VIP Synthesis Design

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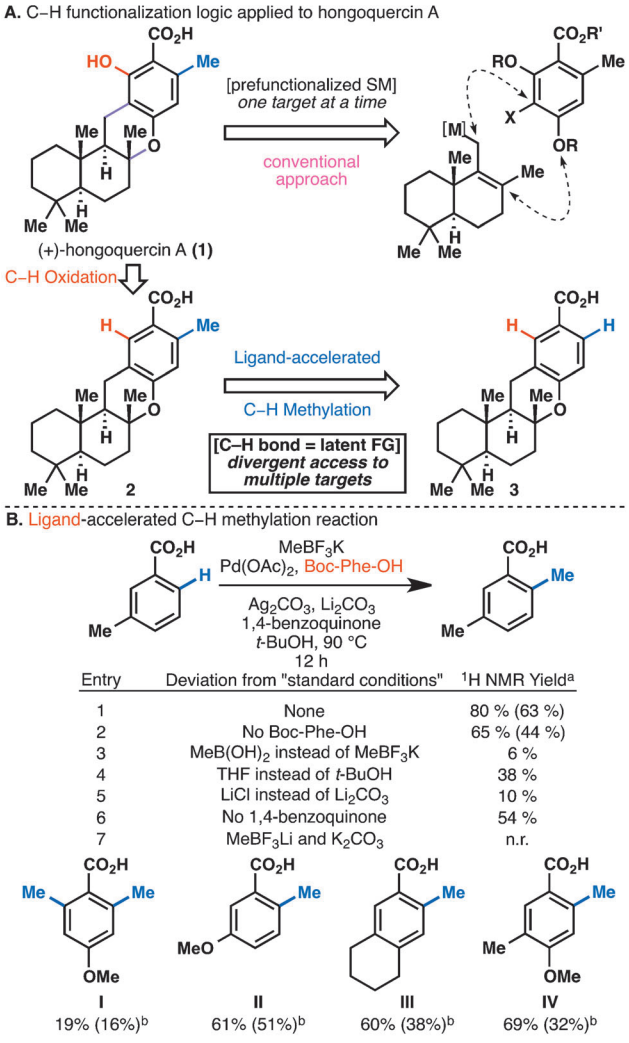
C–H Functionalization Logic Enables Synthesis of (+)-Hongoquercin A and Related Compounds**

Brandon R. Rosen, Leah R. Simke, Peter S. Thuy-Boun, Darryl D. Dixon, Jin-Quan Yu, and Phil S. Baran**

Advances in the strategy and methodology of C–H functionalization have begun to alter the way organic chemists approach the synthesis of arenes.[1] Given the widespread occurrence, versatility, and accessibility of benzoic acids, one of our groups (J.-Q.Y.) has developed a diverse suite of reactions for their functionalization.[2] The expansive reaction scope, robust operational procedures, and high chemoselectivity have already contributed to the application of these methods in total synthesis.[3] Although C–H functionalization reactions in the context of drug analogue syntheses have been reported,[4] there are few examples using C–H functionalization in the divergent[5] functionalization of natural product cores.[6] The structure of (+)-hongoquercin A (**1**, Figure 1 A), a sesquiterpenoid antibiotic of fungal origin,[7] inspired our groups to pursue a strategically unique pathway which required the invention of a ligand-accelerated reaction for C–H alkylation (Figure 1 B). Herein, a synthesis of **1** is reported in which the benzoic acid moiety of core structure **3** serves to direct two sequential site-selective C–H functionalization events (methylation and oxidation). The successful employment of this logic in the context of a synthesis of **1**, as well as the preparation of eight analogues by functionalization of the intermediate **3**, demonstrates the feasibility of such C–H disconnections in the retrosynthetic analysis of complex molecules.

With the above C–H disconnection strategy in mind, it was envisioned that **1** could arise from sequential C–H activation reactions of the sites *ortho* to the carboxylic acid, thus leading to **3**. In the forward sense, the conversion of **3** into **2** would require the development of a ligand-accelerated C–H methylation reaction, and oxygenation of **2** might be accomplished using a palladium-catalyzed hydroxylation (Figure 1 a). The core structure **3** could be easily accessed from (+)-chromazonarol (**4**, previously prepared on gram scale in six steps from (+)-sclareolide)[8] by formation of the corresponding aryl triflate and hydroxycarbonylation. Most importantly, **3** would serve as the central intermediate from which numerous analogues could be prepared using the plethora of C–H functionalization reactions available.



