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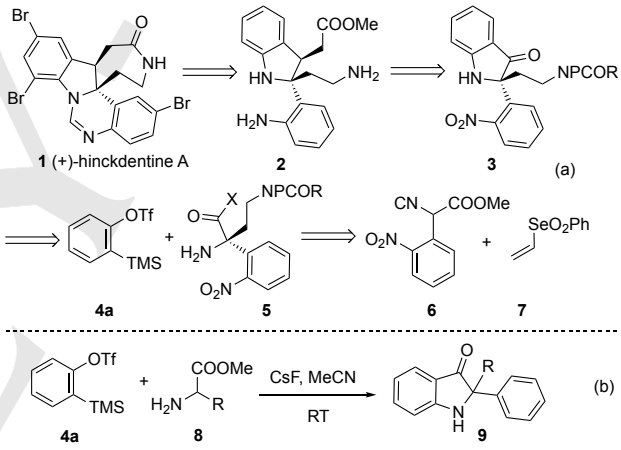
# Heteroannulation of Arynes with α-Amino Imides: Synthesis of 2,2-Disubstituted Indolin-3-ones and Application to the Enantioselective Total Synthesis of (+)-Hinckdentine A

Rubén O. Torres-Ochoa, Thomas Buyck, Qian Wang and Jieping Zhu*

**Abstract:** *A novel heteroannulation reaction between the α-amino imides and the in situ generated arynes has been developed for the synthesis of the 2,2-disubstituted indolin-3-ones. An enantioselective total synthesis of the marine alkaloid (+)-hinckdentine A was subsequently accomplished featuring this reaction as a key step. A catalytic enantioselective Michael addition of an α-aryl-α-isocyanoacetate to phenyl vinyl selenone was employed for the construction of the enantioenriched α-quaternary α-amino ester.*

**H**inckdentine A (**1**, Scheme 1) was isolated by Blackman, Taylor and co-workers from the bryozoan *Hincksinoflustra denticulata*, collected from Tasmanian eastern coast.[1] The structure, unambiguously determined by single crystal X-ray analysis, is characterized by a unique brominated indolo[1,2-*c*]quinazoline and a hexahydroazepin-2-one motif. The bioactivity of this natural product has not been examined due to its extremely low availability (isolation yield: 0.0005%). Nonetheless, the presence of indoline, azepinone and pyrimidine motifs in the same structure renders it a highly appealing compound in medicinal chemistry and an intriguing target for synthetic chemists.[2] The total synthesis of the racemic 8-desbromo analogue and the natural product itself have been achieved by the groups of McWhorter[3] and Kawasaki,[4] respectively. An elegant enantioselective synthesis of (+)-hinckdentine A, featuring a key asymmetric dearomative cyclization of functionalized *N*-acyl tetrahydrocarbazole, has recently been accomplished by Kitamura, Fukuyama and co-workers.[5]

As a continuation of our research program dealing with the total synthesis of indoline-based polycyclic natural products,[6] we became interested in (+)-hinckdentine A (**1**). Our retrosynthetic analysis is outlined in Scheme 1a. We planned to construct the pentacyclic ring system of **1** from the amino ester **2** via a sequence of amidine formation, lactamization and bromination reactions. Compound **2** could be prepared from 2,2-disubstituted indolin-3-one **3**, which was envisaged to be prepared by a formal [3+2] heteroannulation between benzyne generated *in situ* from *ortho*-(trimethylsilyl)phenyl triflate (**4a**)[7] and a suitably functionalized α,α-disubstituted α-amino acid derivative **5**.[8-9] The latter could in turn be synthesized by an organocatalytic enantioselective Michael addition of methyl α-isocyano acetate **6** to phenyl vinyl selenone (**7**).[10] Critical to the success of this synthesis would rely on the one step synthesis of the indolin-3-one **3** from **4a** and **5**. The incorporation of this strategic step into the synthesis was inspired by the work of Okuma who reported the synthesis of **9** by reaction of the α-monosubstituted amino ester **8** with 2 equivalents of **4a** (Scheme 1b).[11-12] We report herein the difficulties encountered in our attempted heteroannulation between **4a** and **5**, the subsequent development of a new heteroannulation protocol and its implementation in the realization of an enantioselective total synthesis of (+)-hinckdentine A (**1**).




