# Negishi Cross-Coupling Reaction as a Route to Isocombretastatins

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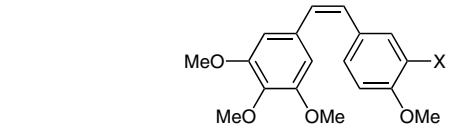
**Abstract:** A series of isocombretastatins A has been synthesized by a new method based on the Negishi cross-coupling reaction in 19–84% yields. Five of the synthesized compounds exhibit high cytotoxic activity in nanomolar concentrations ($IC_{50}$ = 1–100 nM) towards Jurkat, K562, Colo357, and A549 cell lines.

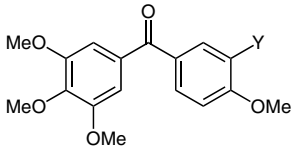
**Key words:** isocombretastatins, antitubulin agents, turbo Grignard reagent, Negishi cross-coupling, cytotoxicity

Microtubules are dynamic proteins composed of tubulin and are an attractive pharmacological target for anticancer drugs.[1] Combretastatins (Figure 1) belong to the family of the most potent antitubulin agents whose phosphate and ammonium salts are currently undergoing clinical trials.[2] Despite the remarkable therapeutic activity, (*Z*)-stilbenes are characterized by high tendency to double-bond isomerization during handling and storage leading to *E*-isomers, that dramatically reduces their activity.[3,4] The phenstatins (bisarylketones) exhibit high potency as tubulin polymerization inhibitors which are not prone to isomerization (Figure 1).[5] The high antitumor activity of their 1,1-diarylethene analogues (Figure 1) was found during the past several years.[6] In contrast to their natural parent combretastatins, isocombretastatins A (isoCA) can be synthesized without the necessity of the double-bond geometry control. They do not suffer from the potential *E*/*Z* isomerization and, in terms of structure–activity relationship, they show that the optimal bridge length between two aromatic pharmacophores is not necessarily two atoms like in natural combretastatins.[6] Notably, isocombretastatins A display the similar order of tubulin polymerization inhibitory activity in comparison with the best representatives of the combretastatin family.[6,7]

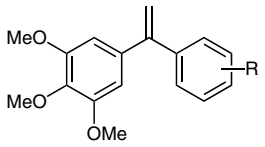
There is a number of reported synthetic routes to isocombretastatins using the Wittig reaction,[6a,8] cross-coupling of Grignard reagents[9] and arylboronic acids[10] with alkenyl halides or phosphates, the palladium-catalyzed coupling of *N*-tosylhydrazone with aryl halides[11] or triflates,[6b] nucleophilic addition of aryllitium or magnesium reagents to




CA-4 X = OH
CA4P X = $OP(O)(ONa)_2$
AVE8062 X = NH-Ser




phenstatin Y = OH
phenstatin phosphate Y = $P(O)(ONa)_2$




isocombretastatins A

**Figure 1** Structure of combretastatins and their analogues

acetophenone derivatives[12] or to Weinreb amides[13] and subsequent transformation of obtained tertiary alcohols, the regioselective hydrostannation of terminal arylalkynes and further Stille reaction or sequential iodolysis–Negishi coupling.[14]

Previously, we developed a mild and stereoselective method for synthesizing CA-4 analogues using Negishi cross-coupling.[15] This approach has been extended in the current report for the preparation of isoCA via the sequence of a three-step, one-pot reaction, using palladium-mediated cross-coupling of alkenylzinc reagents with different aryl halides (Scheme 1). The proposed method provides access to various 1,1-diarylethenes bearing different substitution patterns.

In terms of structure–activity relationship, the 3,4,5-trimethoxyphenyl fragment of antitubulin ligands appears to be critical for efficient colchicine-site binding.[16] Therefore the proposed methodology is based on the preparation of an organometallic reagent bearing a trimethoxyphenyl fragment. Such an approach afforded the desired cross-coupling products using different types of aryl halides without the synthesis of a number of organometallic compounds. The corresponding aryl-substituted terminal alkyne **2** was prepared from commercially available 3,4,5-trimethoxybenzaldehyde (**1**) via Corey–Fuchs alkyne synthesis.[17] The reaction of arylacetylene **2** with B-Br-9-BBN afforded poor yield of the desired α-bromostyrene, because of cleaving the methyl aryl ether.

