Branch-Selective Alkene Hydroarylation by Cooperative Destabilization: Iridium-Catalyzed ortho-Alkylation of Acetanilides

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Abstract: An iridium(I) catalyst system, modified with the wide-bite-angle and electron-deficient bisphosphine d’ppb (1,4-bis(di(pentafluorophenyl)phosphino)butane) promotes highly branch-selective hydroarylation reactions between diverse acetanilides and aryl- or alkyl-substituted alkenes. This provides direct and ortho-selective access to synthetically challenging anilines, and addresses long-standing issues associated with related Friedel–Crafts alkylations.

Anilines are privileged building blocks for medicinal chemistry and materials science,[1] and many methods have been developed to access substituted derivatives.[2–7] However, a long-standing deficiency resides in the lack of general procedures for the ortho-selective introduction of branched alkyl substituents. Palladium-catalyzed cross-couplings of secondary alkyl organometallics are not well suited to this task, partially because of competitive isomerization after transmetalation, which can lead to linear adducts.[3] ortho-Selective Friedel–Crafts reactions are an appealing approach, which, in practice, is effective only in certain simple cases.[9] Well established problems associated with controlling the site and extent of alkylation usually predominate, and competitive coordination of the acid catalyst to the aniline nitrogen atom means that, where feasible, harsh reaction conditions are required.[9] Consequently, a method that addresses these issues by providing direct and mild access to ortho-branched anilines is likely to have widespread application.

Recently, we reported a method that overturns the linear selectivity of Murai-type hydroarylations[10,11] to provide access to branched adducts 1b (Scheme 1a).[12,13] All steps up to iridium(III)–alkyl intermediates 3a and 3b are fast and reversible, with linear adduct 3a likely favored on steric grounds. Our “cooperative destabilization” strategy employs a novel bisphosphine, d’ppb, with a wide bite angle to increase bond angle y and compress angles x’/x'', thereby enhancing steric destabilization of 3a/3b.[14] Destabilization is most acute for 3b, as this has a bulkier secondary alkyl ligand, and consequently, reductive elimination by path b is amplified to provide branched products 1b at the expense of linear isomers 1a.[14] This process employs weakly coordinating carbonyl directing groups, and tolerates both aryl- and alkyl-substituted alkylens. Related branch-selective hydroarylation methods invariably require strongly coordinating N-based directing groups and are limited to styrenes[15a–d] or, more recently, enol ethers as the olefinic partner.[15e,16,17] In this report, we extend our strategy to the branch-selective ortho-alkylation of acetanilides (Scheme 1b).[18] Significantly, this work expands our approach to encompass a) electron-rich aresnes, and b) inherently more demanding six-ring metalla-cycles (2 vs. 4). Indeed, to the best of our knowledge, this study outlines the first intermolecular branch-selective Muri-type alkene hydroarylations that proceed via six-ring chelates. In combination with earlier work,[12] these results suggest that a unified approach to branch-selective alkene hydroarylation is achievable and underpin ongoing efforts towards enantioselective variants.

Preliminary studies involved exposing acetanilide 5a and styrene to an Ir’ system derived from [Ir(cod)]BARF and d’ppb (Table 1). At 120°C in dioxane, adduct 6a was formed.

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Selected optimization results.

**Aniline scope.** –

*ortho*-Substituted anilines **5f-5j** have two different *ortho* C–H bonds available, and regioselectivity is strongly influenced by the *meta*-substituent. For **5f-5h**, hydroarylation occurred preferentially at the less hindered site to afford adducts **6f-6h** (4:1 to > 25:1 *ortho*-regioselectivity); the structures of **6h** and iso-**6h** were determined by single-crystal X-ray diffraction. **6i** and **6j**, hydroarylation was moderately selective for the *ortho* C–H bond adjacent to the heteroatom substituent. *Para*-Substituted anilines **5k** and **5m** participated smoothly, and products **6k** and **6m** were formed in good yield. Conversely, hydroarylation using *para*-trifluoromethyl derivative **5l** was not efficient, and adduct **6l** was formed in 21% yield. Complete branch selectivity and complete selectivity for mono-*ortho*-arylation (> 95:5 mono/bis) were observed for **6f-6m**.

We have also examined the scope of the alkene component using acetanilide **5f**; and, again, complete branch selectivity was achieved in all cases (Table 3). Electronically diverse styrenes are well tolerated, and the target compounds **7a-7e** were formed in moderate to quantitative yield, with complete selectivity for mono-arylation at the less hindered position. Processes involving alkyl-substituted alkenes required separate optimization. Changing the precatalyst counterion from triflate to BARF and switching the solvent from dioxane to 1,2-DCB provided a system that delivered diverse **8** in 92% yield. Isopropyl groups are challenging to install using Pd-catalyzed cross-couplings, and the present method provides a direct and atom-economic alternative. Sterically

| Entry | R   | X     | γ [mol %] | Solvent | T [°C] | t [h] | Yield [%] |
|-------|-----|-------|----------|---------|--------|-------|-----------|
| 1     | H   | BARF  | 200      | dioxane | 120    | 24    | 34        |
| 2     | H   | BARF  | 200      | dioxane | 100    | 24    | 17        |
| 3     | H   | BARF  | 200      | dioxane | 80     | 24    | <5        |
| 4     | H   | BARF  | 200      | dioxane | 120    | 72    | 22        |
| 5     | H   | BF3   | 200      | dioxane | 120    | 24    | 32        |
| 6     | H   | OTf2  | 200      | dioxane | 120    | 24    | 85        |
| 7     | H   | OTf2  | 450      | dioxane | 120    | 24    | 85        |
| 8     | H   | OTf2  | 200      | 1,2-DCB | 120    | 24    | 61        |
| 9     | H   | BARF  | 200      | 1,2-DCB | 120    | 24    | 72        |
| 10    | H   | OTf2  | 200      | xylene  | 120    | 24    | 58b       |
| 11    | H   | OTf2  | 200      | PhCl    | 120    | 24    | 60b       |
| 12    | CH3 | OTf2  | 200      | dioxane | 120    | 24    | <5        |

[a] Yields of isolated products unless stated otherwise, > 25:1 branched/linear in all cases. [b] Determined by H NMR analysis with 1,3,5-trimethoxybenzene as the internal standard. TF = trifluoromethanesulfonyl.
demanding alkenes are challenging, and the conversion of 5f into 7h occurred in only 33% yield; however, even here, branch selectivity was maintained.

