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Total Synthesis of Hibispeptin A via Pd-Catalyzed C(sp^3)−H Arylation with Sterically Hindered Aryl Iodides

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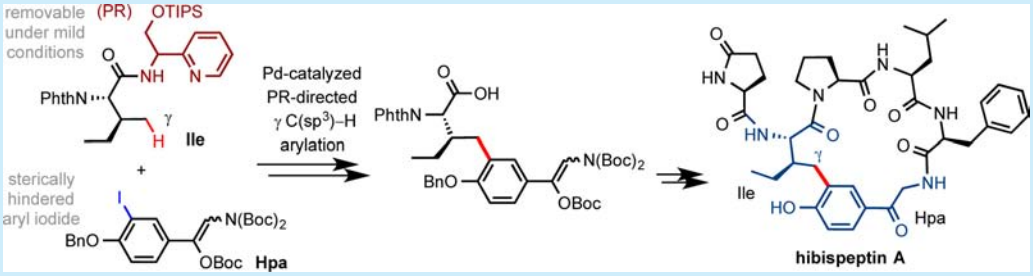
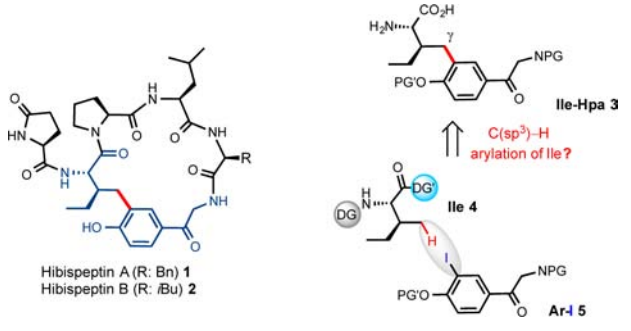
Supporting Information



ABSTRACT: To access the key Ile-Hpa pseudodipeptide motif in hibispeptins, a series of bidentate carboxamide-based auxiliary groups have been explored to facilitate the palladium-catalyzed arylation of unactivated γ-C(sp^3)−H bonds of Ile precursor with aryl iodides. A new pyridylmethylamine-based auxiliary group PR is introduced, which permits the use of more sterically hindered ortho-substituted aryl iodide substrates and can be removed under mild conditions. Pd-catalyzed PR-directed γ-C(sp^3)−H arylation enabled the first total synthesis of hibispeptin A.

The hibispeptins are pseudohexameric cyclic peptide natural products isolated from the root bark of *Hibiscus syriacus*, which has long been used as antipyretic and anthelmintic herbal medicine in Asia (Scheme 1).[1] Their

Scheme 1. Structure of Hibispeptins Featuring an Ile-Hpa Motif



structures feature a unique C−C cross-link between the γ-methyl of an isoleucine (Ile) residue and the arene group of a 4-hydroxy phenacylamine (Hpa) residue. We envisioned that we could employ Pd-catalyzed auxiliary group directed arylation to construct the key Ile-Hpa motif **3** (Scheme 1) via reaction of a γ-methyl C(sp^3)−H bond of an Ile precursor (see **4**) with a suitable aryl iodide (see **5**).[2−8] Despite significant advances of C(sp^3)−H arylation chemistry over the past decade, use of complex and sterically hindered aryl coupling partners remains a substantial challenge.[9] Herein, we report the development of a removable pyridylmethylamine-based auxiliary group (PR) for Pd-catalyzed arylation of unactivated γ-C(sp^3)−H bonds of isoleucine with sterically hindered ortho-substituted aryl iodides. PR-directed C−H arylation of isoleucine enabled us to accomplish the first total synthesis of hibispeptin A.

Our synthesis of hibispeptin A commenced with an investigation of the Pd-catalyzed γ-C−H arylation reaction of Ile substrate **8** directed by the N-linked picolinamide (PA)[7a] auxiliary group (Scheme 2A). Our previous studies have shown that the PA auxiliary group is effective at facilitating Pd-catalyzed arylation of γ-C(sp^3)−H bonds of amino acid substrates with aryl iodides under mild reaction conditions.[2b] These C−H arylation reactions likely proceed through a kinetically favored five-membered palladacycle intermediate via a Pd$^{II/IV}$ catalytic cycle (see **6** and **7** in Scheme 2) to give the γ-arylated product. Our initial attempts at the arylation of Ile **8** with 1.5 equiv of 3-acylphenyl iodide **9** under our previously reported conditions[2b] (with 1.5 equiv of Ag_2CO_3 in *t*AmylOH at 80 °C) provided the desired product **10** in ∼30% yield. The yield of **10** was improved to 51% by the addition of 20 mol % of the dibenzyl phosphate ($(BnO)_2PO_2H$) additive[10] at 50 °C for 3 days. In addition to **10**, γ,γ′-bis-arylated side product **11** was also obtained in 10% yield. In comparison, γ-C−H arylation of Ile **8** with ary iodide **12** bearing an ortho methoxy group gave a notably decreased yield of product **13** (31%), along with ∼5% of bis-arylated product **14**. Use of more forcing reaction conditions, such as additional equivalents of aryl iodide or a higher reaction temperature, led to a decreased yield of **13** with increased formation of **14** and other side products. The

