Alkynylbenzaldehyde Cyclizations Catalyzed by Ag(I) Complexes of Chiral Pyridine Containing Macrocyclic Ligands (Pc-L*)

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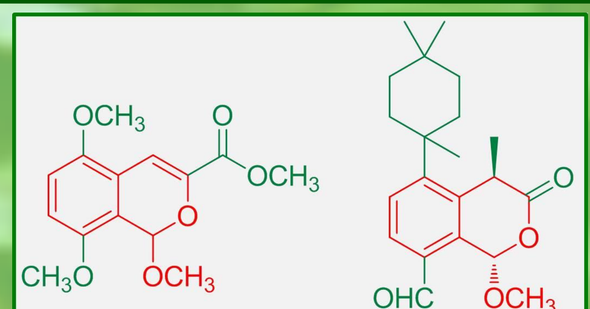
Introduction

The tandem acetalization/cycloisomerization of ortho-alkynylbenzaldehydes gives 1-alkoxy-*1H*-isochromene derivatives that showed useful medicinal properties.[1] For example, the methyl 1,5,8-trimethoxy-*1H*-isochromene-3-carboxylate was patented as a potential antitumor agent against breast cancer.[1b] Moreover, the structure of isochromane is the key structure of some diterpenes from Antarctic sponge Dendrilla Membranosa.[2]



Methyl 1,5,8-trimethoxy-1H-isochromene-3-carboxylate

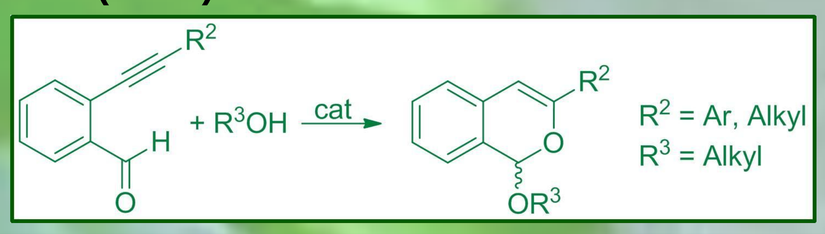
Membranolide B

Aim of the work

- ✓ **Development of a new catalytic system for the effective and selective synthesis of 1-alkoxy-*1H*-isochromenes.**
- ✓ **Preliminary study of the enantioselective version of the reaction.**
- ✓ **Study of the reaction mechanism by ^{1}H NMR spectroscopy.**

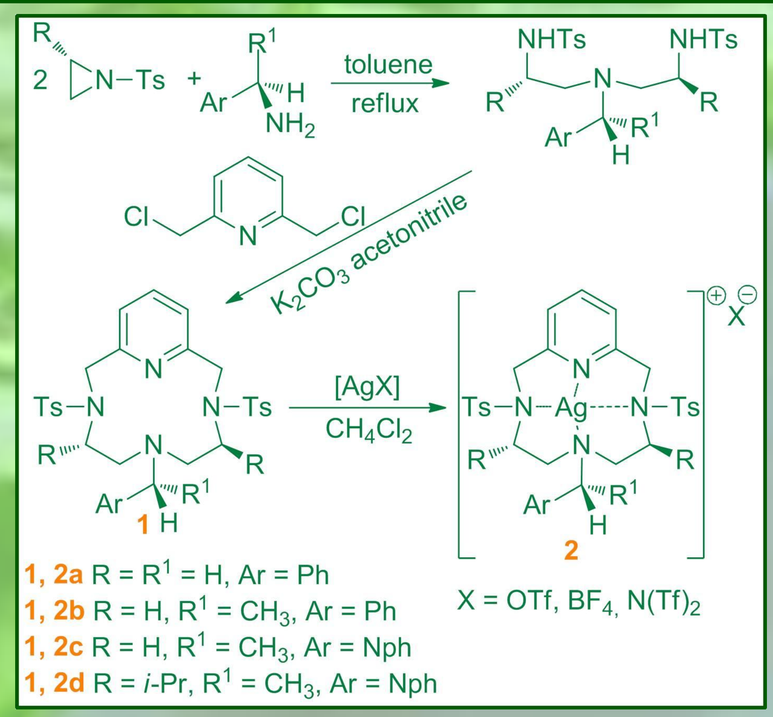
Reaction under investigation

Starting from pioneering work of Yamamoto,[3] some tandem processes using different metal salts have been reported, but only one enantioselective version of this reaction recently appeared.[4] We report herein the preliminary results of a clean, regio- and stereoselective synthesis of 1-alkoxy-1H-isochromenes catalyzed by novel silver(I) complexes of pyridine containing macrocyclic ligands (Pc-L*).



Silver complexes synthesis

The pyridine-based 12 membered tetraaza macrocyclic ligands (Pc-L*), 1, can be obtained in good overall yields, starting from commercially available primary amines.[5] The crucial step, *i.e.* the macrocyclization, was run under heterogeneous conditions. This synthetic methodology allows to avoid high dilution techniques and to obtain 1 in 70-80% yields. Metal complex formation with ligands 1a-1d was investigated with different silver(I) salts. All complexes were isolated and characterized.



