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Synthesis of Potent Bicyclic Bisarylimidazole c-Jun N-Terminal Kinase Inhibitors by Catalytic C−H Bond Activation

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The privileged bisarylimidazole framework is found in a variety of potent kinase inhibitors, some of which have entered clinical trials. Bicyclic bisarylimidazole derivatives, such as the c-jun N-terminal kinase 3 (JNK3) inhibitor **1** (Figure 1),[1] have recently been developed to enhance affinity and particularly selectivity, which remains a key challenge in kinase inhibitor drug discovery efforts.

Bicyclic bisarylimidazole inhibitors, exemplified by inhibitor **1**, represent challenging synthetic targets. Indeed, the synthesis of **1** required 14 linear steps and was accomplished in less than 6% overall yield.[1] Herein, we report an efficient asymmetric synthesis of **1** in 11 linear steps and 13% overall yield with the key bicyclic imidazole core generated through catalytic C−H bond functionalization. We also successfully incorporated substituents in the C7 and C8 positions, substitution patterns difficult to access by the previously reported synthetic route, and in doing so observed the first examples of diastereocontrol in metal-catalyzed C−H bond activation. Moreover, evaluation of the compounds synthesized by this route resulted in the identification of a JNK3 inhibitor even more potent than **1**.

In our retrosynthetic analysis of the bicyclic bisarylimidazole framework, we envisioned installing the C5 pyrimidine by a cross-coupling with **2** (Figure 1). Synthesis of the bicyclic imidazole core would be accomplished via rhodium-catalyzed C−H activation/annulation of **3.** A van Leusen cycloaddition could be employed to generate **3** from **4**, which can be readily prepared from commercially available starting material.

The synthesis of inhibitor **1** commenced with the condensation of (S_s)-*tert*-butanesulfinamide and commercially available *tert*-butyldimethylsiloxyacetaldehyde to provide **5** in 86% yield (Scheme 1).[2] The addition of vinylmagnesium bromide to **5** proceeded with 91:9 dr, and after chromatography the major diastereomer was obtained in 69% yield. Acidic cleavage of the silyl and *tert*-butanesulfinyl groups provided **6** in nearly quantitative yield.[2] Condensation of **6** with glyoxylic acid followed by treatment with 4-fluorophenyl tosylmethyl isonitrile[3] generated the desired enantiomerically pure imidazole in 92% yield.[4] Protection of the resulting primary alcohol as a *tert*-butyl diphenyl silyl (TBDPS) ether provided **7** in 98% yield.

Owing to the steric hindrance introduced by the C6 substituent, forcing conditions were required to achieve good conversion in the C−H activation/annulation step. Ultimately, cyclization of **7** was accomplished by using 5% $[RhCl(coe)_2]_2$ and 15% PCy_3 to generate the active catalyst with 5% $MgBr_2$ as an additive and toluene as solvent at 180 °C to provide **8** in 50% yield and with 92% ee

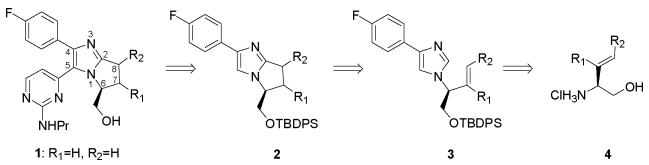
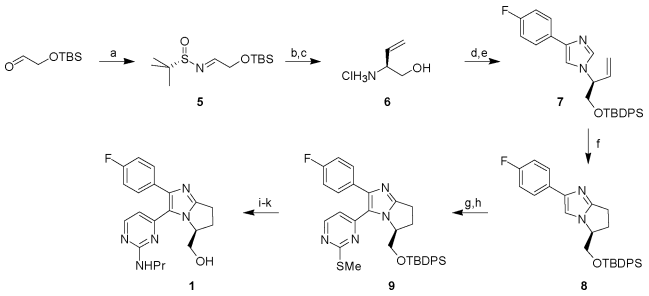


Figure 1. Retrosynthesis of bicyclic bisarylimidazole kinase inhibitors.