Entry	Deviation from "standard conditions"	^{1}H NMR Yield[a]
1	None	80 % (63 %)
2	No Boc-Phe-OH	65 % (44 %)
3	$MeB(OH)_2$ instead of $MeBF_3K$	6 %
4	THF instead of *t*-BuOH	38 %
5	LiCl instead of Li_2CO_3	10 %
6	No 1,4-benzoquinone	54 %
7	$MeBF_3Li$ and K_2CO_3	n.r.

I: 19% (16%)[b] II: 61% (51%)[b] III: 60% (38%)[b] IV: 69% (32%)[b]

Figure 1. a) C–H disconnection approach to (+)-**1**. b) Development of a ligand-accelerated C–H methylation. [a] Yields were determined by NMR analysis of the crude reaction mixture with CH_2Br_2 as an internal standard. Yields given within parentheses refer to yields of products isolated from reactions run on a 0.1 mmol scale. For detailed reaction procedures, see the Supporting Information. [b] Yields within parentheses refer to reactions in which Boc-Phe-OH was omitted. Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran.

A prerequisite of this plan was the development of a ligand-accelerated C–H methylation reaction. After sub-

[*] B. R. Rosen, L. R. Simke, P. S. Thuy-Boun, Dr. D. D. Dixon, Prof. Dr. J.-Q. Yu, Prof. Dr. P. S. Baran
Department of Chemistry, The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, CA 92037 (USA)
E-mail: pbaran@scripps.edu

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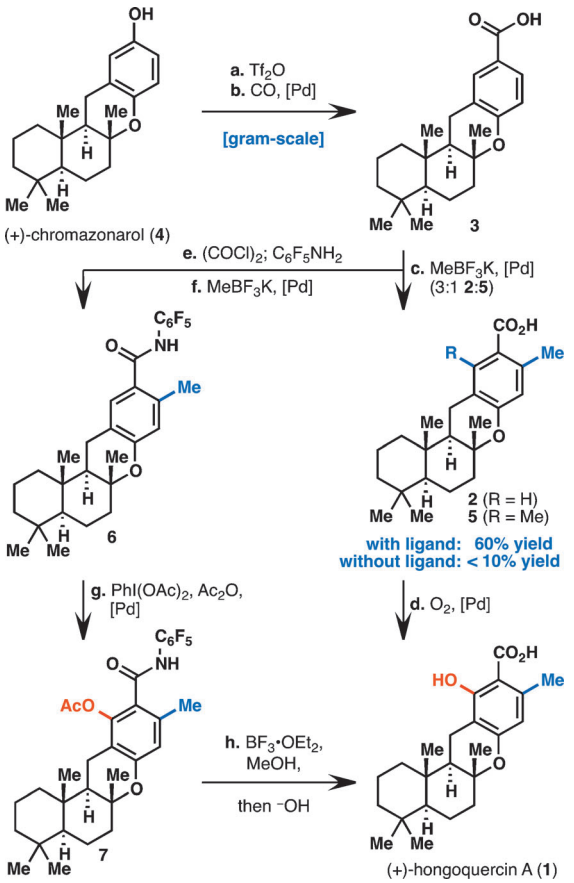
stantial optimization, the use of $MeBF_3K$ in the presence of catalytic $Pd(OAc)_2$ with the amino-acid-derived ligand Boc-Phe-OH provided optimal results with *m*-toluic acid (Figure 1b, entry 1). Omission of either Boc-Phe-OH or 1,4-benzoquinone resulted in diminished conversion (entries 2 and 6), while other methyl sources, solvents, and bases also gave inferior results (entries 3–5 and 7). These conditions were then applied to several other commercially available benzoic acids, thus providing the alkylated products (**A**–**D**) in satisfying yields.[9] In most cases, monoalkylation resulted in the major product (ca. 6:1–15:1), but the reaction of *p*-anisic acid gave predominantly bisalkylation with low conversion. The full substrate scope and mechanism of this transformation will be the subject of a separate report.

