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Advanced Synthesis & Catalysis

One-pot Synthesis of Isoquinoline-Fused Isoquinolines via Intramolecular Hydroamination/Aza-Claisen Type Rearrangement Cascade

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Abstract: A one-pot, two-step synthesis of isoquinoline-fused isoquinolines from α-amino acid esters and 2-alkynyl benzaldehydes are reported. The strategy comprises an unconventional Pictet-Spengler reaction between α-amino acid esters and 2-alkynyl benzaldehydes to give isoquinoline intermediates. Subsequent gold-catalyzed intramolecular hydroamination furnishes isoquinoline-fused isoquinolines. The scope of this strategy is further extended to prepare multisubstituted isoquinoline-fused isoquinolines via subjecting the N-allylated isoquinoline intermediates to gold-catalyzed intramolecular hydroamination followed by aza-Claisen type rearrangement.

Keywords: aza claisen-type rearrangement; hydroaminati-on; isoquinoline-fused isoquinolines

Introduction

The past decade has witnessed a paradigm shift in the drug design process. The inadequacy of the traditional single-target drug approach to treat modern complex diseases led to the development of multi-target drugs.[1] This feat could be achieved by coalescing two different privileged chimeric cores into a single scaffold.[2] In view of that, various combinations of fused-heterocyclic frameworks are under development.[3]

The intramolecular hydroamination reaction is an efficient synthetic method for the synthesis of interesting heterocycles whereby the addition of nucleophilic –NH group to C–C triple bond is carried out. Gold-based catalysts as the carbophilic π-acid are proved to be promising and effective in carrying out intramolecular hydroamination reactions of alkynes. Several groups have reported a gold-catalyzed transformation for the synthesis of 1,2-dihydroquinolines,[4] indole-1-carboxamides,[5] azepines,[6] isoindolines and isoquinolines,[7] indoles,[8] pyrrolidines.[9] and tetrahydroisoquinolines.[10]

Tetrahydroisoquinoline and 1,2-dihydroisoquinoline are privileged scaffolds frequently found in various alkaloids and pharmaceutical agents with a broad spectrum of bioactivities.[11–14] Besides that a molecular framework that combines isoquinoline moiety with other pharmacophores units shows interesting pharmacological and material properties. For example, Berberine is an alkaloid found in *Coptis chinensis* plant and is used for the treatment of diabetes (Figure 1).[15]

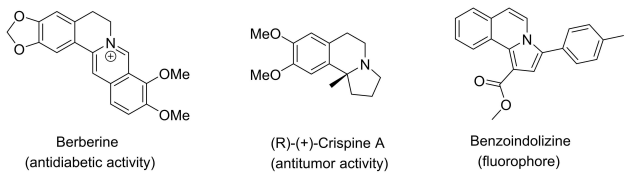


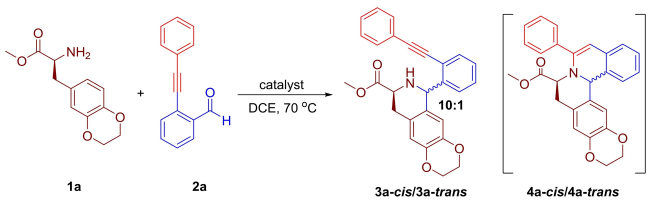
Figure 1. Biologically active 1,2,3,4-tetrahydro isoquinoline-fused heterocycles.

Pyrrolo-fused isoquinoline alkaloid, (+)-Crispine A is obtained from *Clathrus crispus* and exhibits cytotoxic activity against HeLa human cancer cells.[16] Whereas, benzoindolizine is a π-conjugated isoquinoline-fused pyrrole that displays fluorescence and is effectively used for biological imaging.[17] Recently, Cheng and co-workers reported the preparation of isoquinoline-fused triazines through iodine- and base-mediated [3+3] cycloaddition by hydrazide and α-halohydroxamate.[18] Larock et al. synthesized isoquinoline-fused indolines and pyrroles via copper-catalyzed tandem reaction between o-haloarylalkynes and indoles/pyrroles.[19] Lately, synthesis of isoquinoline-fused benzimidazoles from 2-alkynylbenzaldehydes and o-phenylenediamines /aliphatic amines was reported by Mishra.[19] Similarly, Ouyang also developed the synthesis of isoquinoline-fused benzimidazoles using copper-catalyzed electrophilic cyclization of 2-ethynylbenzaldehydes with *o*-benzenediamines.[20] In 2016, Ausekle reported a one-pot synthesis of isoquinoline-fused indoles/pyrroles from 1-bromo-2-(2,2-difluorovinyl)benzenes and indoles/pyrroles through intramolecular Pd-catalyzed C–H arylation.[21] Kumar et al. prepared isoquinoline-fused pyridines via Knoevenagel/Michael/cyclization reactions.[22] Wang and co-workers synthesized isoquinoline-fused triazepines using [4+3] annulation of cyclic azomethine imines with propargylic carbamates.[23] To the best of our knowledge, there is no report on the synthesis of isoquinoline-fused isoquinoline scaffold. Inspired by the worthiness of isoquinoline-fused heterocycles in terms of their usefulness in various fields, we herein report a one-pot/two-step synthesis of isoquinoline-fused isoquinolines through an unconventional Pictet-Spengler reaction followed by an intramolecular hydroamination/aza-Claisen-type reaction cascade.

