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Metal triflate-catalyzed cyclization of arylvinylcarbinols: formal synthesis of (±)-dichroanone and (±)-taiwaniaquinone H†‡

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A formal synthesis of diterpenoids *viz.* the taiwaniaquinoids (±)-dichroanone (1a) and (±)-taiwaniaquinone H (1b) possessing an all carbon quaternary stereocenter has been reported. The key step involves a metal triflate-catalyzed cyclization of arylvinylcarbinols, prepared from β-cyclocitral. The reaction possibly follows a stepwise mechanism *via* the intermediacy of arylallyl carbocationic species.

Diterpenoids possessing a fused 6,5,6-*abeo*-abietane skeleton (**1a–e**, Fig. 1) have gained substantial interest owing to their significant biological properties and interesting architecture.[1] They are a family of carbotricyclic diterpenoids bearing an unusual 4a-methyltetra- (and hexa-) hydrofluorene skeleton. Taiwaniaquinoids are *abeo*-abietanes isolated from different East Asian conifers *viz.* the Taiwanese pine tree *Taiwania cryptomerioides*, which they were named after.[2] Recently, various merosesquiterpenes (**1f–h**) possessing similar *abeo*-abietane type cores with an additional isoprene unit have also been isolated from various sources.[3] Merosesquiterpenes containing a sesquiterpene unit joined to a phenolic (such as **1f–h**) or quinone moiety are another vital group of natural products with potential biological activities.[4] Reportedly, a few members of taiwaniaquinoids are found to exhibit potent cytotoxic activity against KB epidermoid carcinoma cancer cells,[5] and one of them, standishinal (**1e**), could be a promising candidate in breast cancer therapy due to its aromatase inhibitory potential.[6]

These biological activities together with their intriguing carbotricyclic structure make taiwaniaquinoids attractive synthetic targets, which led to the development of numerous efficient approaches. These include the synthesis by Banerjee[7] and Node[8] *via* a Pd(0)-catalyzed intramolecular Heck cyclization, a Nazarov cyclization by Trauner,[9] an enantioselective approach following a Pd(0)-catalyzed decarboxylative allylation by Stoltz,[10] an iridium-catalyzed borylation and a palladium-catalyzed asymmetric α-arylation by Hartwig,[11] a Lewis acid-promoted synthesis of a carbotricycle by Fillion,[12] a sequential cationic cyclization by Chiu,[13] a Friedel–Crafts acylation/alkylation approach by She,[14] and an intramolecular Friedel–Crafts alkylation by Alvarez-Manzaneda[15] and Majetich.[16] Recent efforts include a thermal 6π-electrocyclization,[17] a semisynthetic approach involving the cleavage of the C7–C8 double bond of abietane diterpenes by Alvarez-Manzaneda,[18] from commercially available methyl dehydroabietate by Gademann,[19] and others, to address the core carbocyclic structure.[1,20] We envisioned that a catalytic approach to the carbotricyclic core of the type **3a** (Table 1) using a metal-triflate as a Lewis acid could offer an excellent platform for the total synthesis of various taiwaniaquinoids (Fig. 1). We also reasoned that an enantioselective method can be realized using an enantioenriched ligand-accelerated Lewis acid catalyzed cyclization. Herein, we report an efficient metal triflate-catalyzed cyclization of arylvinyl carbinols of the type **2a** to give **3a** (Table 1).

We examined the cyclization of arylvinyl carbinol **2a**[21] using various metal triflates to affect the synthesis of the carbotricyclic structure of taiwaniaquinoids (Table 1). Initial attempts afforded

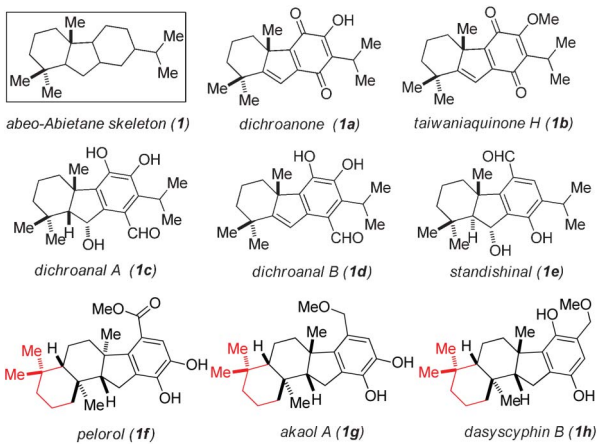

Fig. 1 Representatives of the taiwaniaquinoids and related structures.