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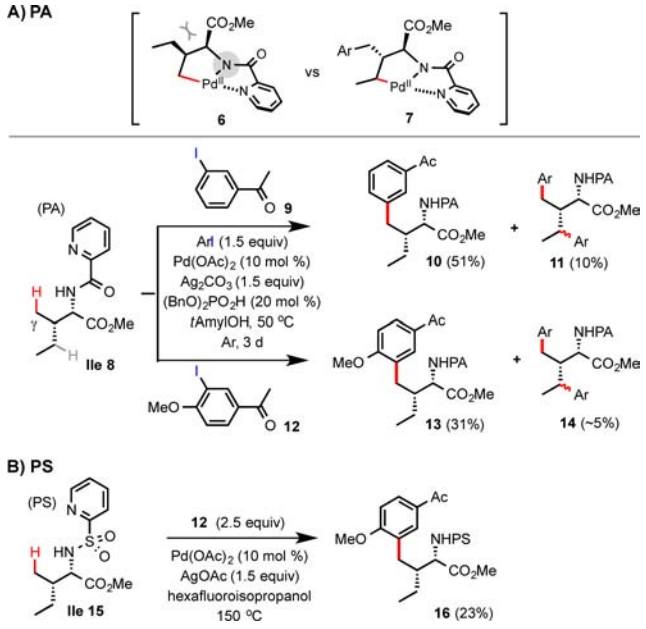
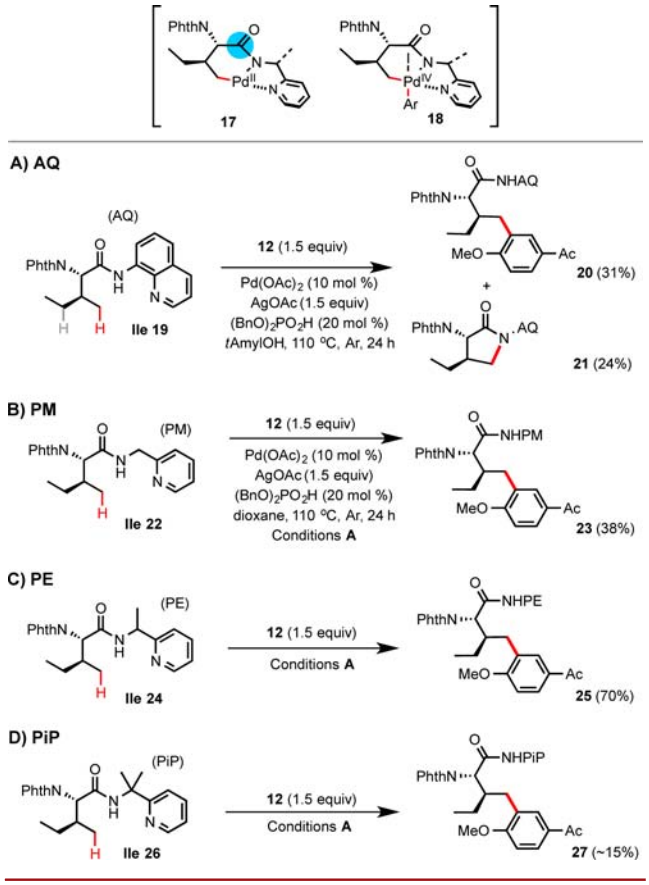
Scheme 2. γ-Me Arylation of Ile through a Five-Membered Palladacycle Mediated by N-Linked Auxiliary Groups



Scheme 3. γ-Me Arylation of Ile through a Six-Membered Palladacycle Mediated by C-Linked Auxiliary Groups



arylation of Ile **8** with a more complex aryl iodide (see **42** in Scheme 5) gave an even further diminished yield (<20%). We reasoned the first γ-Me arylation of **8** was sterically disfavored due to the cis-configuration of the α-CO_2Me and β-Et groups of palladacycle intermediate **6**. Although methylene groups are generally less reactive than methyl groups, the γ′-methylene C−H arylation of **10** proceeds through palladacycle intermediate **7** with a more favorable trans-configuration of the α-CO_2Me and the β-benzyl groups.[11] Similarly, the arylation of Ile **15**, equipped with Carretero's pyridyl sulfonamide (PS) directing group,[5a] with **12** gave product **16** in 23% yield (Scheme 2B).