Results and Discussion

Initially, various 2-alkynyl benzaldehydes **2** were prepared from 2-bromobenzaldehydes and alkynes by Sonogashira conditions.[24] We commenced current studies with methyl (*S*)-2-amino-3-(3,4-dimethoxyphenyl)propanoate **1a** and 2-(phenylethynyl) benzaldehyde **2a** as a model substrate to explore the possible reaction for the one-pot, two-step synthesis of methyl (8*S*)-6-phenyl-9,12,13,15b-tetrahydro-8*H*-[1,4]dioxino[2,3-*g*]isoquinolino[1,2-*a*]isoquinoline-8-carboxylate **4a** (Scheme 1).

In view of that, we aimed at the recognization of the suitable metal catalysts which could assist a difficult Pictet-Spengler reaction and subsequent intramolecular hydroamination consecutively. Accordingly, when **1a** and **2a** was reacted in the presence of various silver catalysts such as $AgNO_2$, Ag_2O, AgOTf and $AgSbF_6$, no desired product was obtained and the less reactive L-3,4-dihydroxyphenylalanine methyl ester was recovered. Also, gold catalysts such as AuCl (10 mol%) and $AuCl_3$ (10 mol%)[26] were ineffective to catalyze this reaction and afforded either gold-alkyne complex or Pictet-Spengler product **3a** in poor yield. When TFA (20 equiv.) was used as a single catalyst, only Pictet-Spengler product **3a** was yielded in 83% yield. As the sole catalysts failed to initiate the one-pot cascade reaction, a dual catalytic system was tested. For that reason, one equivalent of TFA in combination with AuCl (10 mol%) was employed in the reaction, and no any product was observed. No desired product was observed despite increasing the TFA to 10 equivalents in the same reaction. Next, the combination of $BF_3.OEt_2$ (1 equiv.) with AuCl (10 mol%) afforded Pictet-Spengler product **3a** in 68% yield. When the same reaction was carried out at 55 °C in the presence of $BF_3.OEt_2$ only, the yield of **3a** was increased to 73% (**3a-*cis*** : **3a-*trans*** = 10:1). Consequently, neither a single catalyst nor a combination of catalysts proved to be useful in promoting this transformation. Nonetheless, it was found that the Pictet-Spengler reaction between **1a** and **2a** could be smoothly carried out with one equivalent of $BF_3.OEt_2$ at 55 °C for 16 h in 1,2-dichloroethane (DCE). We next explored optimization for the intramolecular hydroamination of **3a-*cis***, a major product of Pictet-Spengler reaction. Accordingly, the use of silver catalysts such as $AgNO_3$ and AgOTf yielded the desired product in only a trace amount with the recovery of starting materials. When the silver catalyst was replaced by the gold catalyst like $AuCl_3$, the desired product methyl (6*S*)-2,3-dimethoxy-8-phenyl-5,13*b*-dihydro-6*H*-isoquinolino[1,2-*a*]isoquinoline-6-carboxylate **4a-*cis*** was obtained in 27% yield. Proton NMR of **4a-*cis*** showed characteristic singlet peaks corresponding to H_a proton



Scheme 1. One-pot synthesis of isoquinolino[1,2-*a*] isoquinoline **4a**.

at 5.14 ppm and H_b proton at 6.68 ppm respectively. The **4a-*cis*** was further confirmed by X-crystallographic study (Figure 2).[27]

When AuCl was used under the same conditions, the yield of **4a-*cis*** was increased to 85%. Finally, lowering the reaction temperature to 25 °C drastically increased the yield of the desired product **4a-*cis*** to 93%. It is worth noting that when **3a-*trans*** was subjected to identical reaction condition, the rate of the reaction was slower than its *cis* isomer and the **4a-*trans*** was obtained in 16 h. Mechanistically, AuCl activates the C–C triple bond of **3a** by coordination and 6-*endo-dig* nucleophilic attack of the nitrogen atom is performed and subsequent removal of the catalyst gives cyclized product **4**.

We next attempted the whole reaction sequences in a two-step one-pot way. Therefore, **1a** and **2a** were reacted in the presence of $BF_3.OEt_2$ (1 equiv.) in DCE at 55 °C for 16 h. After the generation of Pictet-Spengler products *in situ*, AuCl (10 mol%) was added and the reaction mixture was stirred at room temperature for 8 h to obtain **4a-*cis*/4a-*trans*** (10:1) in 73% yield.