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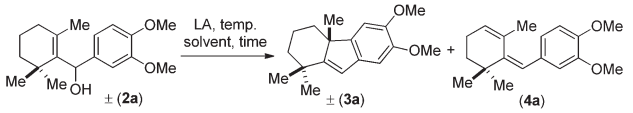
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra. For crystallographic information of compounds **3o** and **8**, see CCDC 926020 and 926021. See DOI: 10.1039/c3ra41497c

‡ This paper is dedicated to Professor Sukh Dev on the occasion of his 90th birthday.

Table 1 Optimization of cyclization of arylvinylcarbinols[a]



Entry	Catalyst (mol%)	Solvent	Temp.	Time	% Of ± (**3a**)	% Of (**4a**)
1.	$Cu(OTf)_2$ (10 mol%)	CH_2Cl_2	rt	24 h	78%	12%
2.	$Sn(OTf)_2$ (10 mol%)	CH_2Cl_2	rt	24 h	82%	11%
3.	$Zn(OTf)_2$ (10 mol%)	CH_2Cl_2	rt	12 h	60%	25%
4.	$Bi(OTf)_3$ (10 mol%)	CH_2Cl_2	rt	12 h	70%	16%
5.	$In(OTf)_3$ (10 mol%)	CH_2Cl_2	rt	12 h	56%	23%
6.	$Sm(OTf)_3$ (10 mol%)	CH_2Cl_2	rt	12 h	45%	37%
7.	**$Sn(OTf)_2$ (10 mol%)**	**CH_2Cl_2**	**40 °C**	**09 h**	**98%**	**00%**
8.	**$Cu(OTf)_2$ (10 mol%)**	**CH_2Cl_2**	**40 °C**	**09 h**	**96%**	**00%**
9.	$Cu(OTf)_2$ (10 mol%)	PhMe	90 °C	12 h	88%	00%
10.	$Cu(OTf)_2$ (10 mol%)	THF	70 °C	18 h	60%	15%
11.	$Cu(OTf)_2$ (10 mol%)	Et_2O	35 °C	12 h	72%	13%
12.	$Sn(OTf)_2$ (10 mol%)	dioxane	75 °C	12 h	80%	06%
13.	$Sn(OTf)_2$ (10 mol%)	DMF	90 °C	12 h	42%	40%
14.	$Sn(OTf)_2$ (10 mol%)	THF	70 °C	12 h	79%	15%
15.	$Sn(OTf)_2$ (10 mol%)	PhMe	90 °C	12 h	93%	00%
16.	$Sn(OTf)_2$ (10 mol%)	DMSO	90 °C	12 h	95%	00%
17.	$Sn(OTf)_2$ (10 mol%)	DCE	70 °C	12 h	93%	00%
18.	$Cu(OTf)_2$ (5 mol%)	CH_2Cl_2	40 °C	18 h	90%	00%
19.	$Sn(OTf)_2$ (5 mol%)	CH_2Cl_2	40 °C	18 h	89%	00%

[a] Reactions were carried out with 1.0 mmol of ±(**2a**) in 5 mL of solvent. Isolated yields after column chromatography are reported.

the required product along with the elimination product **4a** (entries 1–6). Further optimization (entries 7–17) revealed that 10 mol% of $Sn(OTf)_2$ (condition A) and $Cu(OTf)_2$ (condition B) in refluxing dichloromethane resulted in a sole cyclization product in 98% and 96% yields (entries 7,8), respectively. On decreasing catalyst loadings to 5 mol%, we found that the reaction required more time to complete (entries 18,19). With the standard protocol, we then probed a diverse set of arylvinyl carbinols **2b–i** for the cyclization. Impressively, Fig. 2 clearly depicts the generality of our strategy to construct 4a-methyltetra-hydrofluorene structures in good to excellent yields (up to 99%) in 9–12 h. The arylvinyl carbinols **2a–h** containing one or more electron-donating groups were found to be superior to arylvinyl carbinol **2i** (see ESI† for details) in this process.

