JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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

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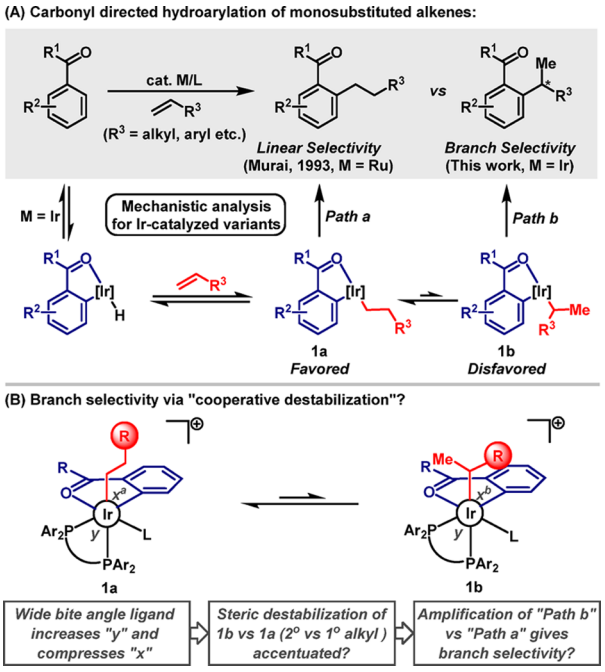
Supporting Information

ABSTRACT: Highly branch-selective, carbonyl-directed hydroarylations of monosubstituted alkenes are described. The chemistry relies upon a cationic Ir(I) 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-directed aryl C−H activation (Scheme 1A).[1] This protocol provides access to linear hydroarylation products and is considered a milestone in the development of atom-economical methodology.[2] In the ensuing years, a wide range of related π-bond insertion protocols have emerged that use a variety of late transition metal catalysts.[3,4] 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.[5−9] 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.[10,11] 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.[11]

At the outset of our investigations, we were drawn to cationic BINAP-ligated Ir(I) catalysts that were reported by Shibata for ketone-directed hydroarylation of styrenes.[4c] 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.[8] The predominance of linear products likely reflects a higher equilibrium preference for linear Ir(III) intermediate **1a** over sterically disfavored isomer **1b** (Scheme 1A).[12] Access to a branch-selective manifold thus

Scheme 1

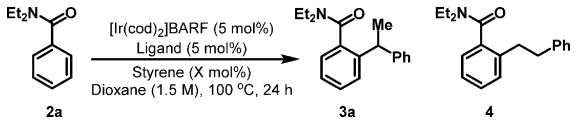


requires acceleration of reductive elimination *Path b* over *Path a*. Our reaction design was guided by two observations that are common in the organometallic literature. First, reductive elimination is accelerated by wide bite angle bisphosphine ligands in a range of transition-metal-catalyzed C−C bond formations.[13] 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.[14] Second, it has been observed that bulkier alkyl groups undergo faster reductive elimination, perhaps due to sterically induced destabilization.[15] We considered whether these two effects could be combined to promote branch-selective alkene hydroarylation (Scheme 1B, cartoon representation).[16] Specifically, wide bite angle ligand systems should compress bond angle $x^{a/b}$, 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

Received: June 9, 2014
Published: July 14, 2014

   dx.doi.org/10.1021/ja505776m | J. Am. Chem. Soc. 2014, 136, 10258−10261

Table 1. Catalyst System Optimization



entry	ligand	styrene equiv (mol%)	yield[a] (%)	3a:4[a]
1	*rac*-BINAP	450	100	29:71
2	dppm	450	73	8:92
3	dppe	450	82	23:77
4	dppp	450	52	60:40
5	dppb	450	28	100:0
6	d^Fppe[b]	450	100	36:64
7	d^Fppb[c]	450	100	100:0
8	d^Fppb[c]	200	100	100:0

[a]Yields and selectivities were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as a standard. [b]d^Fppe = 1,2-bis(di(pentafluorophenyl)phosphino)ethane. [c]d^Fppb = 1,4-bis(di(pentafluorophenyl)phosphino)butane.

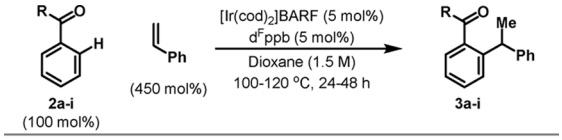
selectivity. As such, branched products are potentially accessed by ligand-controlled exploitation of the Curtin−Hammett scenario.

