries 3 and 6), we prepared \( \text{dFppb} \), a previously unreported ligand that is the pentafluorophenyl analogue of dppb (see the Supporting Information). Gratifyingly, this system provided adduct 3a in quantitative yield and with complete branch selectivity. With \( \text{dFppb} \) as ligand, the loading of styrene can be decreased from 450 to 200 mol% and reaction efficiency is maintained (entry 7 vs 8).

Further directing group scope was explored using 450 mol% of the alkene partner because these conditions provide faster reactions in more-challenging cases (Table 2). The protocol tolerates a range of amide-based directing groups, including secondary amide 2c. In all cases, the products 3a–d were isolated in good to excellent yields and with complete or very high levels of branch selectivity. Aryl and alkyl ketones 2e–h are also viable directing groups; again, products 3e–h were isolated in uniformly good yields and with high levels of branch selectivity. Esters will also direct branch-selective hydroarylation but provide lower yields of the product compared to amide- and keto-based directing groups. For example, hydroarylation using \( \text{Br} \) provides adduct 3i with 9:1 selectivity but in only 18% yield. In all cases, the mass balance of the reactions consisted of unreacted starting material, and bis-ortho-alkylation was not observed. At the current level of development, primary amides and aldehydes are not suitable directing groups.

We have examined the effects of arene substitution using a range of \( \text{N,N-diethylbenzamide derivatives (NDB)} \) (Table 3). Substitution \( \text{para} \) to the directing group is well tolerated, and potentially sensitive functionality, such as aryl bromides (3k) and esters (3l), survives the catalysis conditions. In the case of 3l, product regioselectivity clearly highlights the stronger directing ability of amides vs esters. The effects of substitution \( \text{meta} \) to the directing group are more subtle. For electronically neutral or bulky groups, substitution appears to be sterically controlled and occurs at the less hindered \( \text{ortho} \) site (e.g., 3n and 3p). If the \( \text{meta} \) substituent is small and inductively withdrawing, then high selectivity for the more hindered \( \text{ortho} \) position is achieved (3m and 3q). In the case of adduct 3o, a balance between these two control factors seemingly results in low \( \text{ortho} \) positional selectivity. Finally, if the arene already possesses substitution \( \text{ortho} \) to the directing group (e.g., 2r to 3r), then functionalization at the remaining \( \text{ortho} \) site is not achievable (vide infra).
aspect provides a limitation in scope but is also a beneficial control factor that prevents bis-ortho-functionalization in other cases.

Importantly, the protocol also exhibits good scope with respect to the alkene partner (Table 4). Electronically distinct styrenes 5a–d are tolerated, and targets 6a–d were produced in moderate to excellent yield and with complete branch selectivity. Alkyl-substituted alkenes also participate, and hydroarylation of pent-1-ene 5e with amide 2a provided 6e in 78% yield and, again, with complete branch selectivity. The process can be extended to other systems, although bulky substituents on the alkene do result in lower chemical efficiency (e.g., 2a to 6h). However, even for sterically demanding examples, high branch selectivity is maintained. In the case of 6g, introduction of an isopropyl group was achieved under an atmospheric pressure of propene. This represents a simple alternative to notoriously challenging Pd-catalyzed cross-couplings of isopropyl organometallics.10a The reaction was run at 120 °C. A propene atmosphere was used.

Deuterium labeling and exchange experiments have elucidated key mechanistic features of the current process. Hydroarylation of deuterio-5a, which is labeled at the terminal vinylic positions, with benzamide 2a provided deuterio-6a, where deuterium is transferred to the methyl, methine, and ortho positions (Scheme 2A). The observed scrambling indicates that both oxidative addition and alkene hydrometalation are reversible and supports reductive elimination as the product-determining step (cf. Scheme 1A). Subjecting 2q to the catalysis conditions in the absence of alkene, but in the presence of D₂O, showed deuteration incorporation at both ortho positions and also at the methylene sites of the directing group (Scheme 2B). The greater level of ortho incorporation suggests that oxidative addition into the aryl C(sp²)−H bond is easier than that into the C(sp³)−H bond of the directing group. Equal levels of deuteration incorporation at both ortho positions indicate that site-selective reductive elimination (and not site-selective oxidative addition) determines the regioselectivity of hydroarylation, which occurs selectively at C-6 (see Table 3). An analogous experiment on reaction product 3q showed no detectable exchange at the remaining ortho site and preferential deuteration incorporation at the methylene positions of the directing group. Directed oxidative addition into the C(sp²)−H bond of 3q requires coplanar alignment of the NEt₂ moiety with the secondary alkyl substituent on the arene. Presumably, this is disfavored on steric grounds; consequently, bis-ortho alkylation is not observed in any of the cases we have examined to date. An analogous rationalization accounts for the lack of reactivity observed with ortho-substituted amide 2r (see Table 3).