Next, the substrate scope of this two-step, one-pot cascade reaction for the synthesis of isoquinolino[1,2-*a*]isoquinolines **4** was investigated (Table 1). Various 2-alkynyl benzaldehydes **2** were successfully participated in the reaction and all the products were obtained in good yield. Under the standard reaction conditions, heterocyclic 2-alkynyl benzaldehydes also worked well to yield major products (**4b-*cis***, **4e-*cis***, **4f-*cis***, **4h-*cis***, **4k-*cis*** and **4n-*cis***) in good yield. However, the **3t-*cis*** and **3u-*cis*** prepared from 2- (phenylethynyl)furan-3-carbaldehyde and 2-(phenylethynyl)thiophene-3-carbaldehyde failed to undergo hydroamination to afford **4t-*cis*** and **4u-*cis***. The transformation of **3v-*cis*** bearing trimethylsilyl group into **4v-*cis*** encumbered the steric hindrance. Compound **3w-*cis*** having 2-ethynylphenyl moiety did not afford cyclized product **4w-*cis*** probably due to the formation of a gold acetylide complex which blocked further cyclization. The presence of either electron-donating (**4f-*cis***, **4g-*cis***, **4h-*cis***, **4k-*cis***, **4l-*cis***, **4n-*cis***, **4p-*cis***, **4r-*cis*** and **4s-*cis***) or withdrawing groups (**4c-*cis***, **4d-*cis*** and **4o-*cis***) on the aryl ring (R^3) did not have much influence on the product formation.

The scope of the current strategy is then further extended for the synthesis of multi-substituted isoquinoline-fused isoquinolines. Accordingly, **3a-*cis*** was alkylated with allyl bromide in the presence of K_2CO_3 to obtain **5a-*cis***. At the outset of our study of the aza-Claisen-type rearrangement reaction, we screened various metal catalysts, additives and solvents and the results are summarized in Table 2. Initially, the use of metal catalysts such as $InCl_3$, $AgSbF_6$, AgOTf, $AuCl_3$ and AuCl did not afford the desired product **6a-*cis*** and the starting material was recovered (Table 2, entries 1–7). The use of 1,2-bis(diphenylphosphino)benzene (dppBz) as a ligand in the same reaction was ineffective (Table 2, entries 8–9). The screening of various solvents for the AuCl catalyzed reaction failed to yield the cyclized product (Table 2, entries 10–14). Switching the use of gold salt to gold complex (PPh_3)AuCl (10 mol%) in the reaction was futile (Table 2, entry 15). Pleasingly, when the reaction was carried out in the presence of (PPh_3)AuCl (100 mol%) in 1,2-dichloroethane at 70 °C for 16 h, a new product was obtained in 37% yield with unreacted starting material **3a-*cis*** (Table 2, entry 16).

The use of (PPh_3)AuCl (10 mol%)/Ag_2CO_3 combination did not yield the **6a-*cis*** product (Table 2, entry 17). Next, (PPh_3)AuCl was tested with a combination of silver salts $AgOCOCF_3$/$AgNTf_2$, and we observed only slight increase in the yield (40%) (Table 2, entries 18–19). We then tested the same reaction in different solvents; however, the yield was improved to merely 45% in CH_3CN (Table 2, entries 20–23). Switching the gold complex (PPh_3)AuCl/silver salt combination to PPh_3AuNTf_2 afforded **6a-*cis*** in 40% yield (Table 2, entries 24). Decreasing the reaction temperature from 70 °C to 25 °C led to product formation in 55% yield (Table 2, entries 25). The efficiency of metal-catalyzed reaction was diminished in toluene (Table 2, entries 26). The product **6a-*cis*** was obtained in excellent yield in acetonitrile (Table 2, entries 27). Finally, the utilization of a double amount of PPh_3AuNTf_2 (20 mol%) at 25 °C in CH_3CN for 12 h afforded the desired product **6a-*cis*** in 87% isolated yield (Table 2, entries 28).

With optimized conditions in hand, we next investigated the substrate scope of aza-Claisen-type rearrangement (Table 3). Substrates bearing either electron withdrawing or donating group (R^2) on the phenyl ring afforded corresponding products (**6e**, **6f** and **6g**) in excellent yields. Gratifyingly, substrates functionalized with substituted allyl group undergo a smooth cyclization and prenyl group transformation to give products **6d**, **6e**, and **6f** in good yield. The functionalization of the allyl chain has impact on the distereoselectivity.