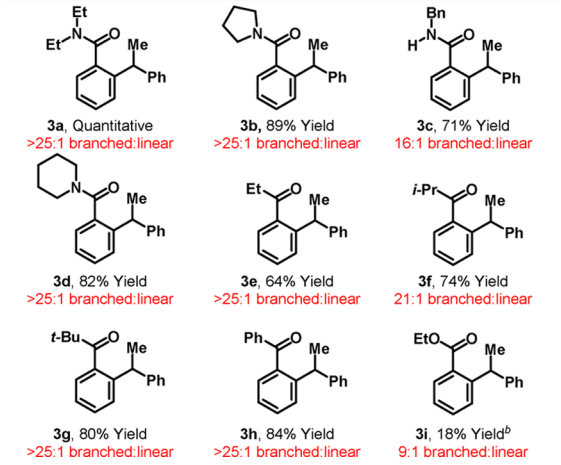
As a benchmark reaction, hydroarylation of styrene with *N,N*-diethylbenzamide was conducted under Shibata's conditions using *rac*-BINAP as ligand (Table 1, entry 1).[4c] The process was chemically efficient but delivered a 29:71 mixture of branched to linear products (**3a** vs **4**). To probe the 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.[17] 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 d^Fppb, 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.[17,18] With d^Fppb 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 ketone-based directing groups. For example, hydroarylation using **2i** provided 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.[19]

We have examined the effects of arene substitution using a range of *N,N*-diethylbenzamide derivatives **2j−r** (Table 3). Substitution *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**,

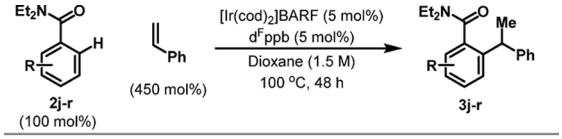
Table 2. Scope of the Carbonyl-Based Directing Group[a]

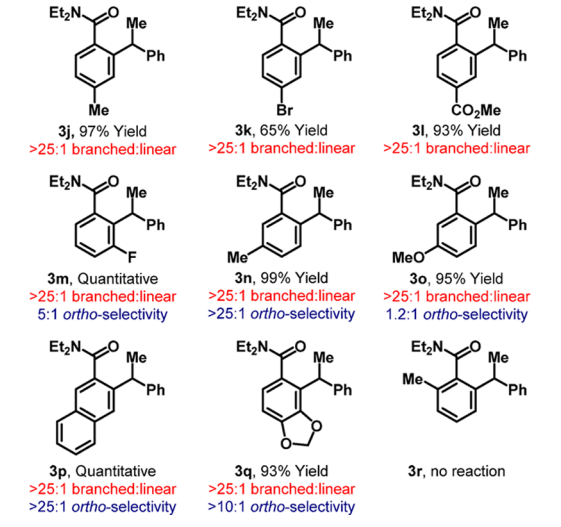




[a]Selectivites were determined by ^{1}H NMR analysis of crude material. [b]The reaction was run at 150 °C.

Table 3. Substitution on the Arene[a]



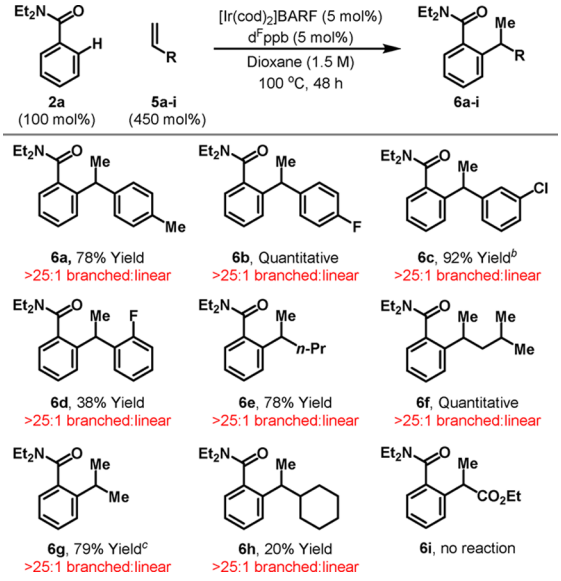


[a]Selectivites were determined by ^{1}H NMR analysis of crude material.