With a reliable set of reaction conditions for C–H alkylation in hand, the preparation of **3** was pursued. As shown in Scheme 1, treatment of **4** with Tf_2O resulted in the corresponding aryl triflate, which underwent hydroxycarbonylation using $Pd(OAc)_2$, dppf, and KOAc under 1 atm of CO to give **3** (gram-scale),[10] which was characterized by X-ray crystallographic analysis. Gratifyingly, the reaction of **3** under our optimized methylation conditions afforded the carboxylic acid **2** in 45% yield, along with the bisalkylated product **5** in 15% yield and 32% of recovered **3**. Interestingly, omission of either Boc-Phe-OH or 1,4-benzoquinone from this reaction had much more dramatic effects than with *m*-toluic acid, as conversion fell below 10%. Prolonged reaction times or higher temperatures resulted in an increase in the amount of **5** formed, thus diminishing the isolated yield of **2** and complicating purification.

At this stage, all that remained to complete the synthesis of **1** was the hydroxylation of **2**.[2j] Exposing **2** to 1 atm of O_2 in the presence of $Pd(OAc)_2$ and KOAc in DMA at 115°C resulted in only recovered starting material. Increasing the pressure of O_2 to 10 atm resulted in approximately 15–20% yield of isolated **1** along with substrate decomposition. Unfortunately, an extensive survey of reaction conditions (e.g., solvent, temperature, base, etc.) did not improve the yield.[11] These results are likely due to a combination of steric factors and catalyst instability in the relatively harsh oxidation conditions, thus highlighting a significant limitation in C_{sp^2}–H oxidation.

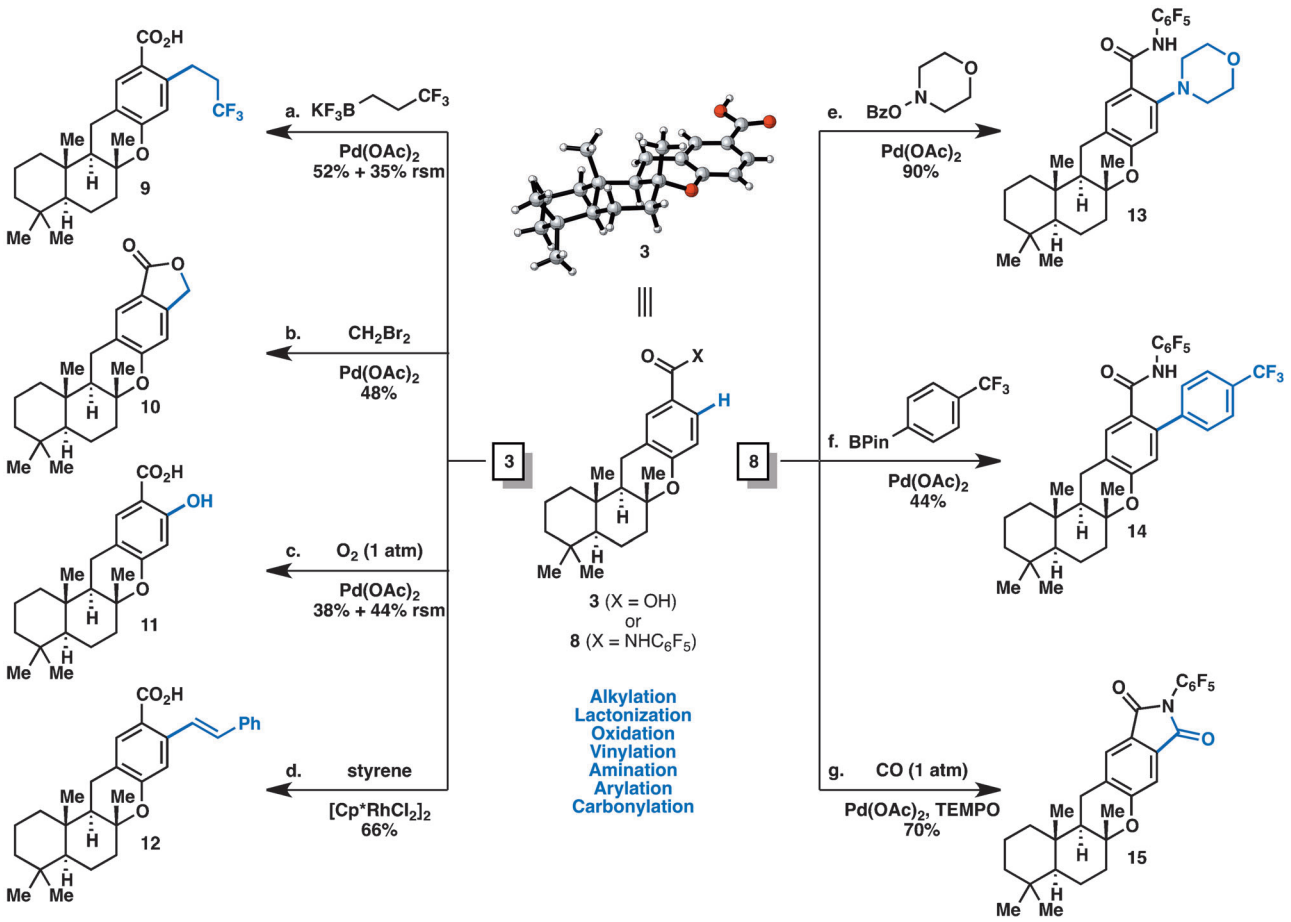
Although this ultimate oxidation proved challenging, it was reasoned that converting the carboxylic acid of **3** into a suitable amide would improve the C–H functionalization reactions, possibly overcoming any difficulties that thwarted initial experiments.[6a,12] For example, electron-deficient aryl amides have been shown to be powerful directing groups for many transformations where benzoic acids have failed and can be readily cleaved using a variety of methods.[12a] Thus, treating **3** with oxalyl chloride and catalytic DMF afforded the corresponding acid chloride, which furnished amide **8** in 76% yield when heated with $C_6F_5NH_2$ in refluxing toluene. Gratifyingly, palladium-catalyzed methylation proceeded to give **6** in 60% yield and set the stage for the final C–H oxidation reaction. In the event, extensive exploration revealed that exposure of **6** to catalytic $Pd(OAc)_2$ in the presence of stoichiometric $PhI(OAc)_2$, Ac_2O, and NaOAc affords the acetoxylated amide **7** in 54% yield. It is noteworthy that under widely used acidic conditions for acetoxylation (e.g. $AcOH/Ac_2O$, 100°C),[12b,13] decomposition of **6** occurred, and these weakly basic conditions were necessary to obtain **7**.