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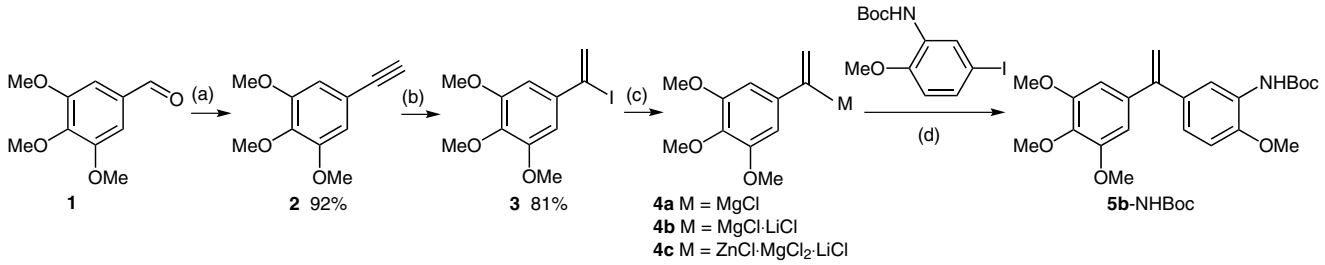
The regiochemical control of the hydrostannation of terminal arylalkynes reported by Alami[14] requires the *para*-π-electron-withdrawing or *ortho*-directing groups. The transformation of arylacetylene **2** to halostyrene **3** was best achieved by α-selective Ni-catalyzed hydroalumination followed by iodination reaction, according to the method proposed by Hoveyda et al.[18] (Scheme 1). Hydroalumination of arylacetylene **2** proceeds with a strong preference for α-vinylaluminum species in the presence of 2 mol% Ni(dppe)$Cl_2$ (Scheme 1). α-Iodostyrene **3**[20] was synthesized in 75% overall yield. Compound **3** was converted into the corresponding alkenylmagnesium derivatives **4a** and **4b** by the exchange reactions with *i*-PrMgCl or turbo Grignard reagent (*i*-PrMgCl·LiCl) under mild conditions (–20 °C, 20 min, Scheme 1).[15,19] Alkenylmagnesium derivative **4b** was treated with 1 M $ZnCl_2$ solution in THF at –20 °C over one minute to give organozinc reagent **4c** (Scheme 1). Organometallic reagents **4a**–**c** were used in Kumada or Negishi cross-coupling reactions with the corresponding aryl iodides or bromides in the presence of palladium catalysts. A number of palladium complexes was tested during the optimization of cross-coupling reactions with Boc-protected 3-amino-4-methoxyphenyl iodide (Table 1). Only trace amounts of the desired product **5b**-NHBoc were achieved by Kumada cross-coupling with organomagnesium reagent **4a** in the presence of SPhosPd$(OAc)_2$ (Table 1, entry 6). The reaction using Grignard reagent **4b** give the product **5b**-NHBoc in 41% yield in the presence of the same catalyst (Table 1, entry 11). The highest yield of 1,1-diarylethene **5b**-NHBoc was achieved by Negishi cross-coupling reaction of alkenylzinc reagent **4c** with the corresponding aryl iodide catalyzed by SPhosPd$(OAc)_2$ in THF at room temperature (76%, Table 1, entry 14).

Using these optimized conditions a range of isocombretastatins **5a**–**k**,[21] containing the donor and acceptor aromatic fragments, as well as heteroaromatic moieties, was synthesized in good yields 58–84% (Table 2). Isocombretastatins containing the *N*-acetylphenyl group (**5f** and **5g**) were isolated in modest yields 19–26% (Table 2). In vitro cytotoxicity of the synthesized compounds **5a**–**k** was investigated toward Jurkat, K562, Colo357, and A549 cell lines. The obtained data are summarized in Table 2. Some synthesized compounds (**5a**–**e**) manifest high antiproliferative activity in nanomolar range of concentrations ($IC_{50}$ = 1–100 nM).

In conclusion we have developed an efficient synthesis to isocombretastatins A, using palladium-mediated Negishi cross-coupling reaction of α-alkenylzinc reagents with different aryl halides. The proposed route permits to synthesize isoCA analogues in good yield via the sequence of three-step, one-pot reactions. Several prepared compounds possess promising cytotoxic properties.