A plausible mechanism for the formation of carbotricycles is shown in Scheme 1. We hypothesize that aryl dienes **4** can be formed easily through intermediate arylallyl cation **6**,[15] which in turn could undergo a Friedel–Crafts type cyclization in the presence of a Lewis acid. However, at the same time, one can not rule out the possibility of cyclization *via* a concerted mechanism for the formation of **3** following 5-*endo* cyclization.[21b]

To validate this hypothesis, we synthesized compound **2j** (see ESI† for details). It is interesting to note that, under the influence of 10 mol% of $Sn(OTf)_2$ and $Cu(OTf)_2$, **2j** afforded only furan derivative **8** as the sole product in almost quantitative yields (Scheme 2). This indicates a stepwise process *via* a stable arylallyl cation **6**, which might be involved in the cyclization step.

To illustrate the synthetic versatility of our approach, we undertook the formal synthesis of (±)-dichroanone (**1a**) and

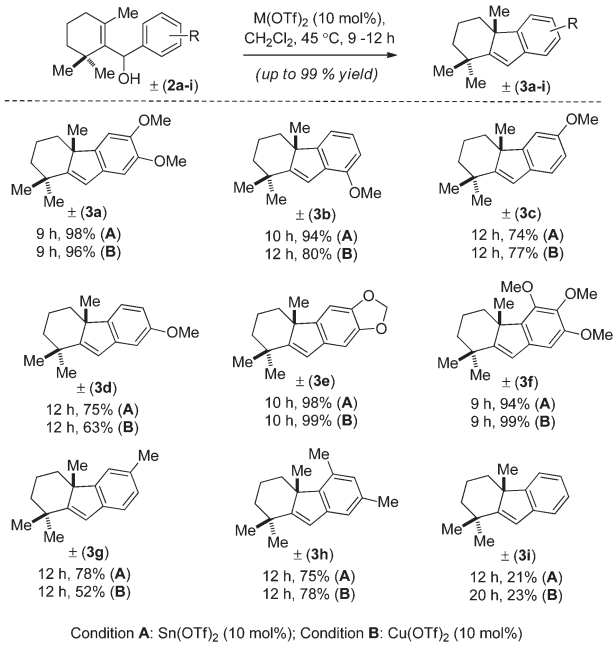
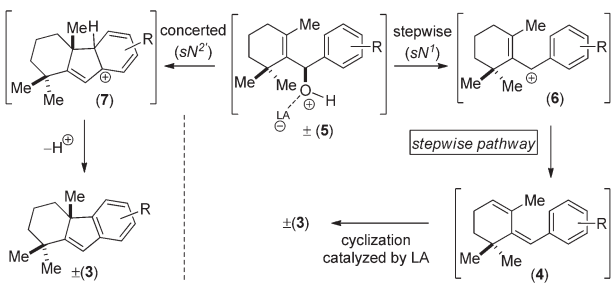


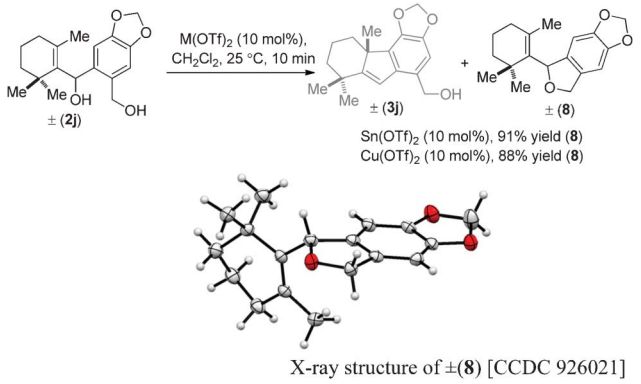
Fig. 2 Substrate scope of the metal triflate catalyzed cyclization.

taiwaniaquinone H (**1b**) starting from arylvinylcarbinols **2k–m**. As shown in Scheme 3, bromoarenes **9c**, **9g**, and **9i** (see ESI† for details) were treated with *n*-BuLi followed by treatment with aldehyde **10** to afford **2k–m**. These arylvinylcarbinols were cyclized in the presence of 10 mol% of $Sn(OTf)_2$ and $Cu(OTf)_2$.