product regioselectivity clearly highlights the stronger directing ability of amides vs esters. The effects of substitution *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 *ortho* site (e.g., **3n** and **3p**). If the *meta* substituent is small and inductively withdrawing, then high selectivity for the more hindered *ortho* position is achieved (**3m** and **3q**).[20] In the case of adduct **3o**, a balance between these two control factors seemingly results in low *ortho* positional selectivity. Finally, if the arene already possesses substitution *ortho* to the directing group (e.g., **2r** to **3r**), then functionalization at the remaining *ortho* site is not achievable (*vide infra*). This

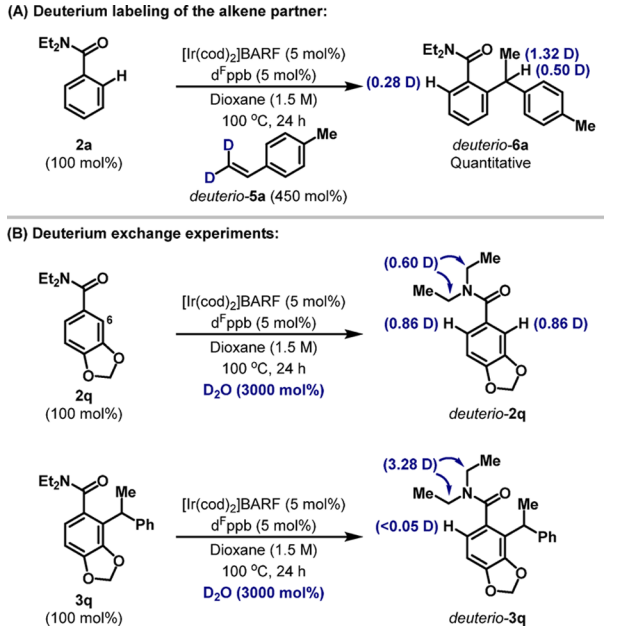
dx.doi.org/10.1021/ja505776m | J. Am. Chem. Soc. 2014, 136, 10258−10261

Table 4. Scope of the Alkene[a]



[a]Selectivites were determined by ^{1}H NMR analysis of crude material. [b]The reaction was run at 120 °C. [c]A propene atmosphere was used.

Scheme 2



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] Electron-deficient alkenes do not participate, and attempted hydroarylation of ethyl acrylate with **2a** did not deliver adduct **6i**.

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 D_2O, showed deuterium incorporation at both *ortho* positions and also at the methylene sites of the directing group (Scheme 2B).[21] The greater level of *ortho* incorporation suggests that oxidative addition into the aryl C(sp^2)–H bonds is easier than that into the C(sp^3)–H bonds of the directing group.[22] Equal levels of deuterium 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 deuterium incorporation at the methylene positions of the directing group. Directed oxidative addition into the C(sp^2)–H bond of **3q** requires coplanar alignment of the NEt_2 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 counter-intuitive strategy of "cooperative destabilization". This offers a regioisomeric alternative to the Murai 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/

1), for a Ph.D. studentship. J.F.B. is indebted to the Royal Society for a University Research Fellowship.

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(17) The following bite angles are reported in ref 14a: BINAP, 92.4°; dppm, 72°; dppe, 85°; dppp, 91°; and dppb, 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 buried volume is observed. This latter parameter quantifies ligand steric properties: Clavier, H.; Nolan, S. P. *Chem. Commun.* **2010**, *46*, 841.

(18) (*R*)-SDP, which was used by Shibata to promote branch-selective hydro*hetero*arylation at the 2-position of indoles (see ref 8), is not a suitable ligand and provides only traces (<5%) of **3a**/**4**.

(19) Our qualitative observations indicate the following ranking of directing group efficiency: tertiary amides > secondary amides ∼ ketones > esters. A detailed study will be reported in due course.

(20) Secondary directing effects of fluoro and methoxy substituents have been noted in other metal-catalyzed hydroarylation processes. For example, see: Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283 and references cited therein.

(21) Hydroarylation of styrene with **2q** under "standard" conditions, but with H_2O (3000 mol%) as an additive, afforded **3q** in 59% yield with selectivities comparable to those shown in Table 3.

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