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Use of a Tandem Prins/Friedel-Crafts Reaction in the Construction of the Indeno-Tetrahydropyridine Core of the Haouamine Alkaloids: Formal Synthesis of (−)-Haouamine A

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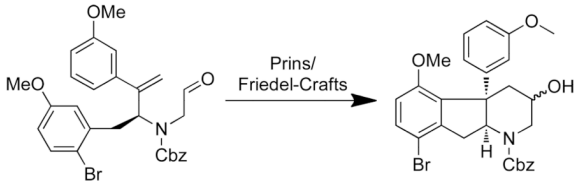
Abstract



A tandem Prins/Friedel-Crafts reaction useful for the construction of the indeno-tetrahydropyridine core of the haouamine alkaloids and a formal synthesis of (−)-haouamine A are described.

Haouamines A and B were isolated in 2003 from a marine ascidian (*Aplidium haouarianum*) collected off of the southern coast of Spain (Figure 1).[1] The potent and selective cytotoxic activity displayed by haouamine A against the HT-29 human colon carcinoma cell line (IC_{50} = 0.1 μg/mL) has made it an appealing target for total synthesis.[2–4] The structural features comprise a congested indeno-tetrahydropyridine core fused to an 11-membered paracyclophane containing a strained, non-planar aromatic ring. In addition, the presence of a quaternary stereogenic center and the unusual biosynthetic oxidation pattern make the haouamines a formidable synthetic challenge.

To date, the only total syntheses of houamines A and B have been reported by Baran and workers, who used either an alkyne/pyrone Diels-Alder cycloaddition or a cyclohexenone to phenol oxidation to install the paracyclophane moiety.[2] A number of other workers have focused on the preparation of the indeno-tetrahydropyridine core. With the exception of an intramolecular Mizoroki-Heck sequence reported by Ishibashi and coworkers,[3c] all other approaches sequentially form each of the rings in the core. Both of the Rawal[4a] and Trauner[4b] laboratories have used a Friedel-Crafts alkylation to prepare the indene ring from a tetrahydropyridine-containing starting material. Herein, we report an approach to the indeno-tetrahydropyridine core in which the indene and tetrahydropyridine rings are formed concurrently in a tandem Prins/Friedel-Crafts reaction and the use of this reaction in a formal synthesis of (−)-haouamine A.

Our approach was based on forming the indenotetrahydropyridine core **3** from an amino acid starting material as shown in Scheme 1. In this scenario, an acid-promoted Prins reaction of

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Supporting Information Available. Experimental information for the preparation of new compounds including X-ray data and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

enal **4** would form a carbocation that could in principle be attacked by an aromatic ring in an intramolecular Friedel-Crafts reaction. Deriving confidence from a few previously reported examples,[5] we began by preparing test substrates **8a–8d** from the Weinreb amide **5** (Scheme 2; see Supporting Information for detail).

Enals **8** were treated with various protic and Lewis acids (Table 1). Treating **8a** with camphorsulfonic acid resulted in a clean reaction yielding the bridged tricyclic compound **9a** (entry 1). This product presumably results from a Prins reaction followed by a dehydration yielding an intermediate allylic cation, which is then intercepted by the arene in an intermolecular Friedel-Crafts manner at the less hindered allyl carbon. In contrast, the use of various Lewis acids (entries 2–4) resulted predominantly in the fused tricyclic product **10a**, in which the initial Prins cation intermediate is intercepted directly by the tethered arene. When **8b** was treated with protic acid (entry 5), the bridged tricycle **9b** was obtained exclusively. When Lewis acids were used instead (entry 6), significant amounts of the bridged tricycle **9b** were observed in addition to **10b**, which was still the major product. The formation of **9b** could be minimized if the reaction was performed in a polar aprotic solvent such as nitromethane (entries 7 and 8). Whithin products **9b** and **10b**, Friedel-Crafts aromatic substitution occured para to the methoxy group. When enal **8c** was treated under protic or Lewis acid conditions (entries 9–12), no appreciable amounts of Friedel-Crafts products were obtained, demonstrating the requirement for the arene to be electron rich. Reaction of **8d**, lacking the vinylic phenyl group, led solely to **11**, resulting from a direct Friedel-Crafts acylation–dehydration reaction (Scheme 3).