As shown in Scheme 4, we observed that **2k** afforded solely **3l**, where the cyclization was followed by elimination leading to carbotricyclic α-methylstyrene derivative **3l** as the major product (95–97%) *via* an intermediate carbotricycle **3k**. Under similar conditions, **2l** afforded carbotricycle **3m** in 86–90% yields along with regioisomer **3n** in 6–8% yields (Scheme 4). In the case of **2m**, the cyclization provided **3o** in 93% yield as the sole product in the presence of $Sn(OTf)_2$. However, in the case of $Cu(OTf)_2$, a small amount of aryldiene **4b** (8%) was obtained together with **3o** (88%). It is noteworthy that, upon prolonged reaction time, $Cu(OTf)_2$ also provided **3o** as the sole product in 96% yield, which supports the theory that the cyclization might also proceed through an aryldiene **4** (Schemes 1 and 4).[22]



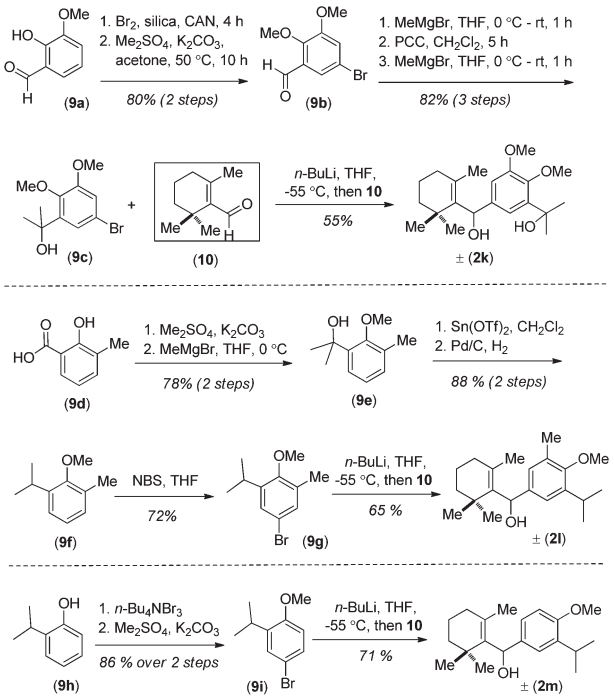
Scheme 1 Plausible mechanism of the metal triflate catalyzed cyclization.



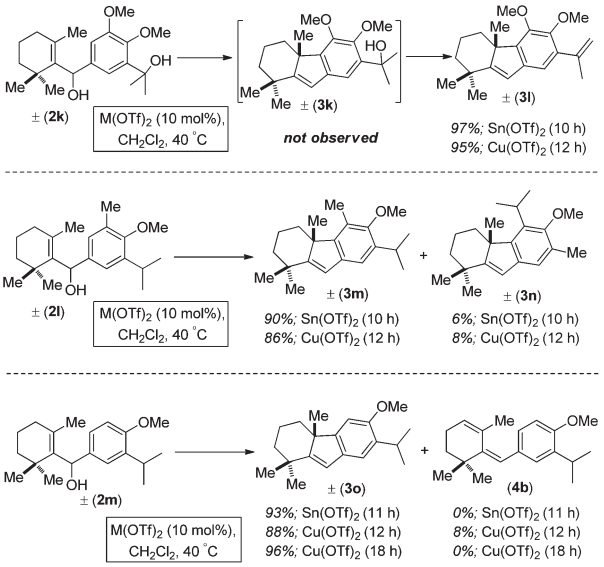
Scheme 2 Cyclization of **2j** in the presence of $Sn(OTf)_2$ and $Cu(OTf)_2$.