**Scheme 1.** Hinckdentine A and retro-synthetic analysis.

We began our synthesis by investigating the heteroannulation between **4a** and racemic α,α-disubstituted α-amino ester **5a** (Scheme 2a).[13] The reaction afforded, under Okuma's conditions, the *N*-phenylated compound **10a** as a major product (76% yield) together with a small amount of the desired indolin-3-one **3a**. Systematic survey of reaction conditions by varying the fluoride sources (CsF, KF, TBAT, TBAF), the solvents (THF, dichloroethane, dioxane), the temperature and the additives (bases or crown ether) failed to improve the yield of **3a**. Suspecting that the presence of the amide NH in the side chain of **5a** could serve as a proton donor to trap the phenyl anion intermediate **11**, the *N*-2,4-dimethoxybenzyl protected amino ester **5b** was prepared and submitted to the heteroannulation with **4a**. However, *N*-phenylated product **10b** was again isolated as a major product in 65% yield. That the protonation of the anionic intermediate **11** outcompeted the desired cyclization was presumably due to the moderate electrophilicity and the steric hindrance around the neopentylic methoxycarbonyl group. Indeed, no example of α-quaternary α-amino esters was reported as coupling partner in Okuma's paper. Taking advantage of the

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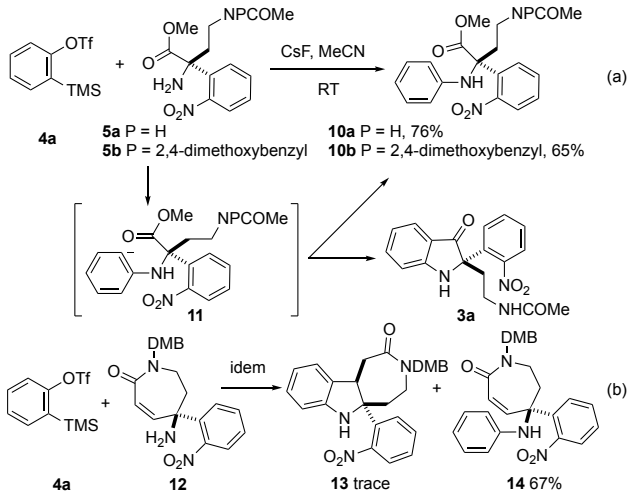
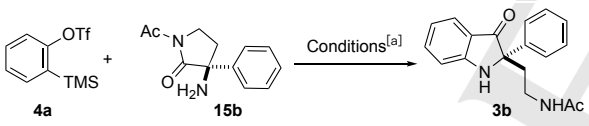
ready access to α-quaternary α-amino ester **10b**, its cyclization via intramolecular Friedel-Crafts acylation was briefly examined. Unfortunately, no cyclization of **10b** was observed in the presence of various Lewis and Brønsted acids. Alternatively, we also examined the reaction of **4a** with γ-amino-α,β-unsaturated amide **12** aiming at a one-step synthesis of tricycle **13**.[14] However, the reaction afforded once again the *N*-phenylated product **14** as a major product (67% yield) together with a trace amount of **13** (Scheme 2b).




**Scheme 2**. Initial attempts on the heteroannulation. Reaction conditions: **4a** (0.2 mmol), **5** (0.1 mmol), CsF (0.3 mmol). Abbreviation: DMB = 2,4-dimethoxybenzyl.