**Scheme 1** Synthetic methodology to isocombretastatins A. *Reagents and conditions*: (a) $CBr_4$ (1.5 equiv), $Ph_3P$ (3 equiv), $CH_2Cl_2$, 0 °C, 2.5 h, 93%; BuLi (3.6 equiv, 2.5 M solution in hexane), THF, –78 °C, 2 h, 99%; (b) DIBAL-H (2 equiv), Ni(dppe)$Cl_2$ (2 mol%), THF, r.t., 2 h; $I_2$, THF, –78 °C, 1.5 h, 81%; (c) *i*-PrMgCl (2 M solution in THF) or *i*-PrMgCl·LiCl (0.97 M solution in THF), –20 °C, 20 min; $ZnCl_2$ (1 M solution in THF), –20 °C, 1 min; (d) aryl iodide (1 equiv), palladium complex (4 mol%), r.t., 24 h.

**Table 1** Cross-Coupling Optimization

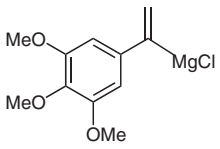
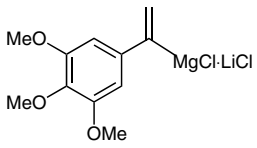
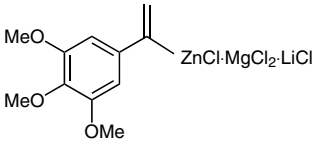
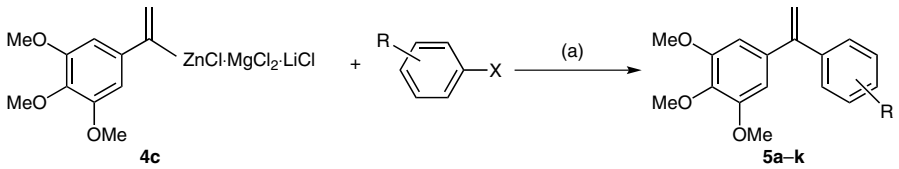
| Entry | Organometallic reagent | Solvent | Catalyst | Yield (%) |
|---|---|---|---|---|
| 1 |  | THF | $(A^{ta}\text{-Phos})_2PdCl_2$ | 0 |
| 2 | | | $Pd(Ph_3P)_4$ | 0 |
| 3 | | | DPE-Phos$Pd_2(dba)_3$ | 0 |
| 4 | | | SPhos$Pd_2(dba)_3$ | 0 |
| 5 | | | DPE-PhosPd$(OAc)_2$ | 0 |
| 6 | | | SPhosPd$(OAc)_2$ | 4 |
| 7 |  | THF + NMP | $Fe(acac)_3$ | 0 |
| 8 | | DME | $Fe(acac)_3$ | 0 |
| 9 | | THF | $(A^{ta}\text{-Phos})_2PdCl_2$ | 0 |
| 10 | | THF | $Pd(Ph_3P)_4$ | 0 |
| 11 | | THF | SPhosPd$(OAc)_2$ | 41 |
| 12 |  | THF | $(A^{ta}\text{-Phos})_2PdCl_2$ | 0 |
| 13 | | | $Pd(Ph_3P)_4$ | 15 |
| 14 | | | SPhosPd$(OAc)_2$ | 76 |