These results allowed us to narrow our strategy for synthesizing the core of haouamine A (Scheme 4): (1) use Lewis instead of protic acids to obtain product having the desired ring system, (2) further drive the selectivity using nitromethane as solvent,[6] (3) preinstall the vinyl aromatic group, and (4) use a blocking group to force formation of an ortho C–C bond in the Friedel–Crafts step (following precedent set by Rawal[4a]).

This route required the unusual amino ester **13**, which was prepared from **12**[7] by a route analogous to that of Jackson and coworkers (Scheme 5).[8] We found that this conversion could be attained in higher overall yield by cross-coupling **12** with 3-iodoanisole followed by treatment with NBS. The second aryl ring was installed by preparing Weinreb amide **14** from ester **13** using the Merck protocol (*i*-PrMgCl, MeNH(OMe)·HCl),[9] followed by addition of 3-methoxyphenylmagnesium bromide. Methylenation of the resulting aryl ketone **15** was effected cleanly in a two-step Peterson olefination protocol to yield **16** in good overall yield.[10] Finally, the two-carbon aldehyde was attached by *N*-alkylation with TBS-protected 2-bromoethanol, deprotection, and oxidation of the resulting alcohol to produce enal **18**.

The enal **18** was then subjected to a variety of protic and Lewis acid conditions in an attempt to promote a Prins/Friedel-Crafts reaction (Scheme 6). However, the only observable product in all cases resulted from the cyclization of the Boc amide onto the aldehyde with concomitant loss of isobutylene to produce the hydroxy oxazolidinone **20**. Since it became obvious that the Boc protecting group was not compatible with the required acid conditions, the enal substrate was then re-tuned with a change in protecting group. Boc deprotection and reprotection of the free amine in the form of a Cbz group, followed by a similar homologation sequence performed previously (Scheme 5) yielded enal **19**.

Acid treatment of the Cbz-protected enal **19** was more promising (Table 2). Use of CSA yielded a mixture of allylic alcohols **21** resulting from a simple Prins reaction (entry 1). Although we had expected according to the model study to obtain the bridged tricycle **22**, further treatment of **21** with CSA with heating under prolonged reaction times did not

produce a Friedel-Crafts reaction. In contrast, use of $AlCl_3$ in methylene chloride did yield a Prins/Friedel-Crafts product exclusively, albeit the undesired bridged tricycle **22** rather than the expected fused tricycle **24** (entry 2). We next turned to the use of $AlCl_3$ in nitromethane, since the use of this solvent was predicted to favor formation of **24** over **22** (entry 3). Under these conditions, chlorohydrins **23** were obtained, apparently from the addition of a chloride anion originating from the Lewis acid. These results suggest that the presence of a bromine on the Friedel-Crafts arene nucleophile of **19** decreases its reactivity. Gratifyingly however, when Lewis acids bearing "non-nucleophilic" anions were used in nitromethane (entries 4–5) in the form of BF_3 or $Al(OTf)_3$, the requisite fused Prins/Friedel-Crafts tricycle **24** was obtained exclusively as a mixture of diatereomers at C2.

The mixture of diastereomers **24** was oxidized to the ketone and the Cbz protecting group was removed by hydrogenolysis with concomitant hydrodebromination to produce the haouamine tricyclic core **26** (Scheme 7). Since **26** was identical in all respects to an intermediate prepared in a synthesis of haouamine A by Fürstner and coworkers,[3b] this constitutes a formal synthesis of (−)- haouamine A.