**Table 1**. Optimization of reaction conditions.

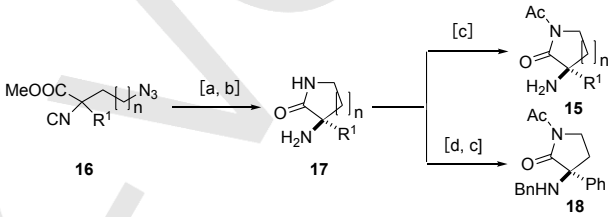



| Entry | F⁻ source | Additive | Solvent | t (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | TBAF | – | MeCN | 1 | 42 |
| 2 | KF | 18-C-6 | MeCN | 1 | 59 |
| 3[c] | CsF | – | MeCN | 24 | 54 |
| 4 | CsF | – | MeCN | 4 | 77 |
| 5 | CsF | 4Å MS | MeCN | 3 | 75 |
| 6 | CsF | $NaHCO_3$ | MeCN | 3 | 75 |
| 7 | CsF | – | DCE | 24 | 0 |
| 8 | CsF | – | THF | 24 | 0 |

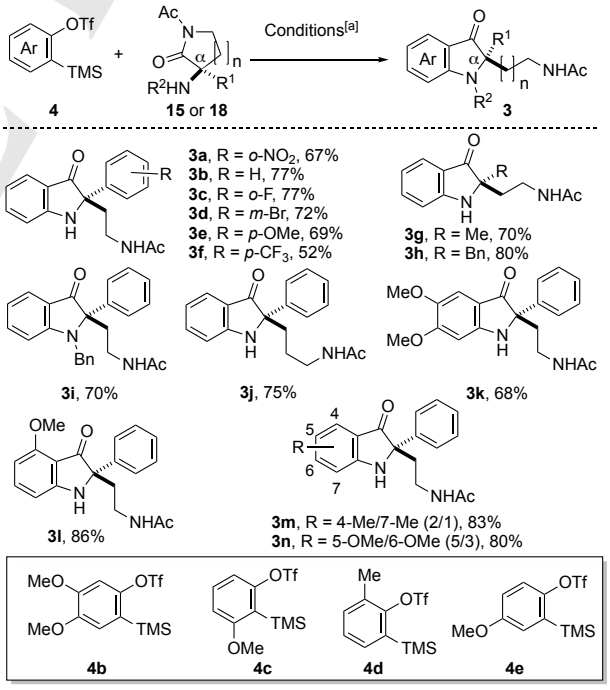
[a] Reaction conditions: **4a** (0.2 mmol), **15b** (0.1 mmol), CsF (0.3 mmol), solvent (*c* 0.085 M), RT; [b] Yields of isolated products; [c] CsF (0.2 mmol).

To drive the reaction towards the desired heteroannulation process, we thought that increasing the electrophilicity of the ester carbonyl group could be a viable option. Taking advantage of the aminoethyl side chain of compound **5**, we opted a cyclic imide function as a moderately activated form of the carboxylic acid.[15] To our delight, the formal [3+2] cycloaddition between **4a** and **15b** indeed occurred to produce the desired 2,2-disubstituted indolin-3-one **3b**. As it is seen from Table 1, the best conditions found consisted of performing the reaction in acetonitrile at room temperature in the presence of CsF (3.0 equiv, entry 4). Under these conditions, compound **3b** was isolated in 77% yield. The dramatic reactivity difference between α-amino esters **5** and α-amino imide **15b** indicated that the outcome of the heteroannulation reaction is highly sensitive to the subtle electrophilicity differences of the carbonyl groups.

In light of the importance of the indoxyl structure in natural products,[16] its application as building blocks in organic synthesis[17] and fluorescent dyes,[18] we set out to examine the generality of this heteroannulation protocol. The synthesis of imides is depicted in Scheme 3. Hydrolysis of the isocyano group in **16** followed by reductive lactamization of the ω-azido ester under the Staudinger conditions afforded lactam **17**. Chemoselective acylation of the amide NH (*n*BuLi, then $Ac_2O$) furnished the desired *N*-acyl-3-aminopyrrolidin-2-ones **15** (n = 1) in good to excellent overall yields from **16**.[13] The 1-acetyl-3-amino-3-phenylpiperidin-2-one (**15j**, $R^1$ = Ph, n = 2) was similarly synthesized. On the other hand, reductive *N*-alkylation of **17a** ($R^1$ = Ph, n = 1) with benzaldehyde followed by imide formation afforded **18**.