Scheme 1. Synthesis of Inhibitor **1**



Conditions: (a) (S_S)-*tert*-butanesulfinamide, $CuSO_4$, CH_2Cl_2, 86%; (b) vinylmagnesium bromide, CH_2Cl_2, 0 °C to room temp, 69% (single diastereomer); (c) 4 N HCl, CH_3OH, 99%; (d) 4-fluorophenyl tosylmethyl isonitrile,[3] glyoxylic acid, K_2CO_3, DMF, 92%; (e) TBDPSCl, iPr_2EtN, DMAP, CH_2Cl_2, 98%; (f) $[RhCl(coe)_2]_2$, PCy_3, $MgBr_2$, toluene, 180 °C, 50%, 92% ee; (g) Br_2, CH_2Cl_2, −78 °C, 94%; (h) 2-methylthio-4-trimethylstannylpyrimidine,[6] $Pd_2(dba)_3$·$CHCl_3$, PPh_3, LiCl, CuI, dioxane, 170 °C, 85%; (i) OXONE, THF, H_2O, 79%; (j) propylamine, 78%; (k) Bu_4NF, THF, 100%.

(Scheme 1).[5] Olefin isomerization and reduction products were also isolated in 11% and 6% yield, respectively. Competitive olefin isomerization has been shown to occur under these conditions and is likely responsible for the minor erosion of enantiomeric excess observed during the cyclization.[5c]

Treatment of **8** with Br_2 resulted in bromination of the imidazole ring at the C5 position in 94% yield. The resulting bromide was subjected to Stille cross coupling conditions in the presence of 2-methylthio-4-trimethylstannylpyrimidine[6] to provide **9** in 85% yield (Scheme 1).[7] The requisite amine was generated by oxidation of the thioether to the sulfone (79% yield) followed by the addition of propylamine (78% yield). Quantitative Bu_4NF cleavage of the silyl ether provided **1** in 13% overall yield.

To demonstrate the flexibility of our synthetic approach toward bicyclic bisarylimidazole systems and to explore diastereocontrol in the C−H activation/annulation step, we generated derivatives of **1** containing methyl substituents at the C7 or C8 positions. By employing isopropenylmagnesium bromide in place of vinylmagnesium bromide in the previously described sequence, we were poised to generate a derivative with a C7 methyl substituent

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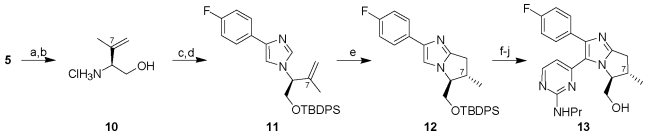
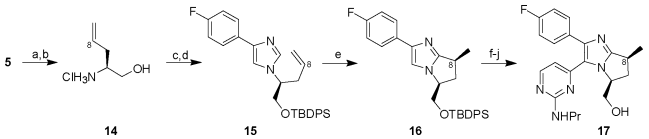
Scheme 2. Synthesis of C7 Methyl Bicyclic Bisarylimidazole Derivative



Conditions: (a) isopropenylmagnesium bromide, CH_2Cl_2, −78 °C to room temp, 90% (single diastereomer); (b) 4 N HCl, CH_3OH, 96%; (c) 4-fluorophenyl tosylmethyl isonitrile,[3] glyoxylic acid, K_2CO_3, DMF; (d) TBDPSCl, *i*Pr_2EtN, DMAP, CH_2Cl_2, 86% (over two steps); (e) $[RhCl(coe)_2]_2$, PCy_3, $MgBr_2$, toluene, 180 °C, 61%, 3:1 dr, 98% ee; (f) Br_2, CH_2Cl_2, −78 °C, 96%; (g) 2-methylthio-4-trimethylstannylpyrimidine,[6] $Pd_2(dba)_3$·$CHCl_3$, PPh_3, LiCl, CuI, dioxane, 170 °C, 66%; (h) OXONE, THF, H_2O, 77% (single diastereomer); (i) propylamine, 93%; (j) TBAF, THF, 87%.