In conclusion, we have successfully demonstrated the utility of a tandem Prins/Friedel-Crafts reaction in the concise construction of the tricyclic core of haouamine A. This culminated in a formal synthesis of (−)-haouamine A, in which the indeno-tetrahydropyridine was constructed in 13 steps from serine. Future efforts will concentrate on evaluating the utility of tandem Prins/Friedel-Crafts reaction in the construction of fused and bridged tricycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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3. For previous formal syntheses of haouamine A, see: (a) Jeong JH, Weinreb SM. Org. Lett. 2006; 8:2309–2312. [PubMed: 16706513] (b) Fürstner A, Ackerstaff J. Chem. Commun. 2008:2870–2872. (c) Taniguchi T, Zaimoku H, Ishibashi H. J. Org. Chem. 2009; 74:2624–2626. [PubMed: 19231835]
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6. We suspect that the dehydration leading to **9** occurs competitively with the desired Friedel-Crafts reaction. In a polar aprotic solvent such as nitromethane, the intermediate Prins carbocation intermediate remains longer lived so as to allow sufficient time for the Friedel-Crafts arene to react directly.

7. Serine iodide **12** is prepared in three steps from serine (methyl ester formation, Boc protection, iodination) in 61% overall yield according to the procedure of Rudd, M. T.; Trost, B. M. *Org. Lett.* **2003**, *5*, 4599–4602.