To circumvent the undesired methylene arylation caused by the unfavorable sterics of PA-coupled Ile **8**, we turned our attention to Daugulis' aminoquinoline (AQ) directing group, which was installed on the C terminus of Ile **19** (Scheme 3A).[7,12] Recently, we have demonstrated that the γ-methyl C(sp^3)−H bonds of Ile **19** can undergo Pd-catalyzed intramolecular amination with amide NH through a kinetically less favored six-membered palladacycle intermediate (see **17**) to form γ-lactam products using the PhI(OAc)$_2$ oxidant.[13] While the Pd-catalyzed AQ-directed γ-Me arylation of Ile **19** with simple aryl iodide **9** proceeded in >70% yield (results not shown Scheme 3A), the same arylation reaction with aryl iodide **12** afforded the desired product **20** in a much lower yield (31%), along with a lactam side product **21** in 24% yield. In a previous study, we also found that pyridyl methylamine (PM) was an effective auxiliary group for Pd-catalyzed intramolecular γ-C(sp^3)−H amination to form γ-lactams.[13] However, arylation of PM-coupled Ile **22** with **12** proceeded under the optimized conditions **A** of 20 mol % $(BnO)_2PO_2H$ and 1.5 equiv of AgOAc in dioxane at 110 °C to give the desired product **23** in moderate yield (38%) (Scheme 3B).[14,15] To our delight, Ile **24** equipped with 2-pyridyl ethylamine (PE),[16] a more conformationally constrained analogue of the PM group, underwent the desired γ-Me arylation with 1.5 equiv of **12** under the general conditions **A** to give product **25** in a much improved yield (70%). Neither bis-arylated products nor C−N cyclization products were observed. However, our attempts at removing the PE auxiliary from product **25** under various conditions, such as Boc activation[2d] and BF_3·Et_2O[7c] treatment, failed to give the desired products in acceptable yields and chiral integrity. In comparison, C−H arylation of Ile **26** equipped with Shi's gem-dimethyl substituted pyridyl methylamine directing group[17] gave a 15% yield of product **27** (Scheme 3C).[18]

The resistance of the PE auxiliary group to intermolecular amide cleavage prompted us to consider an intramolecular cleavage strategy.[2b] We reasoned that we could install a protected OH group at the methyl position of PE (see TIPS protected PR **30**, Scheme 4A). Upon unmasking the TIPS protecting group, a reversible intramolecular acyl transfer from N to O might form a more labile ester intermediate (see **34**, Scheme 4B), which could be irreversibly cleaved to form an ester or hydrolyzed to form a carboxylic acid. PR auxiliary **30** can be readily prepared on a multigram scale from commercially available 2-vinylpyridine **28** using a sequence of dihydroxylation via an epoxide intermediate, selective TIPS protection, N_3 substitution, and reduction. Racemic PR **30** can be readily installed onto Phth-Ile-OH using standard EDCI-mediated amide coupling at rt to give Ile **31**, preserving excellent chiral integrity at Cα of Ile (>98%). To our delight, PR-coupled Ile **31** underwent C−H arylation with 1.5 equiv of **12** to give product **32** in 69% yield under the general conditions **A** (Scheme 4B).[19] Treatment of compound **32** with 1.2 M HCl in MeOH or HF/pyridine in THF at rt gave TIPS deprotected intermediate **33** in excellent yield. Heating compound **32** with 1.2 M HCl in MeOH at 100 °C for 12 h gave a mixture of compound **33** and the corresponding acyl