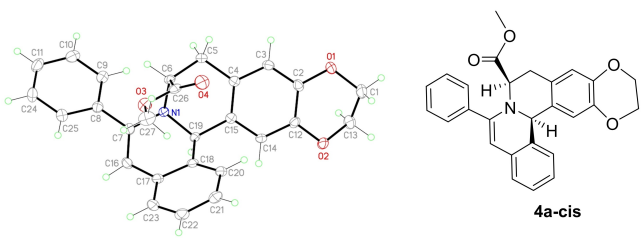
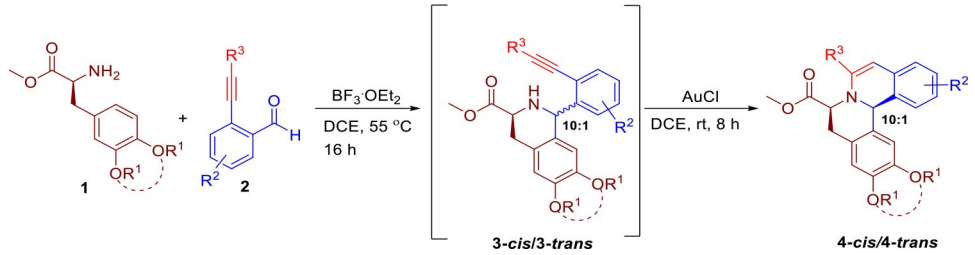
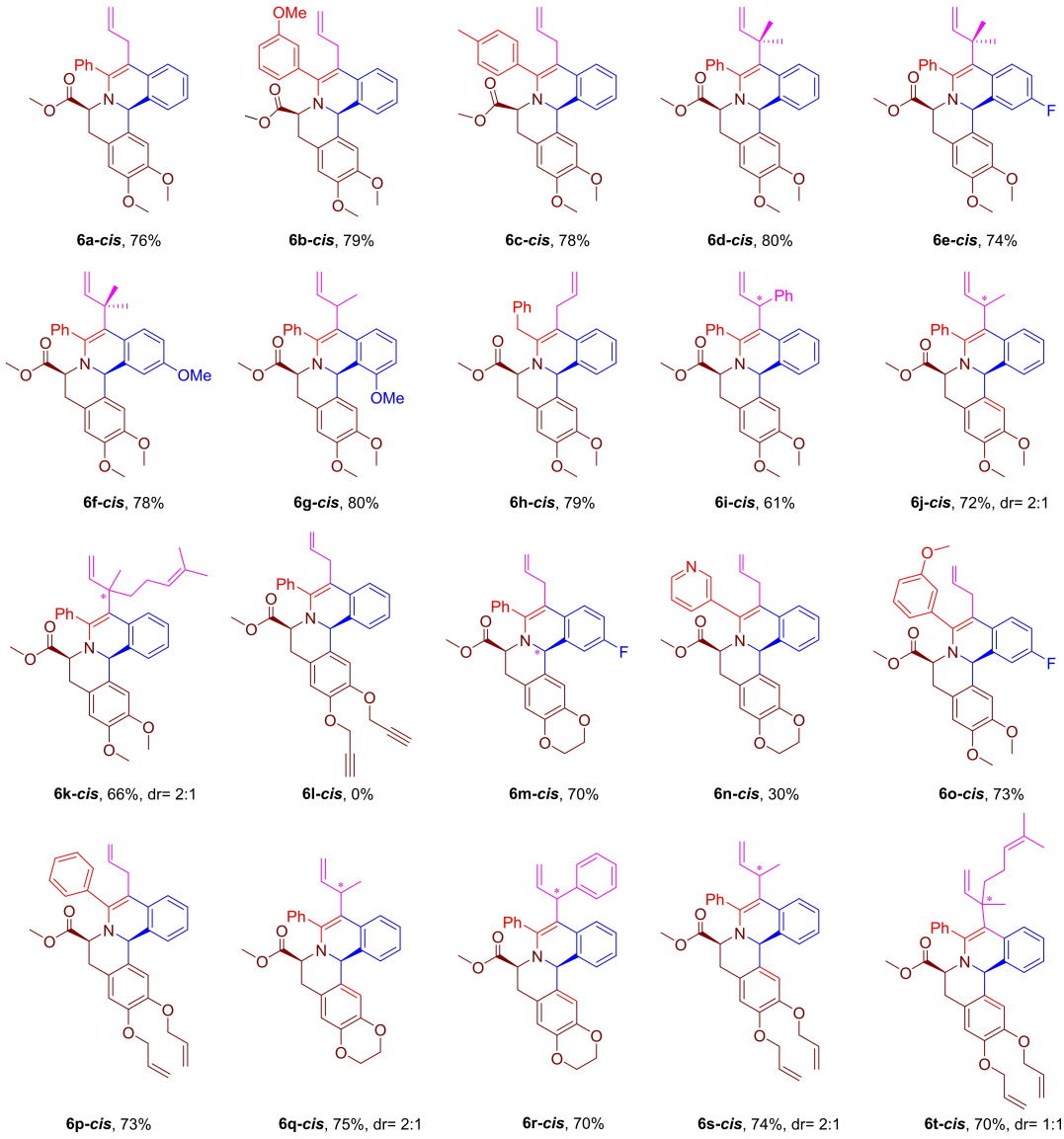


Figure 2. ORTEP diagram of **4a-*cis***.

Table 1. Substrate scope for the synthesis of isoquinolino[1,2-a]isoquinolines **4**.[a]