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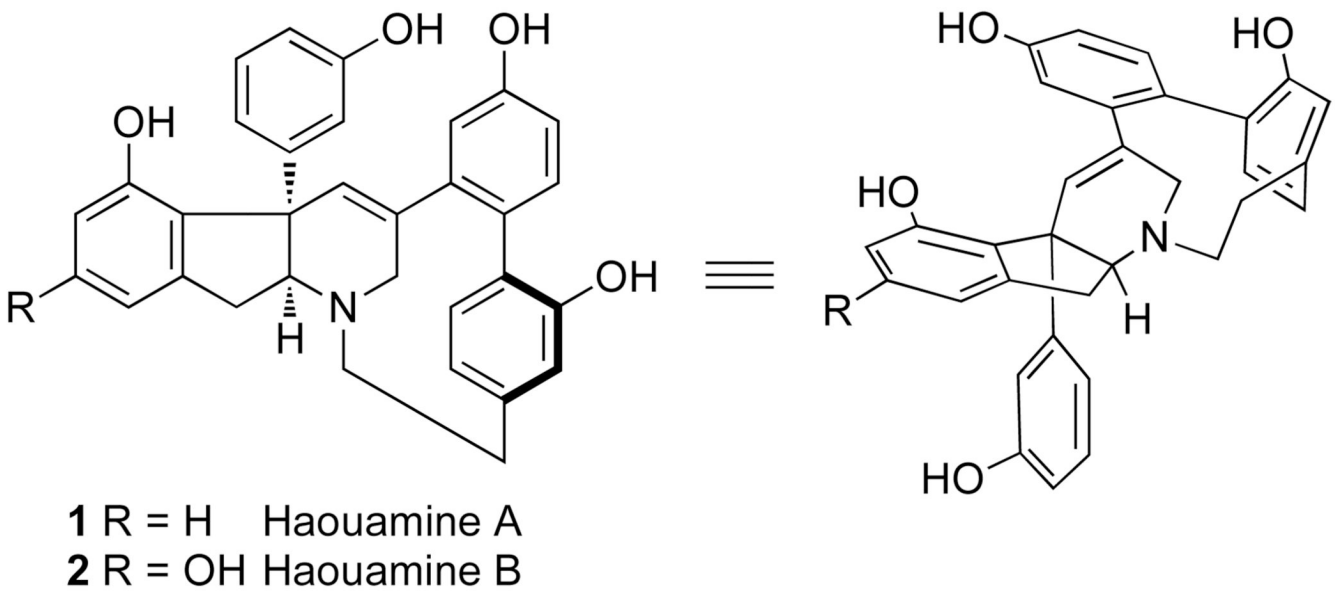
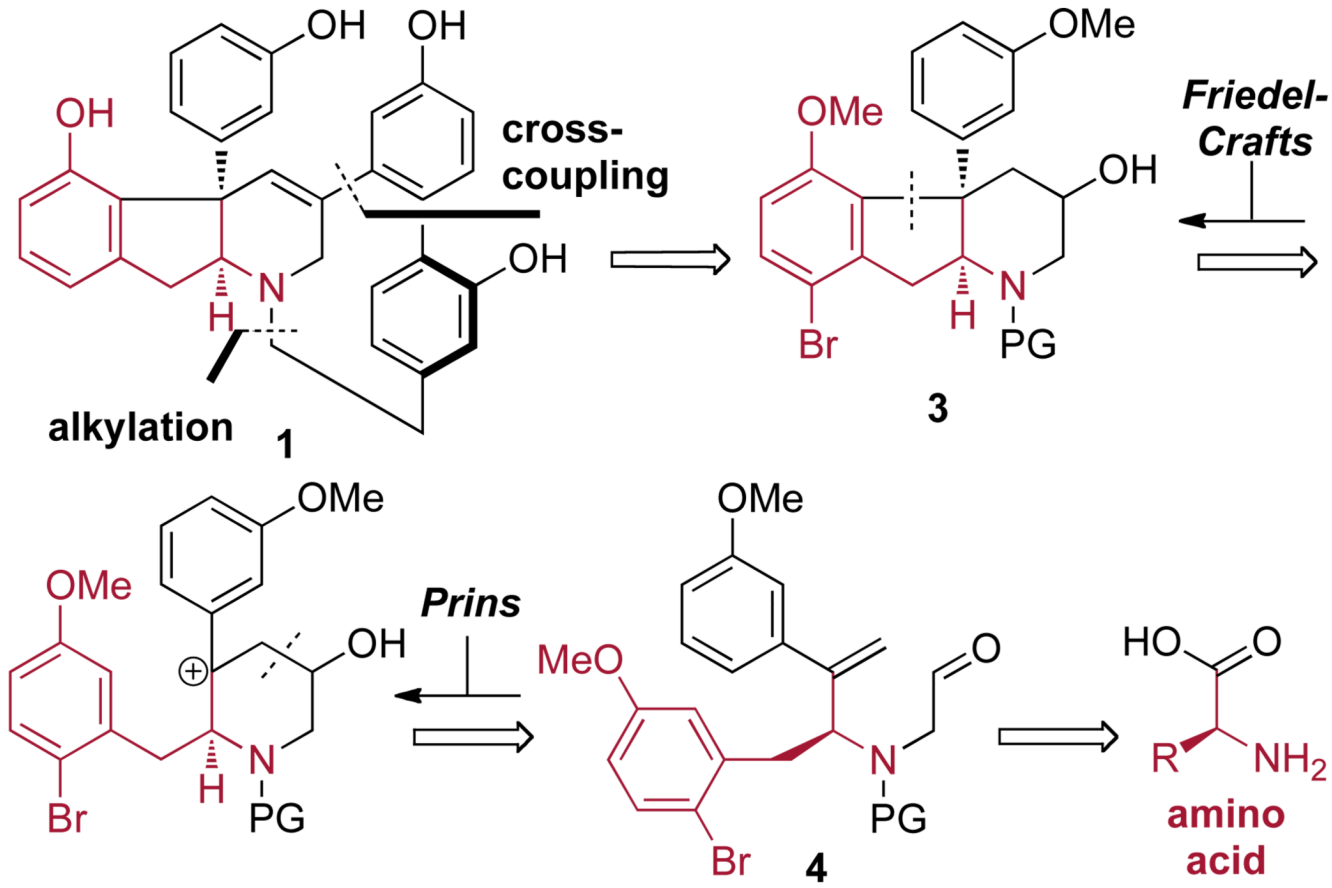
9. Williams JM, Jobson RB, Yasuda N, Marchesini G, Dolling HU, Grabowski EJJ. Tetrahedron Lett. 1995; 36:5461–5464.

10. Various olefination methods involving Wittig and Tebbe reagents failed to produce substantial amounts of the product. The Peterson olefination method was successful only in the cases where the intermediate silane was treated in acid conditions (base conditions were found to be incompatible with the Boc protecting group).