Scheme 1. Synthesis of (+)-Hongoquercin A (**1**). Reagents and conditions: a) Tf_2O, pyridine, CH_2Cl_2, 0°C, 3 h; 91%. b) CO (1 atm), 5 mol% $Pd(OAc)_2$, 20 mol% dppf, KOAc, DMSO, 60°C, 16 h; 80%. c) $MeBF_3K$, 10 mol% $Pd(OAc)_2$, 20 mol% Boc-Phe-OH, Ag_2CO_3, Li_2CO_3, 5 mol% 1,4-benzoquinone, *t*BuOH, 90°C, 12 h; 45% **2**, 15% **5**, 32% **3**. d) O_2 (10 atm), 10 mol% $Pd(OAc)_2$, KOAc, DMA, 115°C, 15 h; ca. 15%. e) i. $(COCl)_2$, cat. DMF, CH_2Cl_2, 5 h; ii. $C_6F_5NH_2$, PhMe, 10 mol% DMAP, 120°C, 12 h; 76%. f) $MeBF_3K$, 10 mol% $Pd(OAc)_2$, Ag_2CO_3, Li_2CO_3, 50 mol% 1,4-benzoquinone, THF, 120°C, 24 h; 60%. g) $PhI(OAc)_2$, 10 mol% $Pd(OAc)_2$, NaOAc, Ac_2O, DCE, 80°C, 24 h; 54%. h) $BF_3{\cdot}OEt_2$, MeOH, 105°C, 48 h, then 6 M NaOH, THF, 80°C, 2 h; 71%. DCE = 1,2-dichloroethane, DMA = *N*,*N*-dimethylacetamide, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, dppf = 1,1′-bis(diphenylphosphino)-ferrocene, Tf = trifluoromethanesulfonyl.