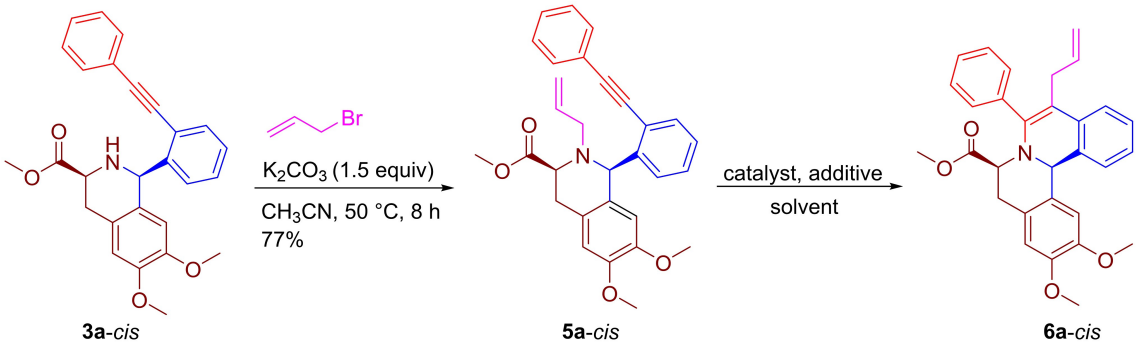




[a] Reaction conditions: Step 1: **1** (1 equiv.), **2** (1 equiv.), $BF_3.OEt_2$ (1 equiv.), MS 4 Å, DCE (10 mL), 55 °C, 16 h. Step 2: AuCl (10 mol%), DCE (15 mL), 8 h.

Accordingly, the substrates **5i-*cis*** and **5r-*cis*** alkylated with cinnamyl chloride furnished **6i-*cis*** and **6r-*cis*** as a single diastereomer. The stereochemistry of **6i-*cis***, as a representative example was confirmed by X-ray crystallographic study[27] (Figure 3). On the other hand, the reaction of **5j-*cis*** and **5k-*cis*** yielded **6j-*cis*** and **6k-*cis*** in 2:1 distereomeric ratio with an efficient migration of the crotyl and neryl groups. The

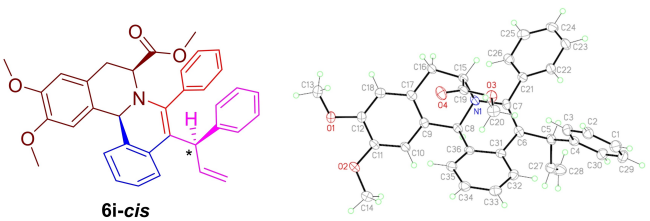
Table 2. Optimization of reaction conditions for the synthesis of **6a-*cis***.[a]



3a-*cis* **5a-*cis*** **6a-*cis***

Entry	Catalyst (mol%)	Additive	Solvent	Temp (°C)	Yield[b]
1	$InCl_3$ (10)	–	DCE	reflux	–
2	$AgSbF_6$ (10)	–	DCE	70	–
3	AgOTf (10)	–	DCE	70	–
4	$AuCl_3$ (10)	–	DCE	70	–
5	AuCl (5)	–	DCE	50	–
6	AuCl (5)	–	DCE	reflux	–
7	AuCl (10)	–	DCE	70	–
8	AuCl (5)	dppBz	DCE	50	–
9	AuCl (5)	dppBz	DCE	reflux	–
10	AuCl (5)	–	CH_2Cl_2	reflux	–
11	AuCl (5)	–	CH_3CN	70	–
12	AuCl (5)	–	toluene	80	–
13	AuCl (5)	–	THF	reflux	–
14	AuCl (5)	–	$CHCl_3$	50	–
15	$(PPh_3)AuCl$ (10)	–	DCE	70	–
16	$(PPh_3)AuCl$ (100)	–	DCE	70	37
17	$(PPh_3)AuCl$ (10)	Ag_2CO_3	DCE	70	–
18	$(PPh_3)AuCl$ (10)	$AgOCOCF_3$	DCE	70	–
19	$(PPh_3)AuCl$ (10)	$AgNTf_2$	DCE	70	40
20	$(PPh_3)AuCl$ (10)	$AgNTf_2$	CH_2Cl_2	reflux	22
21	$(PPh_3)AuCl$ (10)	$AgNTf_2$	toluene	90	40
22	$(PPh_3)AuCl$ (10)	$AgNTf_2$	CH_3CN	70	45
23	$(PPh_3)AuCl$ (10)	$AgNTf_2$	DMF	reflux	–
24	PPh_3AuNTf_2 (10)	–	DCE	70	40
25	PPh_3AuNTf_2 (10)	–	DCE	25	55
26	PPh_3AuNTf_2 (10)	–	toluene	25	12
27	PPh_3AuNTf_2 (10)	–	CH_3CN	25	85
28[b]	PPh_3AuNTf_2 (20)	–	CH_3CN	25	**87**

[a] Reaction conditions: **5a-*cis*** (1 equiv.), catalyst (20 mol%), additive (10 mol%), MS 4 Å, solvent (15 mL), 16 h.
[b] Reaction was stirred for 12 h.



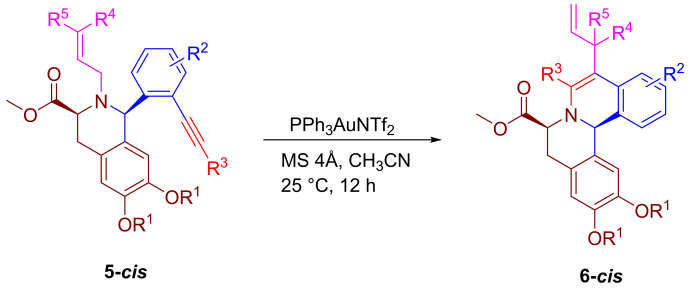
6i-*cis*
one single diastereomer

Figure 3. ORTEP diagram of **6i-*cis*** (Atomic displacement ellipsoids are drawn at the 50% probability level).