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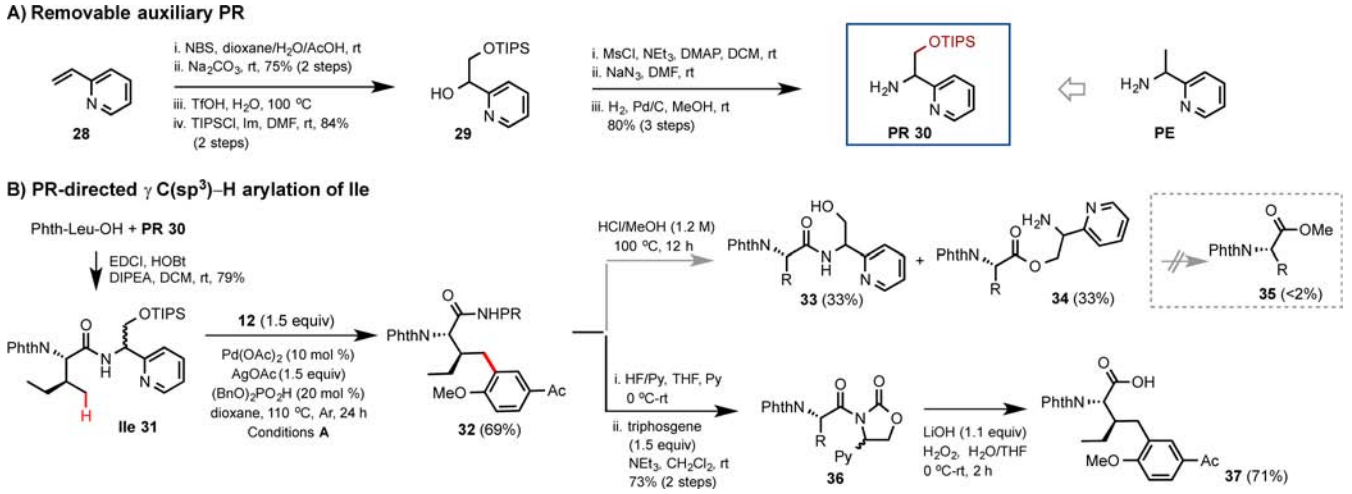
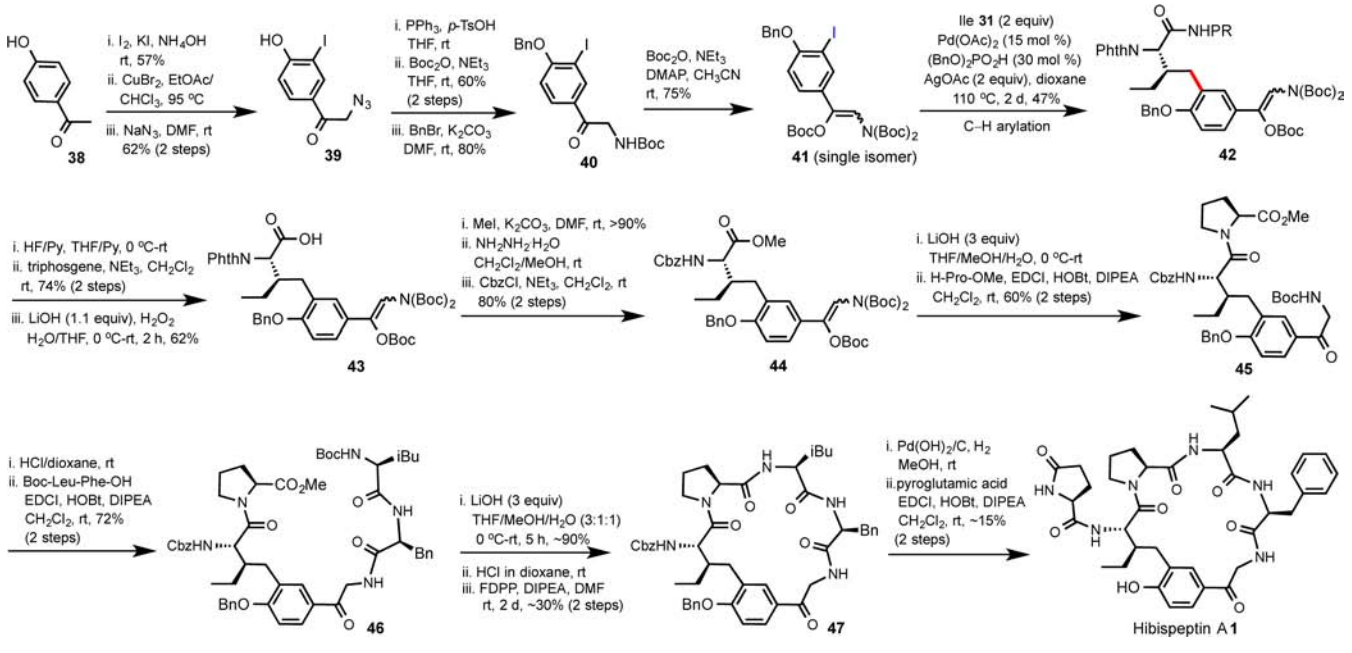
Scheme 4. Development of Removable PR Auxiliary for γ-Me Arylation of Ile with Sterically Hindered Aryl Iodides



Scheme 5. Total Synthesis of Hibispeptin A via Pd-Catalyzed PR-Directed γ-Me Arylation of Ile



transfer product **34** in ∼1:1 ratio. Disappointingly, the desired transesterification of **34** with MeOH did not occur. However, intermediate **33** can readily react with 1.5 equiv of triphosgene at rt to form oxazolidone **36** in good yield. The oxazolidone motif in **36** can be cleanly cleaved by treatment with 1.1 equiv of $LiOH/H_2O_2$ at 0 °C to give free carboxylic acid **37**.