Cleavage of the amide was accomplished using $BF_3{\cdot}OEt_2$ in refluxing methanol, which also resulted in concomitant removal of the acetate group.[14] Addition of NaOH to the reaction mixture and subsequent acidic workup afforded the target **1** in 71% yield. Synthetic **1** exhibited identical spectral properties to those reported by Roll and co-workers (^1H and ^{13}C NMR spectroscopy, IR, m.p.).[7a]

The primary feature of the initial design was the ability of **3** to serve as a point of divergence from which a multitude of hongoquercin congeners could be fashioned. To this end,



Scheme 2. Synthesis of analogues using C–H functionalization. Reagents and conditions: a) $CF_3CH_2CH_2BF_3K$, 10 mol% Pd $(OAc)_2$, 20 mol% Boc-Phe-OH, Ag_2CO_3, Li_2CO_3, 5 mol% 1,4-benzoquinone, *t*BuOH, 90 °C, 18 h; 52% **9**, 35% **3**. b) 10 mol% $Pd(OAc)_2$, $KHCO_3$, CH_2Br_2, 140 °C, 48 h; 48%. c) O_2 (1 atm), 10 mol% $Pd(OAc)_2$, KOAc, 1,4-benzoquinone, DMA, 115 °C, 15 h; 38% **11**, 43% **3**. d) 1.05 equiv **3**, 1 equiv styrene, 5 mol% $[(Cp^*RhCl_2)_2]$, AgOAc, DMF, 120 °C, 24 h; 66%. e) *O*-benzoyl *N*-hydroxymorpholine, 10 mol% $Pd(OAc)_2$, AgOAc, CsF, DCE, 130 °C, 24 h; 90%; f) 4-trifluoromethylphenylboronic acid pinacol ester, 10 mol% $Pd(OAc)_2$, $NaHCO_3$, Ag_2CO_3, 1,4-benzoquinone, DMSO, H_2O, *t*-amyl alcohol, 100 °C, 24 h; 44%. g) CO (1 atm), 10 mol% $Pd(OAc)_2$, KH_2PO_4, AgOAc, TEMPO, DCE, 100 °C, 24 h; 70%. Cp* = C_5Me_5, TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl.

a small library of analogues from the C–H activation precursors **3** and **8** was targeted. As depicted in Scheme 2, a range of *ortho*-C–H functionalizations were executed on both **3** and **8**. For instance, the reaction conditions employed for methylation of **3** could also be applied to deliver the trifluoropropylated acid **9**. It is of note that no overalkylation product was detected in the crude reaction mixture. Domino C–H alkylation/lactonization was accomplished using CH_2Br_2 and $Pd(OAc)_2$ to give the lactone **10**.[2i] Contrary to observations with the methylated substrate **2**, substrate **3** was oxidized under 1 atm of O_2, and, although the conversion was modest after 15 hours, no decomposition was observed, and the remaining starting material could be recovered.[2j] Carboxylic acid **3** also proved to be an excellent substrate for rhodium-catalyzed vinylation, as demonstrated by the C–H Heck-type reaction with styrene to give olefin **12**.[2g]

Given the enhanced reactivity of amide **8**, we expected that analogues otherwise difficult to access directly from **3** could also be prepared. Thus, reaction of **8** with a morpholine-derived amine in the presence of catalytic $Pd(OAc)_2$ gave arylamine **13** in 90% yield.[15] A C–H Suzuki-type coupling with $(p\text{-}CF_3)C_6H_4BPin$ afforded the biaryl product **14** in 44% yield.[16] The lower yield in this case was due to the fact that **14** was co-polar with **8**, thus complicating purification, and additional **14** was isolated alongside small amounts of **8**. Carbonylation under 1 atm of CO gave the phthalimide **15**. Interestingly, it was found that TEMPO was an essential additive for this reaction, and only **8** was recovered in its absence.[17] It is notable that, although the yields for several of these reactions are modest, the only other isolable component was recovered starting material, which could generally be separated using standard chromatographic methods (flash chromatography or preparative TLC). This limitation is one that could likely be overcome with further optimization when necessary, whereas for diversity-based and medicinal chemistry applications, we believe that the versatility of these transformations outweighs this shortcoming. Furthermore, these studies complement existing directed *ortho*-lithiation/functionalization methodologies, which may not be as effective at delivering such a broad range of products.[18]

The synthesis of (+)-hongoquercin A (**1**) reported herein serves to highlight the utility of C–H functionalization logic simultaneously in target-based and diversity-oriented synthesis. The use of two different C–H disconnections to forge C–C and C–O bonds in a controlled, site-specific fashion is a unique maneuver in synthesis planning.[19] In the case of the former bond, a ligand-accelerated method for benzoic-acid-directed C–H alkylation was developed. Further studies from our groups on the strategic application of C–H functionalization methodologies continue.

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