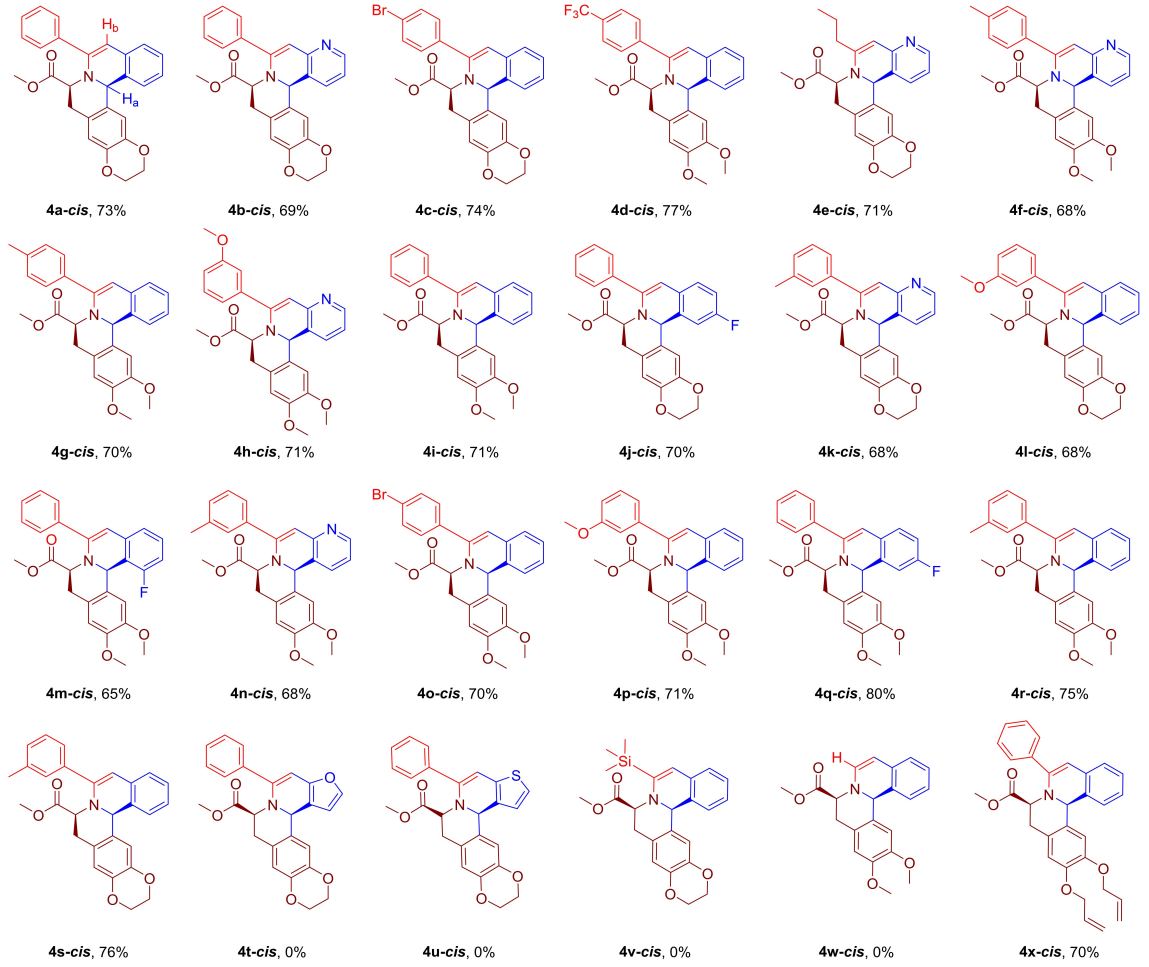
difference in outcome could be attributed to the steric effect of the R^5 group.

The presence of the bulky phenyl substituent in **6i-*cis*** and **6r-*cis*** allowed a complete stereocontrol, whereas sterically less demanding CH_3- and alkyl chain led to diastereomeric mixture (**6q-*cis***, **6s-*cis***, **6t-*cis***). Aza-claisen-type rearrangement of intermediate **6i-*cis*** could form two diastereomers, **9i-*cis*-A** and **9i-*cis*-B**. Molecular modeling revealed that there is a possible steric crowding present in the intermediate **9i-*cis*-B** owing to the presence of a sterically demanding

Table 3. Substrate scope for the synthesis of **6-*cis***.[a]



5-*cis* **6-*cis***



[a] Reaction conditions: **5a**-*cis* (1 equiv.), catalyst (20 mol%), MS 4 Å, solvent (15 mL), 16 h.
[b] Reaction was stirred for 12 h.

phenyl group on the allyl chain and the phenyl groups of attached catalyst -AuP(PPh_3). Whereas, this steric hindrance from allyl substituent is less in **9i-*cis*-A** due to the remoteness between these two bulky groups (Figure 4). We also attempted the cyclization of diastereomers **5-*trans***. Notably, substrates **5a**, **5p**, **5s** and **5u**, under the usual reaction conditions, gave corresponding products **6-*trans*** in good yields (Table 4).