**Table 2** Yields and Cytotoxicity of Isocombretastatins[a]



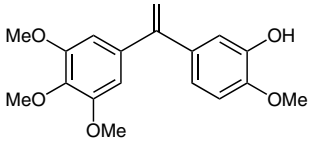
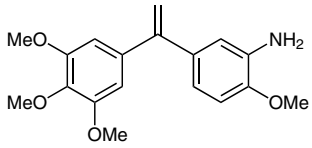
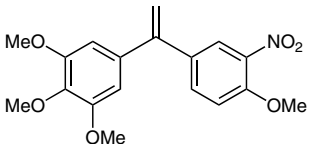
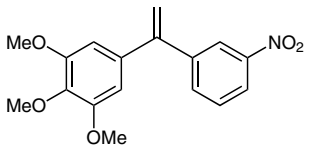
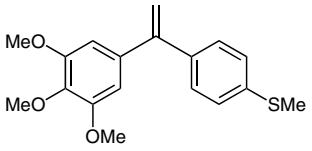
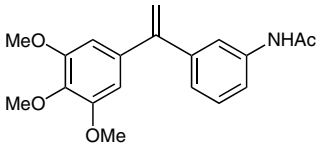
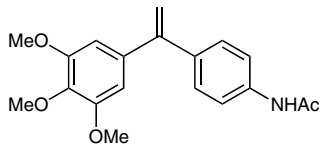
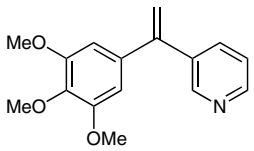
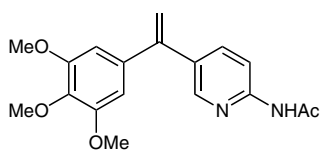
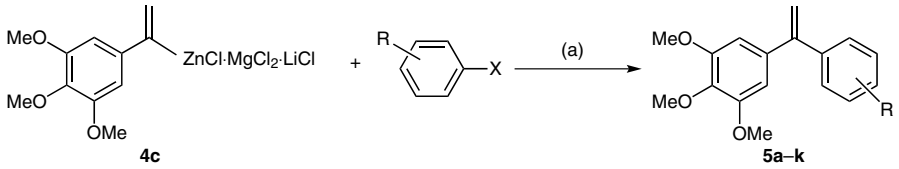
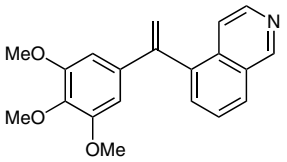
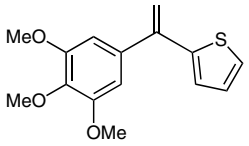

| Product | | Yield (%) | $IC_{50}$ (μM) Jurkat | K562 | Colo357 | A549 |
|---|---|---|---|---|---|---|
| **5a**[b] |  | 79[d] | 0.005 | 0.005 | 10 | 0.1 |
| **5b**[c] |  | 71[d] | 0.005 | 0.005 | 0.005 | 0.01 |
| **5c** |  | 81 | 0.1 | >1 | 0.001 | 0.1 |
| **5d** |  | 66 | >10 | >1 | 0.01 | 0.1 |
| **5e** |  | 84 | 0.5 | >1 | 0.3 | >40 |
| **5f** |  | 19 | >10 | >1 | 5 | >0.1 |
| **5g** |  | 26 | >10 | >1 | >10 | >10 |
| **5h** |  | 63 | >10 | >1 | 10 | 10 |
| **5i** |  | 71 | >10 | >1 | >10 | >10 |



**Table 2** Yields and Cytotoxicity of Isocombretastatins[a] (continued)




| Product | | Yield (%) | $IC_{50}$ (μM) | | | |
|---|---|---|---|---|---|---|
| | | | Jurkat | K562 | Colo357 | A549 |
| **5j** |  | 60 | >10 | >1 | >10 | >10 |
| **5k** |  | 58 | >10 | >1 | >50 | >50 |

[a] Cross-coupling conditions: aryl halides (1 equiv), $Pd(OAc)_2$ (4 mol%), SPhos (6 mol%), THF, r.t., 1–10 h.
[b] At the stage of the cross-coupling reaction the phenolic group was protected as MOM ether.
[c] At the stage of the cross-coupling reaction free amino group was protected as Boc amide.
[d] Overall yield for isocombretastatin preparation including the stage of protecting-group cleavage.

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(20) **Synthesis of 1-Iodo-1-(3′,4′,5′-trimethoxyphenyl)-ethylene (3)**