Next, we proceeded to apply PR-mediated γ-Me C−H arylation to the total synthesis of hibispeptin A (Scheme 5). 4-Hydroxyl acetophenone **38** was first monoiodinated with I_2. An azido group was then installed at the α-position of the carbonyl group via $CuBr_2$-mediated α-bromination followed by S_N2 substitution with NaN_3. Staudinger reduction of the N_3 group, Boc protection, and protection of the phenolic OH with BnBr gave mono-Boc phenacylamine **40** in good yield. Treatment of compound **40** with excess Boc_2O/DMAP gave tri-Boc protected compound **41** in 75% yield.[20] To our delight, arylation of PR-coupled Ile **31** with tri-Boc protected aryl iodide **41** proceeded smoothly to give the desired γ-arylation product **42** in 47% yield under slightly optimized conditions with 15 mol % of $Pd(OAc)_2$ at 110 °C for 2 days. TIPS deprotection of **42** with HF/pyridine, oxazolidone formation with triphosgene, and subsequent cleavage of the acyl oxazolidone with $LiOH/H_2O_2$ gave the key Ile-Hpa residue **43** in good overall yield and excellent purity.

To our surprise, the seemingly straightforward macrocyclization of the C−C cross-linked pentapeptide scaffold of hibispeptin was exceedingly challenging.[21] To address the Cα racemization problem of **43**, the NPhth protecting group of Ile-Hpa **43** was swapped with a Cbz group by treatment with $NH_2NH_2{\cdot}H_2O$ followed by CbzCl to give **44** in good yield. Saponification of **44** and followed by amide coupling with H-Pro-OMe gave tripeptide **45** in excellent yield and with complete retention of chiral integrity at Cα of Ile. The Boc group of tripeptide **45** was removed with HCl in dioxane and then coupled with dipeptide Boc-Leu-Phe-OH using EDCI/HOBt to give pentapeptide **46**. Hydrolysis of the methyl ester of **46** with LiOH and Boc deprotection with HCl in dioxane at rt gave the macrolactamization precursor. The desired macro-

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lactamization at the Pro/Leu site mediated by pentafluorophenyl diphenylphosphinate (FDPP)[22] in dilute DMF solution at rt for 2 days proceeded smoothly to give cyclic pentapeptide **47**. The Cbz and Bn groups of **47** were then deprotected by Pd-catalyzed hydrogenolysis; subsequent coupling with pyroglutamic acid using EDCI/HOBt gave hibispeptin A **1** in moderate yield after silica gel chromatography.

In summary, we have explored a series of bidentate carboxamide auxiliary groups for the palladium-catalyzed arylation of the γ-methyl group of isoleucine to construct the Ile-Hpa pseudodipeptide motif in hibispeptins. We successfully introduced a new pyridylmethylamine-based auxiliary group PR, which permits the use of more sterically hindered ortho-substituted aryl iodide substrates and can be removed under mild conditions. Finally, we applied the PR-directed Pd-catalyzed C−H arylation reaction to the first total synthesis of hibispeptin A.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and ^{1}H and ^{13}C NMR spectra for new compounds. 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

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(18) Compared with PM, the constrained conformation of PE may better facilitate the formation of a kinetically less favored six-membered palladacycle intermediate. On the other hand, the high rigidity of PiP may favor the formation of five-membered palladacycle intermediate.

(19) A single example of an OTBS-protected PR analogue used as a directing group was reported by Yu et al. for alkane dehydrogenation with stoichiometric amounts of Pd: Giri, R.; Maugel, N.; Foxman, B. M.; Yu, J.-Q. *Organometallics* **2008**, *27*, 1667. Pd-catalyzed C−H arylation of an Ile substrate equipped with this TBS protected auxiliary gave a considerably lower yield (~30%) under the same reaction conditions due to partial deprotection of the TBS group.

(20) Mono-Boc protected **40** is much less reactive for the C−H arylation with Ile **31** (<10%).

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