A plausible mechanism for the gold-catalyzed synthesis of **6-*cis*** is depicted in Scheme 2. Initially, a carbophilic cationic gold catalyst coordinates to alkynyl moiety of **5-*cis***. Intramolecular nucleophilic attack of nitrogen lone pairs of **7-*cis*** on the activated C–C triple bond generates a cationic intermediate **8-*cis***. Subsequent concerted aza-Claisen-type rearrangement affords **9-*cis***.[25] Finally, **9-*cis*** undergoes deauration step to give the observed product **6-*cis***.

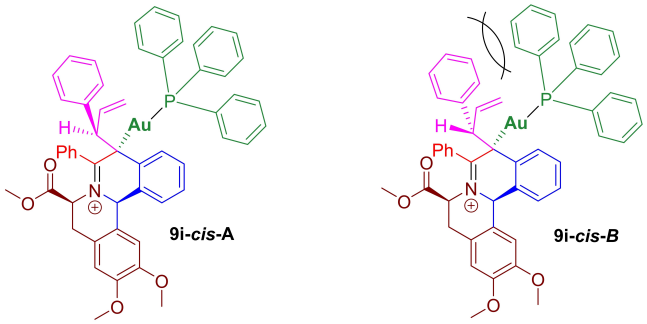
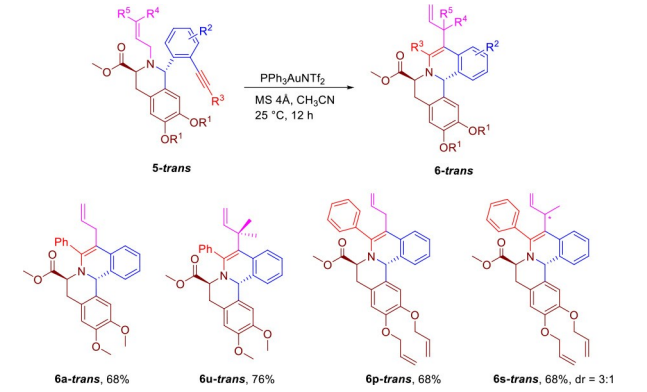
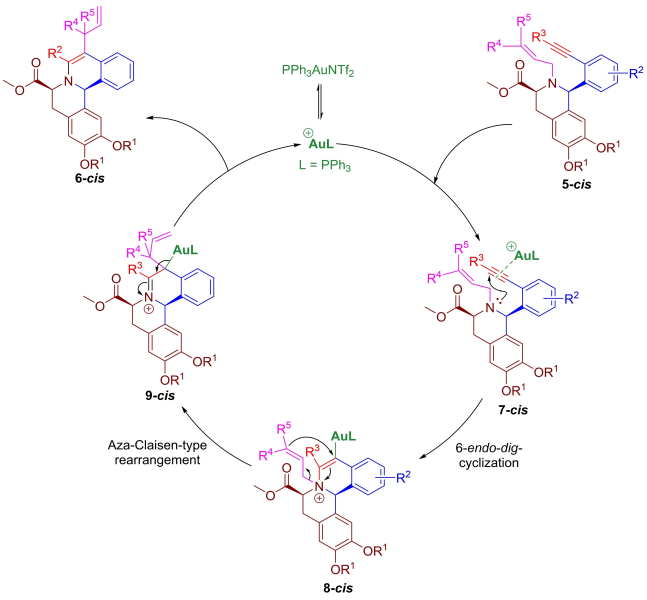


Figure 4. Diastereoselectivity in the reaction of **5i-cis**.

Table 4. Substrate scope for the synthesis of **6-*trans***.[a]



[a] Reaction conditions: **5a-*trans*** (1 equiv.), catalyst (20 mol%), MS 4 Å, solvent (15 mL), 16 h.



Scheme 2. A plausible mechanism for the synthesis of **6-*cis***.

Conclusion

In conclusion, we have demonstrated a one-pot two-step strategy for the rapid synthesis of isoquinoline-fused isoquinoline as a novel scaffold through a sequential Pictet-Spengler cyclization/intramolecular hydroamination. The process proceeds with $BF_3.OEt_2$-mediated Pictet-Spengler reaction between α-amino acids with 2-alkynyl benzaldehydes to afford tetrahydroisoquinolines as a diastereomeric mixture in 10:1 (*cis*:*trans*) ratio. The intramolecular hydroamination of *cis*-tetrahydroisoquinolines in the presence of AuCl undergoes smoothly to give isoquinoline-fused isoquinolines. The scope of this protocol is further broadened by accessing multisubstituted isoquinoline-fused isoquinolines. For that, *cis*-tetrahydroisoquinolines were allylated first and the subsequent gold-catalyzed intramolecular hydroamination/aza-Claisen type rearrangement cascade furnished the substituted isoquinoline-fused isoquinolines in good yield. The diastereoselectivity of the final product is controlled by the substitutents present on the allyl moiety. Sterically demanding phenyl group yields a single diastereomer whereas less bulky methyl or alkyl chain give distereomeric mixture of final products.