$Ph_3P$ (7.86 g, 30 mmol) was added to a solution of $CBr_4$ (4.98 g, 15 mmol) in $CH_2Cl_2$ (60 mL) at 0 °C under argon atmosphere. The resulting solution was stirred at 0 °C for 25 min. 3,4,5-Trimethoxybenzaldehyde (1.96 g, 10 mmol) in $CH_2Cl_2$ (20 mL) was added dropwise. The solution was stirred at 0 °C for 1.5 h. The solvent was removed under reduced pressure, and the resulting oil was purified by column chromatography on silica gel (PE–EtOAc, 4:1) to give 1,1-dibromo-2-(3′,4′,5′-trimethoxyphenyl)ethylene (3.27 g, 9.3 mmol, 93%) as pale yellow crystals. 1,1-Dibromo-2-(3′,4′,5′-trimethoxyphenyl)ethylene (3 g, 8.52 mmol) was dissolved in THF (30 mL) and cooled to –78 °C. *n*-BuLi (12.9 mL, 32.38 mmol, 2.5 M in hexane) was added dropwise for 30 min. The solution was stirred at –78 °C for 2 h. Then sat. $NH_4Cl$ (20 mL) was added, and the solution was warmed to r.t. The solution was extracted with EtOAc, the combined organic layers were washed with brine, dried over $Na_2SO_4$, then concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (PE–EtOAc, 3:1) to give **2** (1.63 g, 8.43 mmol, 99%) as a white solid. Ni(dppe)$Cl_2$ (24 mg, 0.046 mmol) was placed in a dry argon-flushed Schlenk flask equipped with a stir bar and sealed with a septum. THF (5 mL) was added through a syringe, followed by dropwise addition of DIBAL-H (4.18 mL, 1 M solution in toluene, 4.18 mmol) at r.t. (gas evolution occurs as DIBAL-H is added). The resulting solution was cooled to 0 °C and 3,4,5-trimethoxyphenyl-acetylene (445 mg, 2.32 mmol) in THF (4 mL) was added slowly. The resulting black solution was allowed to warm to r.t. and stirred for 2 h. A solution of $I_2$ in THF (5 mL, 1.768 g, 6.96 mmol) was added into the hydroalumination reaction mixture at –78 °C. The resulting dark brown solution was stirred for 1.5 h. Then a sat. solution of sodium potassium tartrate (10 mL) was added to the reaction mixture, followed by stirring for 10 min at r.t. The organic layer was separated, and the aqueous layer was extracted with MeO*t*-Bu, the combined organic layers were washed with brine, dried over $Na_2SO_4$, then concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (PE–EtOAc, 8:1) to give **3** (602 mg, 1.88 mmol, 81%) as light yellow oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 6.72 (s, 2 H), 6.39 (d, *J* = 1.7 Hz, 1 H), 6.02 (d, *J* = 1.7 Hz, 1 H), 3.87 (s, 6 H), 3.84 (s, 3 H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ = 152.56, 138.66, 137.49, 126.95, 107.24, 105.63, 60.96, 56.25.

(21) **Preparation of 5a-OMOM (Typical Procedure)**

A dry argon-flushed Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with a solution of 1-iodo-1-(3′,4′,5′-trimethoxyphenyl)ethylene (**3**, 48 mg, 0.15 mmol) in dry THF (1.5 mL). The solution of *i*-PrMgCl·LiCl (0.17 mL of 0.97 M solution in THF, 0.165 mmol) was added slowly at –20 °C, and the reaction mixture was stirred at this temperature for 20 min to complete the I–Mg exchange. A 1 M solution of $ZnCl_2$ (0.15 mL of 1 M solution in THF, 0.15 mmol) was added dropwise for 1 min at –20 °C, and the reaction mixture was warmed to r.t. 3-(Methoxymethoxy)-4-methoxyphenyl iodide (44 mg, 0.15 mmol) was placed in a round-bottom flask under argon. Solution of $Pd(OAc)_2$ (1.35 mg, 0.006 mmol) and SPhos (3.7 mg, 0.009 mmol) in THF (1 mL) was added, followed by dropwise addition of prepared solution of organozinc reagent (0.15 mmol) over a period of 1 min at r.t. The reaction mixture was stirred at r.t. for 5 h, poured into sat. aq $NH_4Cl$ solution and extracted with EtOAc. The organic layer was washed with brine, dried over $Na_2SO_4$, concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (PE–EtOAc, 5:1) to give **5a**-OMOM (44 mg, 0.122 mmol, 81%) as brown oil. $^1$H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 2.0 Hz, 1 H), 6.98 (dd, *J* = 8.4, 2.0 Hz, 1 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 6.56 (s, 2 H), 5.38 (s, 1 H), 5.34 (s, 1 H), 5.21 (s, 2 H), 3.90 (s, 3 H), 3.87 (s, 3 H), 3.81 (s, 6 H), 3.50 (s, 3 H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ = 153.00, 152.92, 149.88, 149.45, 145.97, 137.30, 134.12, 122.85, 116.87, 112.96, 111.34, 105.74, 95.68, 61.02, 56.36, 56.22, 56.02.



 