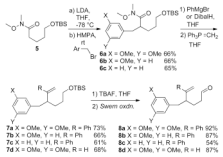


1 R = H Haouamine A
2 R = OH Haouamine B

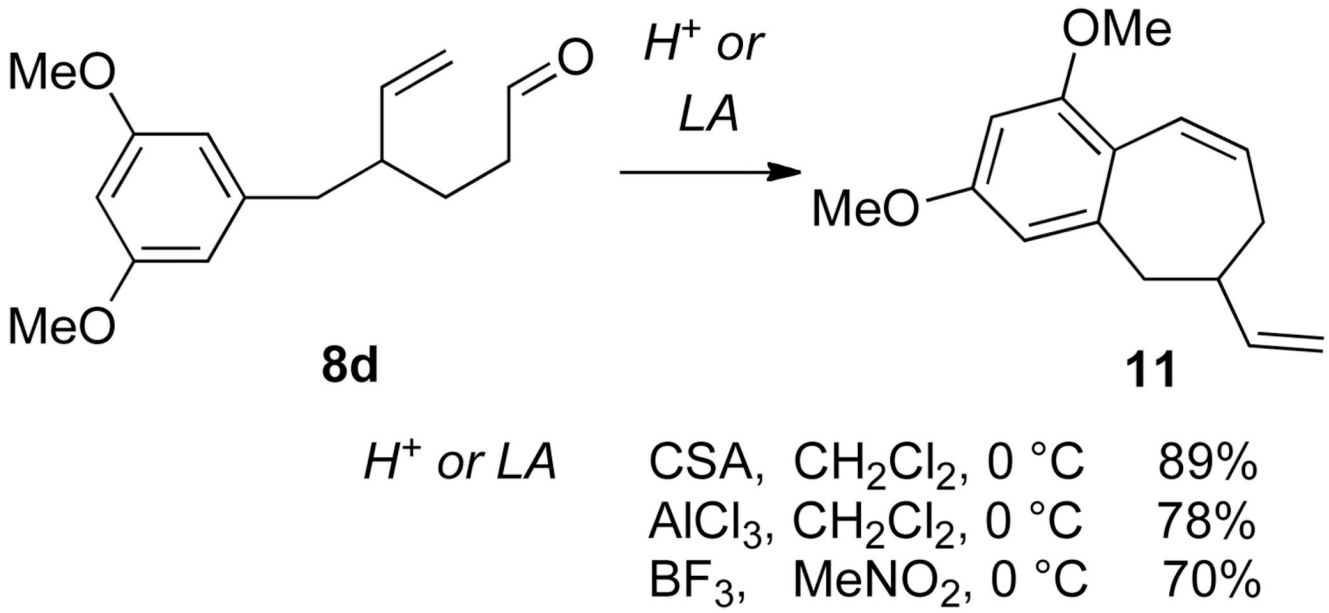
Figure 1.
Haouamines A and B



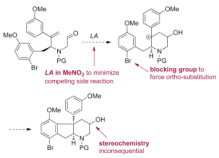
Scheme 1.
Retrosynthetic Analysis of Haouamine A



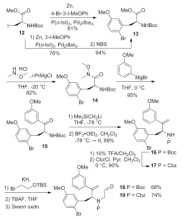
Scheme 2.
Preparation of Model Prins/Friedel-Crafts Substrates



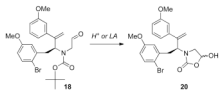
Scheme 3.
Prins/Friedel-Crafts Attempt with **8d**