**Scheme 3**. Synthesis of *N*-acyl 3-aminopyrrolidin-2-ones **15** and **18**. [a] HCl in MeOH, RT; [b] $PPh_3$, $THF/H_2O$, 70 °C; [c] *n*BuLi, $Ac_2O$, THF, -78 °C; [d] PhCHO, $MgSO_4$, DCM, 0 °C to RT, then $NaBH_4$, MeOH, 0 °C.

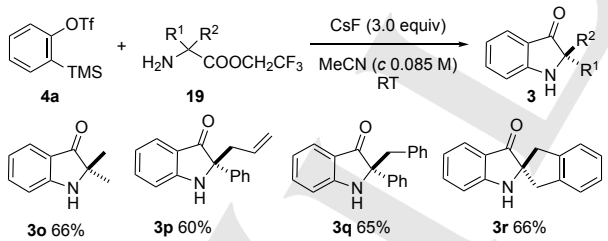



**Scheme 4**. Scope of the heteroannulation reaction between **4** and **15** or **18**. Reaction conditions: **4** (0.2 mmol), **15** or **18** (0.1 mmol), CsF (0.3 mmol), MeCN (*c* 0.085 M), RT.

The scope of the heteroannulation reaction was next examined (Scheme 4). For the α-amino imides, aromatic substituents ($R^1$) bearing the electron donating (MeO) or

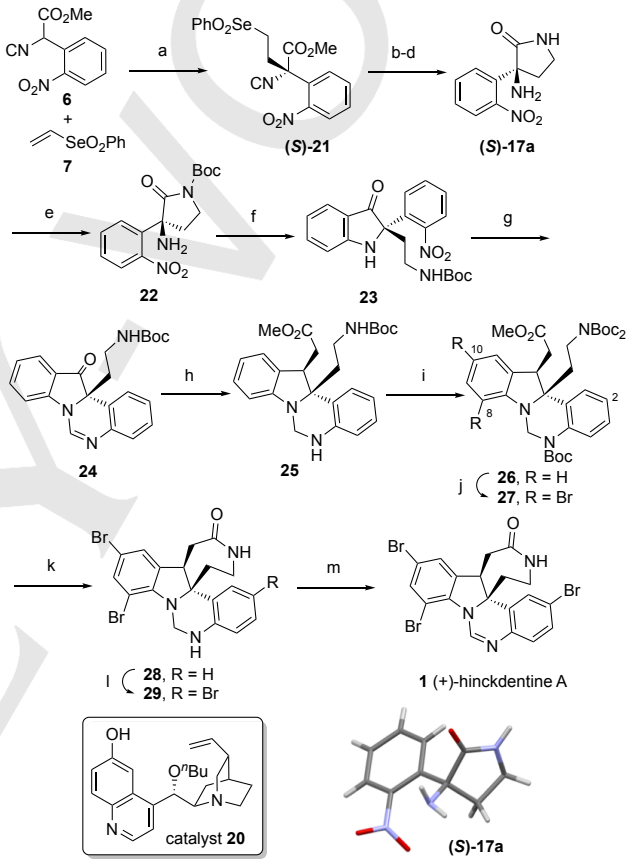
withdrawing groups ($NO_2$, F, Br, $CF_3$) as well as the alkyl substituents ($R^1$ = Me, Bn) at the Cα position of **15** were compatible with the reaction conditions to afford the corresponding 2,2-disubstituted indolin-3-ones in good to high yields (**3a**-**3h**). Secondary amine **18** participated in the reaction to furnish **3i** in 70% yield. Pleasingly, 1-acetyl-3-amino-3-phenylpiperidin-2-one (**15j**, $R^1$ = Ph, n = 2) underwent annulation efficiently with benzyne to afford the C2-aminopropyl substituted indolinone **3j** in 75% yield. Reaction of 4,5-dimethoxy-2-(trimethylsilyl)phenyl triflate (**4b**) with **15b** afforded **3k** without event. Interestingly, the reaction of 3-methoxy-2-(trimethylsilyl)phenyl triflate **4c** with **15b** afforded 4-methoxy indolin-3-one **3l** as a single regioisomer in 86% yield.[8] By inductive effect, the MeO group can stabilize the neighbouring phenyl anion intermediate contributing therefore, together with steric effect, to the observed regioselectivity. In line with this reasoning, the reaction involving 6-methyl-2-(trimethylsilyl)phenyl triflate (**4d**) afforded 4- and 7-methyl indolin-3-ones **3m** in a 2/1 ratio in 83% yield. Similarly, 5-methoxy and 6-methoxy indolin-3-ones **3n** were formed in a 5/3 ratio from 4-methoxy-2-(trimethylsilyl)phenyl triflate (**4e**). The lack of the regioselectivity in these cases is inherent to the benzyne-based annulation reaction.