In summary, we report an efficient system for branch-selective, carbonyl-directed alkene hydroarylation based upon the counterintuitive strategy of “cooperative destabilization”. This offers a regioisomeric alternative to the Murali hydroarylation protocol and is the first step toward the development of related enantioselective processes. Notable features of the current system include its compatibility with a useful range of directing groups, an ability to hydroarylate aryl- or alkyl-substituted alkenes, and complete selectivity for mono-ortho-alkylation. Future studies will focus upon the design of effective chiral ligands and the generalization of this approach to regioselective hydroarylations of 1,1- and 1,2-disubstituted alkenes. Evidently further validation of our catalysis design is still required, but, in broader terms, the strategy outlined here may enable the development of other contrasteric alkene functionalization processes.

**ASSOCIATED CONTENT**

Supporting Information
Experimental details and characterization data. 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.

**ACKNOWLEDGMENTS**

G.E.M.C. and N.G.M. thank the Bristol Chemical Synthesis Doctoral Training Centre, funded by the EPSRC (EP/G036764/...

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(9) In Scheme 1B, and in the previously reported examples where steric crowding is a concern, we have found that the presence of a strong amidine donor ligand may provide destabilization by compressing the aryl ring; see: (a) Pool, J. A.; Lobkovsky, E.; Chirik, P. J. Organometallics 2003, 22, 2797. Bulkier alkyl groups increase the rate of C–H bond-forming reductive elimination from phosphine-ligated Pt complexes: (b) Abis, L.; Sen, A.; Halpern, J. J. Am. Chem. Soc. 1978, 100, 2915. (c) Halpern, J. Acc. Chem. Res. 1982, 15, 332. For insightful studies on the effects of steric and electronics on the rate of C–C bond-forming reductive elimination from phosphine-ligated Pd complexes, see ref 13e.

(10) In Scheme 1B, the structures of 1a and 1b are illustrative and have not been confirmed experimentally. In the Murai hydroarylation, computational studies support reductive elimination from a complex where the alkyl ligand is perpendicular to the plane of the arenne: Matsubara, T.; Koga, N.; Musaev, D. G.; Morokuma, K. Organometallics 2000, 19, 2318.

(11) The following bite angles are reported in ref 14a: BINAP, 92.4°; dpmm, 72°; dppe, 85°; dppp, 91°; and dpbb, 97.7°. A wide bite angle ligand may provide destabilization by compressing the aryl–Ir=alkyl bond angle and/or by providing a more sterically demanding coordination sphere. A better correlation to ligand bite angle than to ligand burial volume is observed. This latter parameter quantifies ligand steric properties: Claviser, H.; Nolan, S. P. Chem. Commun. 2010, 46, 841. (R)-SDP, which was used by Shibata to promote branch-selective hydroarylation at the 2-position of indoles (see ref 8), is not a suitable ligand and provides only traces (<5%) of 3a/4.

(12) For a discussion of factors that affect this type of equilibrium, see: Harvey, J. N. Organometallics 2001, 20, 4887.

(13) For discussions of factors that affect this type of equilibrium, see: Harvey, J. N. Organometallics 2001, 20, 4887.

(14) For discussions of factors that affect this type of equilibrium, see: Harvey, J. N. Organometallics 2001, 20, 4887.

(15) Enantioselective hydroarylation/hydroheteroarylation protocols have been developed, but efficient processes are limited to strained bicycloalkanes: (a) Dotta, R.; Togni, A. Chem. Commun. 2003, 760. (b) Sevov, C. S.; Hartwig, J. F. J. Am. Chem. Soc. 2013, 135, 2116. See also ref 15 and 8.

(16) For a discussion of factors that affect this type of equilibrium, see: Harvey, J. N. Organometallics 2001, 20, 4887.

(17) For a discussion of factors that affect this type of equilibrium, see: Harvey, J. N. Organometallics 2001, 20, 4887.

(18) For a discussion of factors that affect this type of equilibrium, see: Harvey, J. N. Organometallics 2001, 20, 4887.