Experimental Section

General Information

^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on 400-MR automated spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard (TMS). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated Kiselgel 60 F_{254} plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230–400 mesh). High-resolution mass spectra (HRMS) were recorded in ESI mode using TOF mass spectrometer. IR spectra were recorded using a Bruker spectrophotometer. All materials were purchased from commercial sources and used without further purification.

Representative experimental Procedure for the Synthesis of Methyl (8S,15bR)-6-phenyl-9,12,13,15b-tetrahydro-8H-[1,4]dioxino[2,3-g]isoquinolino[1,2-a]isoquinoline-8-carboxylate (4a-*cis*)

To the stirred solution of methyl (*S*)-2-amino-3-(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)propanoate **1a** (63 mg, 0.265 mmol) in DCE (10 mL) was added 2-(phenylethynyl)benzaldehyde **2a** (55 mg, 0.265 mmol), 4 Å MS (70 mg) and $BF_3.OEt_2$ (38 mg, 0.265 mmol) at room temperature and the reaction was heated at 55 °C for 16 h. After completion, the reaction was then allowed to cool down to room temperature, AuCl (6 mg, 0.027 mmol) was added and the reaction was stirred for 8 h. After completion of the reaction, reaction mixture was filtered through celite bed. The filtrate was concentrated under reduced pressure. The crude residue was diluted with aq. $NaHCO_3$ (20 mL) and extracted by ethyl acetate (10 mL × 3). The organic

layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (ethyl acetate in hexanes) to obtain **4a-*cis*** as yellow solid (82 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J=8.1 Hz, 2H), 7.45–7.37 (m, 3H), 7.25–7.14 (m, 3H), 7.01 (d, J=7.4 Hz, 1H), 6.86 (d, J=2.4 Hz, 2H), 6.67 (s, 1H), 5.12 (s, 1H), 4.36–4.26 (m, 4H), 3.82 (d, J=6.1 Hz, 1H), 3.20 (dd, J=15.9, 6.1 Hz, 1H), 3.03 (d, J=15.9 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 148.6, 142.9, 141.7, 135.9, 135.7, 130.1, 129.1, 128.8, 128.3, 126.9, 126.8, 126.7, 124.4, 123.7, 123.2, 117.3, 117.2, 111.7, 64.6, 57.8, 52.8, 50.6, 30.1; HRMS (EI) m/z: $[M]^+$ Calcd for $C_{27}H_{23}NO_4$ 425.1622; Found 425.1586.

Representative Procedure for the Synthesis of Methyl (6S,13bR)-9-allyl-2,3-dimethoxy-8-phenyl-5,13b-dihydro-6H-isoquinolino[1,2-a]isoquinoline-6-carboxylate (6a-cis)

To the stirred solution of **5a-*cis*** (100 mg, 0.21 mmol) in acetonitrile (15 mL) was added 4 Å MS (70 mg) and PPh_3AuNTf_2 (7.9 mg, 0.01 mmol) and the reaction mixture was stirred at room temperature for 16 h. After the complete consumption of starting material, the solvent was removed under vacuum. The crude reside was purified by flash column chromatography (10-15% ethyl acetate in hexanes) to obtain **6a-*cis*** as red liquid (76 mg, 76%).

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.65 (d, J=7.4 Hz, 2H), 7.49–7.41 (m, 4H), 7.24 (t, J=7.4 Hz, 1H), 7.17 (t, J=7.5 Hz, 1H), 6.91 (s, 1H), 6.88 (s, 2H), 5.90 (m, 1H), 5.10 (d, J=17.2 Hz, 1H), 5.05 (s, 1H), 4.98 (d, J=10.1 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.59 (dd, J=16.5, 6.3 Hz, 1H), 3.54–3.51 (m, 1H), 3.43 (dd, J=16.6, 4.9 Hz, 1H), 2.98 (s, 1H), 2.97 (s, 1H), 2.63 (s, 3H); ^{13}C NMR (101 MHz, Acetone-d_6) δ 170.6, 148.7, 147.4, 145.5, 138.3, 136.4, 135.7, 131.1, 130.8, 128.6, 128.1, 126.1, 126.1, 125.9, 123.8, 122.5, 121.8, 118.2, 114.8, 112.5, 112.1, 57.7, 55.4, 55.1, 52.2, 49.7, 41.3, 32.4, 29.7; MS (ESI): *m/z* 468; HRMS (ESI, *m/z*) Calcd. $C_{30}H_{29}NO_4$ $[M+H]^+$: 468.2175; Found 468.2169 $(M+H)^+$.

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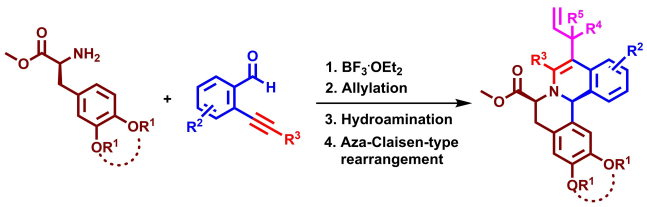
FULL PAPER

One-pot Synthesis of Isoquinoline-Fused Isoquinolines via Intramolecular Hydroamination/Aza-Claisen Type Rearrangement Cascade



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