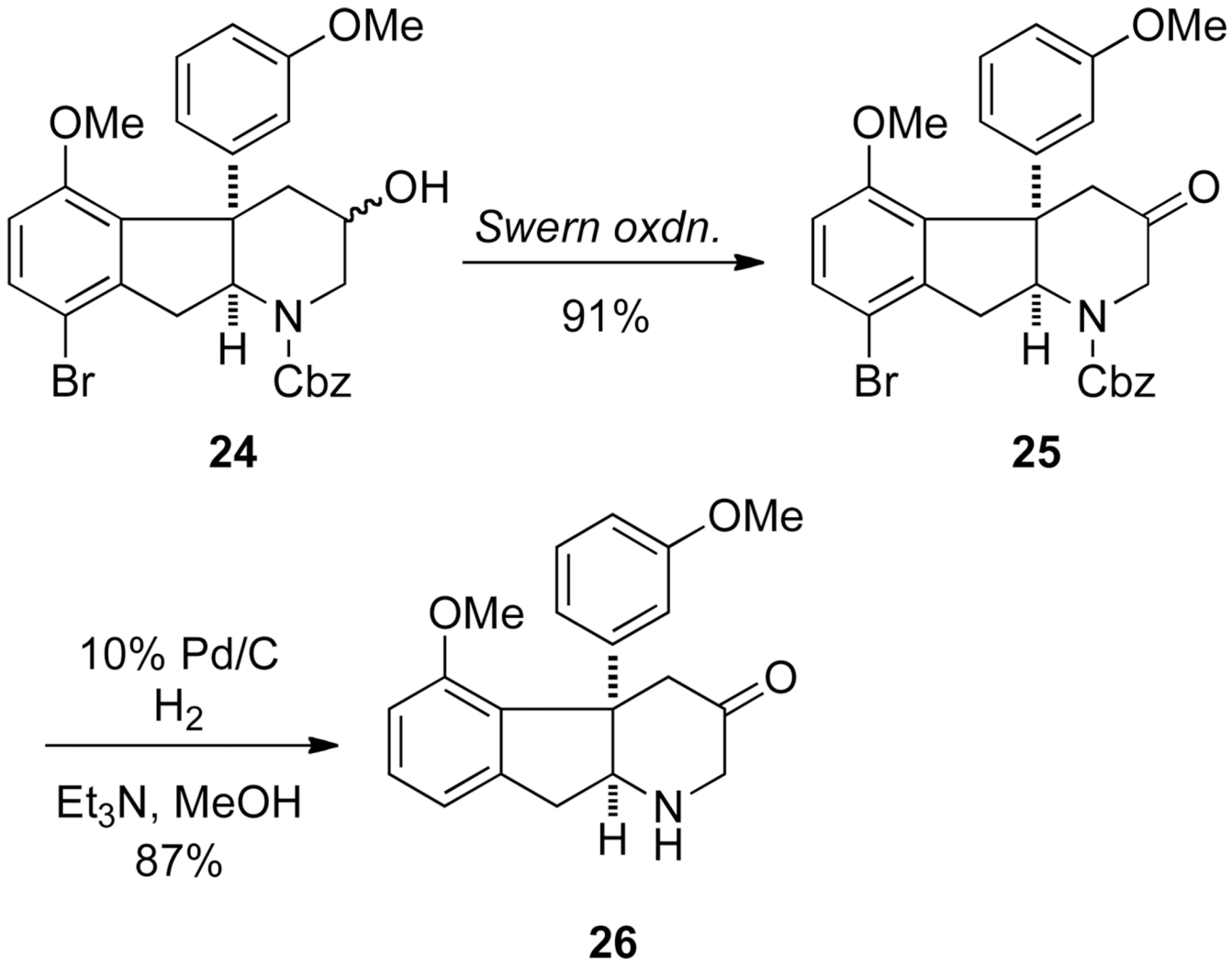
Scheme 4.
Plan for the Prins/Friedel-Crafts Approach to Haouamine A



Scheme 5.
Synthesis of the Enal Substrate for the Prins/Friedel-Crafts Approach to Haouamine A



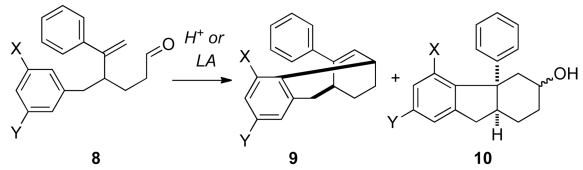
Scheme 6.
Prins/Friedel-Crafts Attempt with Enal 1**8**