A remarkable feature of the new protocol is that it allows direct access to the aminoethyl or aminopropyl substituted indolin-3-ones, found in many bioactive compounds.[16] While the incorporation of the versatile amino group in a side chain is highly beneficial, this is also a limitation of the methodology. To further extend the general applicability of our approach, we decided to examine other moderately activated carboxylic acid derivatives that were compatible with the presence of an unprotected α-amino group. This is highly challenging since the activated α-amino esters are known to undergo facile dimerization to afford the 2,5-diketopiperazines.[19] Gratefully, it was found that the trifluoroethyl ester **19** served well for this purpose. As it is shown in Scheme 5, reaction of **4a** with **19**[13] under standard conditions afforded the corresponding indolin-3-ones **3o-3r** in good yields. It's worth noting that the diketopiperazine formation was not observed in all these examples.




**Scheme 5**. Heteroannulation of trifluoroethyl α-amino esters.

Enantioselective total synthesis of (+)-hinckdentine A featuring this heteroannulation reaction as a key step is shown in Scheme 6. Catalytic asymmetric Michael addition of methyl α-(2-nitrophenyl)-α-isocyanoacetate (**6**) to phenyl vinyl selenone (**7**) in the presence of a quinidine-derived bifunctional catalyst **20** (0.1 equiv) afforded (*S*)-**21** in excellent yield with moderate *ee*.[20] Nucleophilic substitution of the selenonyl group by azide followed by hydrolysis of the isocyano to the amino group and Staudinger reduction/cyclization converted (*S*)-**21** to pyrrolidinone (*S*)-**17a** in good overall yield with an e.r. of 98.5:1.5 after recrystallization ($CH_2Cl_2$/petroleum ether). The absolute configuration of (*S*)-**17a** was confirmed by single crystal X-ray diffraction analysis.[21] Conversion of (*S*)-**17a** to the *N*-Boc imide **22** followed by its reaction with **4a** furnished indolin-3-one **23** in moderate overall yield.[22] Reduction of the nitro group followed by treatment of the resulting aniline with methyl orthoformate in the presence of AcOH afforded tetracycle **24**. The Wittig reaction of **25** followed by 1,4-reduction of the resulting enoate with magnesium in MeOH[23] provided the desired amino ester **25** (d.r. = 10:1) which, after *N*-protection furnished **26.**




**Scheme 6**. Total synthesis of (+)-hinckdentine A. [a] **20** (0.1 equiv), toluene, 4 Å M.S., -20 °C, 95%, e.r. 82:18; [b] $NaN_3$ (1.5 equiv), DMF, 40 °C; [c] HCl in MeOH, RT, 1 h; [d] $PPh_3$ (1.1 equiv), THF/$H_2O$ (v/v = 99:1), 70 °C, 53% overall yield from (*S*)-**21**; [e] $Boc_2O$ (1.75 equiv), DMAP (0.15 equiv), THF, RT; [f] **4a** (2.0 equiv), CsF (2.0 equiv), MeCN, RT, 38% from (*S*)-**17a**; [g] Raney nickel, $H_2$, MeOH, RT then AcOH (3.0 equiv), $HC(OMe)_3$, RT, 83%; [h] methyl (triphenylphosphoranylidene)acetate (5.0 equiv), toluene, reflux then Mg (10.0 equiv), MeOH, RT, 52%; [i] $Boc_2O$ (5.0 equiv), KHMDS (2.5 equiv), toluene, 0 °C then RT, 83%; [j] NBS (2.7 equiv), DMF, 0 °C then RT, 75%; [k] $CH_2Cl_2$/TFA (v/v = 2:3), RT, then $K_2CO_3$ (18.0 equiv), MeOH, RT, 91%; [l] $nBu_4NBr_3$ (1.0 equiv), DMF, 0 °C, quantitative; [m] TPAP (0.2 equiv), NMO (1.4 equiv), 0 °C, 81%. Abbreviations: NMO = *N*-methyl morpholine oxide, TPAP = tetrapropylammonium perruthenate.