The mechanism of the hydroarylation process is likely analogous to that outlined in our earlier work (Scheme 1a).[12] Hydroarylation of [D2]8 with aniline 5f delivered deuterated 7c, in which deuterium incorporation at both the methyl and methine positions indicates reversible alkene hydroamination prior to product-determining C–C bond formation (Scheme 2). The lack of deuterium incorporation at the C6 position suggests that C–H insertion of the Ir catalyst is, in this case, selective for the more sterically accessible ortho C–H bond. Indeed, exposure of aniline 5f to the Ir system in the absence of the alkene, but in the presence of D2O, resulted in 92% deuterium incorporation at the C6 position and in <5% at the C2 position; further exchange experiments are outlined in the Supporting Information. The X-ray structures of 6h and iso-6h[20] show that the secondary alkyl substituent of the products causes the acetamide moiety to twist from the plane of the arene, such that directed insertion of IrI into the remaining ortho C–H bond is challenging; consequently, bis-ortho-alkylation is not observed. This effect must be finely balanced given that ortho-substituted acetanilides 5b–5e participate smoothly in the hydroarylation reaction.

A key feature of the processes described here is the use of the wide-bite-angle and electron-deficient bisphosphine ligand dFppb. The branched/linear selectivity for 5a to 6a/iso-6a has been evaluated as a function of ligand bite angle (Scheme 3).[22] A progression from low linear to complete branch selectivity is observed as the ligand is varied from dFppm to dFppb. Although a strong bite-angle effect is evident, a significant electronic influence is also operative. Non-fluorinated ligands, namely dppm, dppe, dppp, and dppp, show the same bite-angle trend, but provide lower branch selectivities. One explanation is that secondary alkyl ligands a) shorten the iridium–alkyl bond by enhancing s-donation, and b) shorten the iridium–phosphine bonds by increasing p-backbonding.[25] This results in a contraction of the coordination sphere to provide a more congested environment, such that steric destabilization of the branched alkyl–IrIII intermediate is amplified further, and its propensity for reductive elimination increases.

The substituted aniline products enable access to a wide range of challenging bicyclic heteroaromatic compounds (Scheme 4). Pd-catalyzed ortho-bromination of 6a, which was prepared on gram scale, delivered 10 in 88% yield and excellent selectivity.[26] Pd-catalyzed reaction of 10 with ortho-toluidine provided benzimidazole 11 in 89% yield.[27] In this

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**Table 3: Alkene scope.**

| Alkene | Conversion | Ligand | Selectivity |
|--------|------------|--------|-------------|
| Ac-| Me | H | N | R |
| 5f | 120 °C, 48 h | dppb (5 mol%) | 77% Yield |
| 7c | 120 °C, 48 h | dppb (5 mol%) | 0.05 D H | (0.32 D H) |
| [D2]-6f | 200 mol% of alkene | [Ir(cod)]OT (5 mol%) | 77% Yield |
| | D2O (3000 mol%) | [Ir(cod)]OT (5 mol%) | 0.05 D H | (0.92 D H) |
| [D2]-7c | <5% | dppb (5 mol%) | 85% conv. |
| 6h | 120 °C, 48 h | dppb (5 mol%) | 85% conv. |
| 7a | OT: dioxane | dppb (5 mol%) | 85% conv. |
| 7b | OT: dioxane | dppb (5 mol%) | 85% conv. |
| 7c | OT: dioxane | dppb (5 mol%) | 85% conv. |
| 7d | OT: dioxane | dppb (5 mol%) | 85% conv. |
| 7e | OT: dioxane | dppb (5 mol%) | 85% conv. |
| 7f | OT: dioxane | dppb (5 mol%) | 85% conv. |

**Scheme 2.** Deuterium labeling and exchange experiments.

**Scheme 3.** Ligand effects for the hydroarylation of styrene with 5a.
approach, the N-acetyl group is incorporated into the heteroaromatic target. Other transformations required conversion into aniline 12.\[^{[28]}\] This intermediate underwent condensation with ethyl acetoacetate, and subsequent Pd-catalyzed oxidative cyclization delivered indole 13 in 52% yield (over 2 steps).\[^{[29]}\] Classical methods towards heteroaromatic compounds are also effective. For example, the Cohn variant of the Skraup quinoline synthesis delivered 14 in 68% yield.\[^{[30]}\] The processes in Scheme 4 validate concise and diversifiable entries to heteroaromatic targets that might be difficult to prepare by other means.

To conclude, we outline a direct and controlled approach to ortho-branched aniline derivatives, which addresses longstanding issues associated with related Friedel–Crafts alkylations. More fundamentally, this work extends our “cooperative destabilization” strategy\[^{[12]}\] to include processes that involve electron-rich arenes and proceed via six-ring metal-lacycles. Both aspects represent a significant expansion to the emerging area of branch-selective Murai-type hydroarylations.\[^{[13,15]}\] The catalyst design features used here will guide efforts in our laboratory aimed at developing a general and enantioselective alkene hydroarylation method.

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[20] CCDC 1413026, 1413027, 1413028, and 1413029 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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