Scheme 7.
Formal Synthesis of Haouamine A

Table 1

Acid Promoted Prins/Friedel-Crafts Reaction of Enal Substrates **8**



8 **9** **10**

a: X = OMe, Y = OMe; **b:** X = H, Y = OMe; **c:** X = H, Y = H.

entry	enal	H^+ *or* *LA*[a]	solvent	*t* (°C)	yield (%)[b]	
					9	**10 (α:β)**
1	**8a**	CSA	CH_2Cl_2	0	76	—
2	**8a**	$AlCl_3$	CH_2Cl_2	−41	—	90 (1.6:1)
3	**8a**	BF_3	CH_2Cl_2	−41	—	94 (1.1:1)
4	**8a**	$TiCl_4$	CH_2Cl_2	−41	12	85 (1.9:1)
5	**8b**	CSA	CH_2Cl_2	0	72	—
6	**8b**	$AlCl_3$	CH_2Cl_2	−41	28	54 (1.6:1)
7	**8b**	$AlCl_3$	$MeNO_2$	−20	5	74 (1.3:1)
8	**8b**	BF_3	$MeNO_2$	−20	2	84 (1.4:1)
9	**8c**	CSA	CH_2Cl_2	rt	—	__[c]
10	**8c**	$AlCl_3$	CH_2Cl_2	0	—	__[c]
11	**8c**	$AlCl_3$	$MeNO_2$	0	—	5 (1:1)[c]
12	**8c**	BF_3	$MeNO_2$	0	—	7 (1:1)[c]

[a] 1.1 equiv of the protic or Lewis acid was used.

[b] Yield of the isolated product.

[c] The major isolated products in these reactions was that resulting from a Prins reaction only

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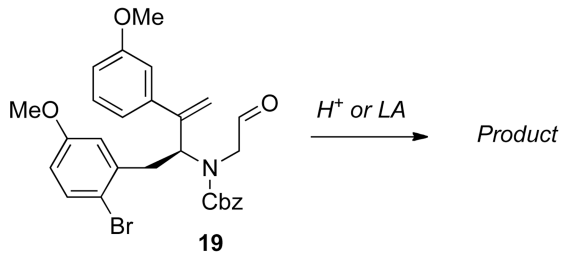
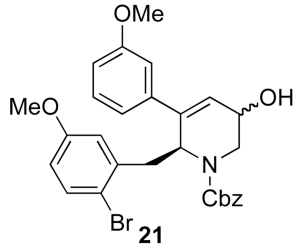
Table 2

Acid Promoted Prins/Friedel-Crafts Reaction of Enal Substrate **19**.



19

Product:



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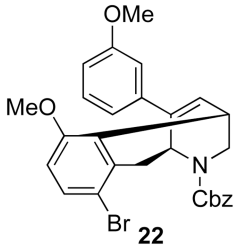

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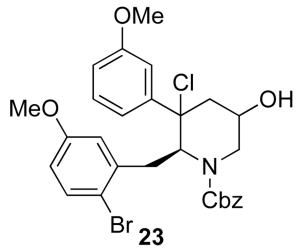

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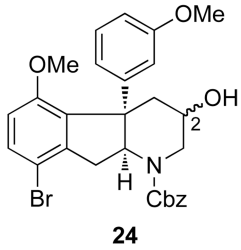

24

entry	H^+ *or LA*[a]	solvent	*t* (°C)	product	yield (%) (α:β)[b]
1	CSA	CH_2Cl_2	rt	**21**	81 (1.6:1)
2	$AlCl_3$	CH_2Cl_2	0	**22**	70
3	$AlCl_3$	$MeNO_2$	−20	**23**	70
4	BF_3	$MeNO_2$	−20	**24**	62 (1.2:1)

entry	H^+ or LA[a]	solvent	t (°C)	product	yield (%) (α:β)[b]
5	$Al(OTf)_3$	$MeNO_2$	−20	**24**	65 (1.5:1)

[a] 1.1 equiv of the protic or Lewis acid was used.

[b] Yield of the isolated product.