For further synthetic elaboration, we undertook the hydrogenation of the carbotricycle **3o**. As envisioned, the hydrogenation of **3o** in the presence of H_2 (1 atm.) and Pd/C afforded *cis*-fused **3p** as the sole product (Scheme 5). We confirmed the *cis*-fusion at the ring junction by carrying out an NOE experiment. The X-ray structure of **3o** (Scheme 5) also clearly depicts a high degree of concavity in carbotricyclic core due to the *gem*-dimethyl groups and a double bond, which restricts the hydrogenation process at the α-face of the carbotricycle **3o**.

Interestingly, compound **3p** could serve as an advanced intermediate for the synthesis of various taiwaniaquinoids possessing similar *cis*-fused carbotricyclic cores such as dichroanal A (**1c**, Fig. 1).



Scheme 3 Synthesis of arylvinylcarbinols ±(**2k–m**) of β-cyclocitral.

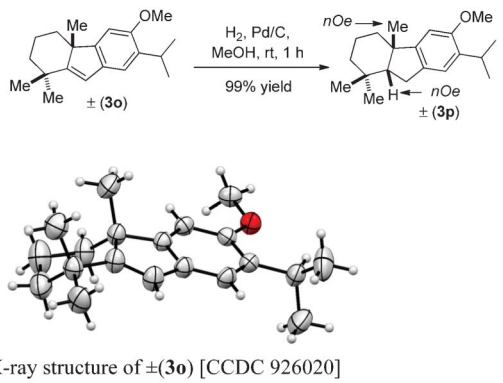


Scheme 4 Substrate scope using arylvinylcarbinols (**2k–m**).

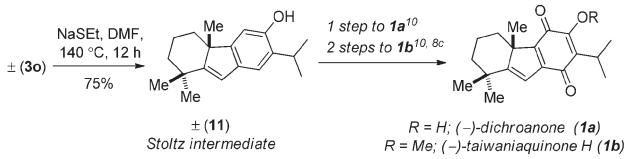
Eventually, demethylation of **3o** using NaSEt in DMF afforded **11** in 75% yield, which turns out to be the formal total synthesis of (±)-dichroanone (**1a**) and (±)-taiwaniaquinone H (**1b**) as shown in Scheme 6.

Conclusions

In conclusion, an efficient method for the synthesis of 4a-methyltetra-hydrofluorenes of taiwaniaquinoids has been developed. The methodology affords a variety of carbotricyclic structures under operationally simple conditions. We also believe that an enantioselective approach to the synthesis of 4a-methyltetra-hydrofluorenes could be achieved by using chiral metal triflate complexes. The extension of this approach to the other *abeo*-abietanes shown in Fig. 1, such as the tetracyclic natural products pelorol (**1f**), akaol A (**1g**), dasyscyphin B (**1h**) as well as an enantioselective approach to 4a-methyltetra-hydrofluorenes having all-carbon quaternary stereocenters is under active investigation.



Scheme 5 The hydrogenation of the carbotricycle ±(**3o**).



Scheme 6 The formal total synthesis of (±)-dichroanone (**1a**) and (±)-taiwaniaquinone H (**1b**).

Experimental

Representative experimental procedure for the metal-triflate catalyzed cyclization of aryl-vinyl carbinols

In an oven-dried round-bottom flask, the arylcarbinols of β-cyclocitral (1.0 mmol; 1.0 equiv.) and $Sn(OTf)_2$ (0.1 mmol; 10 mol%) [**Condition A**] or $Cu(OTf)_2$ (0.1 mmol; 10 mol%) [**Condition B**] were dissolved in dichloromethane (5 mL). The mixture was stirred at 40 °C for the indicated time (9–12 h). Upon completion of the reactions (TLC indicated the complete consumption of the starting material), the reaction mixture was quenched with saturated $NaHCO_3$ solution, diluted with 5 mL of dichloromethane and extracted with 5 mL of water. The organic filtrate was dried over Na_2SO_4 and concentrated in a rotary evaporator under vacuum. The crude products were purified by flash chromatography (10 : 1 hexanes/EtOAc) to afford the Friedel–Crafts alkylation products.

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22 Interestingly, 5 mol% of $BF_3{\cdot}OEt_2$ catalyzes the cyclization of **2k** in only 2–5 min, leading to the formation of **3k** in 90% yield along with 8% of the carbotricyclic diene **3l**.