The selective bromination of **26** turned out to be challenging in accordance with previous observations.[3-5] After having screened different reagents and conditions, we achieved the synthesis of the C8, C10-dibrominated compound **27** in 75% yield by performing the bromination of **26** in DMF at 0 °C using NBS (2.7 equiv) as brominating reagent. All efforts on the tribromination of **26** failed at this stage.

Removal of *N*-Boc groups from **27** followed by a base promoted lactamization afforded pentacycle **28** in 91% yield. Selective C2-bromination of **28** was again a difficult task. After many unsuccessful trials, we were able to realize this transformation in a quantitative yield by performing the reaction in DMF at 0 °C using tetrabutylammonium tribromide as a mild brominating reagent. Finally, oxidation of amine to imine (NMO, TPAP) afforded (+)-hinckdentine A (**1**) in 81% yield {$[\alpha]_D$ + 269 (*c* 1.0, $CHCl_3$), lit:[5] $[\alpha]_D$ + 274 (*c* 2.0, $CHCl_3$)}. The physical and spectroscopic data of our synthetic compound were identical to those reported for the natural product.

In summary, we have developed a new heteroannulation reaction of α-amino imides with arynes for the synthesis of α,α-disubstituted indolin-3-ones. An enantioselective total synthesis of (+)-hinckdentine A (**1**) featuring this reaction as a key step was subsequently developed demonstrating the high synthetic potential of this methodology.

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**Keywords:** Benzyne • heteroannulation • hinckdentine A • natural product • oxindole

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[20] The reaction catalyzed by the quinine-derived catalyst, a pseudoenantiomer of **20**, afforded (*R*)-**21** with higher e.r. (93.5:6.5).

[21] CCDC1812863 (*S*)-**17a** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[22] Insoluble materials were formed in this heteroannulation reaction. Similar phenomenon was observed with the trifluoroacetyl imide derivative of (*S*)-**17a**.

[23] R. Brettle, S. M. Shibib, *J. Chem. Soc. Perkin Trans. 1* **1981**, 2912.

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**Entry for the Table of Contents** (Please choose one layout)

Layout 1:

***Natural Product Synthesis***

*Rubén O. Torres-Ochoa, Thomas Buyck, Qian Wang and Jieping Zhu**_____

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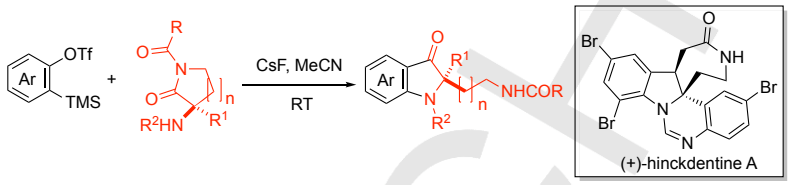
**Heteroannulation of Arynes with α-Amino Imides: Synthesis of 2,2-Disubstituted Indolin-3-ones and Application to the Enantioselective Total Synthesis of (+)-Hinckdentine A**




*Reaction of α-amino imides with the in situ generated arynes afforded the 2,2-disubstituted indolin-3-ones in good to excellent yields. The reaction was implemented as a key step in a concise enantioselective total synthesis of (+)-hinckdentine A, a halogenated marine natural product.*