Scheme 3. Synthesis of C8 Methyl Bicyclic Bisarylimidazole Derivative



Conditions: (a) allylmagnesium bromide, CH_2Cl_2, −78 °C to room temp, 92% (single diastereomer); (b) 4 N HCl, CH_3OH, 94%; (c) 4-fluorophenyl tosylmethyl isonitrile,[3] glyoxylic acid, K_2CO_3, DMF; (d) TBDPSCl, *i*Pr_2NEt, DMAP, CH_2Cl_2, 78% (over two steps); (e) $[RhCl(coe)_2]_2$, PCy_3, $MgBr_2$, toluene, 180 °C, 52%, 92% ee; (f) Br_2, CH_2Cl_2, −78 °C, 80%; (g) 2-methylthio-4-trimethylstannylpyrimidine,[6] $Pd_2(dba)_3$·$CHCl_3$, PPh_3, LiCl, CuI, dioxane, 170 °C, 84%; (h) OXONE, THF, H_2O; (i) propylamine, 91% (over two steps); (j) TBAF, THF, 99%.

(Scheme 2). The sequence proceeded smoothly with excellent yields and selectivity for the generation of enantiomerically pure **11** (74% from **5**).

Treatment of **11** with the previously described rhodium-catalyzed C−H activation/annulation conditions resulted in the formation of **12** in 61% yield as a 3:1 mixture of inseparable diastereomers (Scheme 2).[5] The tetrasubstituted olefin isomerization and olefin reduction products also were isolated in 24% and 3% yields, respectively. For operational simplicity the diastereomers were separated at a later stage in the synthesis.

Bromination of **12** proceeded in 96% yield, and subsequent Stille cross-coupling installed the requisite arene at the C5 position in 66% yield (Scheme 2).[7] Oxidative sulfone formation proceeded in quantitative yield and enabled separation of the diastereomeric mixture by silica gel chromatography. Sulfone displacement and silyl ether cleavage then provided the C7 methyl derivative **13** in 15% overall yield from the commercially available *tert*-butyldimethylsiloxy-acetaldehyde.

The C8 methyl derivative was generated in a similar fashion (Scheme 3). The addition of allylmagnesium bromide to imine **5** proceeded with excellent yield and selectivity. Subsequent transformations generated enantiomerically pure **15** in excellent overall yield (67% from **5**). Treatment of **15** with $[RhCl(coe)_2]_2$ in the presence of PCy_3 and $MgBr_2$ at 180 °C provided the bicyclic imidazole core with 86:14 dr and enabled the isolation of **16** as a single diastereomer in 52% yield with 92% ee (Scheme 3).[5] Consistent with previous studies, olefin isomerization to the internal disubstituted position occurs prior to annulation.[5c] Completion of the synthesis was accomplished by bromination of **16**, Stille cross-coupling[7] to install the pyrimidine, oxidation and formal nucleophilic displacement of the resulting sulfone, and silyl ether cleavage to provide **17** (61% from **16**). The overall yield for the preparation of the C8 methyl derivative **17** from the common aldehyde starting material was 18%.

Table 1. Inhibition of c-Jun N-Terminal Kinase 3

inhibitor	IC_{50} (nM) [a,b]	inhibitor	IC_{50} (nM) [a,b]
1	5.38 (±1.40)		
13	5.29 (±1.25)	*ent*-**13**	1.63 (±0.34)
17	4.85 (±0.54)	*ent*-**17**	8.10 (±1.82)

[a] Homogeneous time-resolved fluorescence assay performed in quadruplicate. [b] IC_{50} values confirmed using standard radioactivity assay (see Supporting Information).

The ability of compounds **13** and **17**, and their enantiomers *ent*-**13** and *ent*-**17**[8] prepared by employing (R_S)-*tert*-butanesulfinamide in the previously described synthetic sequences, to inhibit JNK3 were determined (Table 1). While potency comparable to **1** was observed for **13**, **17,** and *ent*-**17**, a 3- to 4-fold increase in potency was observed for *ent*-**13**.

In summary, we have developed an efficient and flexible synthetic route for the generation of the potent kinase inhibitor **1** with the key transformation being intramolecular alkylation via rhodium-catalyzed C−H bond activation. By utilizing this intramolecular alkylation, our approach easily allows introduction of substituents at the C7 and C8 positions, derivatives that would be much more difficult to access by the previously published route to **1**. Determination of the selectivity profiles of the synthesized analogues and preparation of even more potent compounds are in progress.

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Supporting Information Available: Complete experimental details and spectral data for all compounds described; complete ref 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Researchers at Easai had previously demonstrated that *ent*-**1** had inhibitory activity comparable to that of **1**.[1]

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