1, 2a R = R^1 = H, Ar = Ph
1, 2b R = H, R^1 = CH_3, Ar = Ph
1, 2c R = H, R^1 = CH_3, Ar = Nph
1, 2d R = *i*-Pr, R^1 = CH_3, Ar = Nph

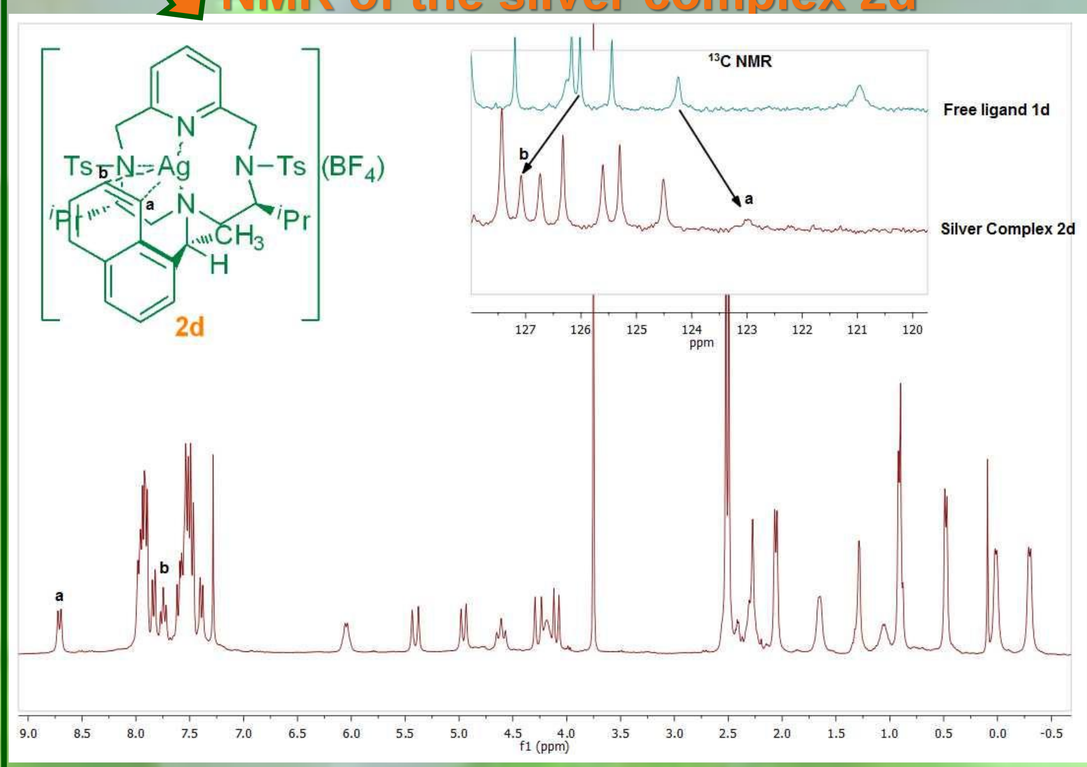
X = OTf, BF_4, $N(Tf)_2$

Ag catalyzed domino addition/annulation reactions[a]

	cat	X	R^2	R^3	R^3OH/ sub	solvent	t (h)	yield %[b] (ee %)
	AgOTf		4-MeO-C_6H_4	Me	-	MeOH	20	71
Solvent optimization	2a	BF_4	4-MeO-C_6H_4	Me	-	MeOH	5	98
	2a	BF_4	4-MeO-C_6H_4	Me	3:1	DCE	1	94
	2a	BF_4	4-MeO-C_6H_4	Me	3:1	toluene	2.5	> 99
Anion effect	2a	OTf	4-MeO-C_6H_4	Me	3:1	toluene	2.5	88
	2a	$N(OTf)_2$	4-MeO-C_6H_4	Me	3:1	toluene	2.5	89
R^3OH/sub ratio effect	2a	BF_4	4-MeO-C_6H_4	Me	6:1	toluene	4	> 99
	2a	BF_4	4-MeO-C_6H_4	Me	1.5:1	toluene	2.5	> 99
	2a	BF_4	4-MeO-C_6H_4	Me	1.05:1	toluene	2	> 99
Catalysts performances and reaction scope	2b	BF_4	$CH_2CH_2CH_3$	Me	-	MeOH	5	95
	2c	BF_4	4-MeO-C_6H_4	Me	-	MeOH	20	> 99
	2d	BF_4	4-MeO-C_6H_4	Me	-	MeOH	7.5	> 99 (12)
	2d	$N(OTf)_2$	4-MeO-C_6H_4	Me	-	MeOH	6	> 99 (6)
	2d	$N(OTf)_2$	$CH_2CH_2CH_3$	Me	-	MeOH	2	> 99
	2d	BF_4	4-MeO-C_6H_4	*i*-Pr	-	*i*-PrOH	24	> 99
	2d	$N(OTf)_2$	4-MeO-C_6H_4	Me	1.2:1	DCM	1.5	> 99
	2d	BF_4	4-MeO-C_6H_4	Me	3:1	toluene	22	93
	2d	BF_4	4-MeO-C_6H_4	Cy	3:1	toluene	22	> 99

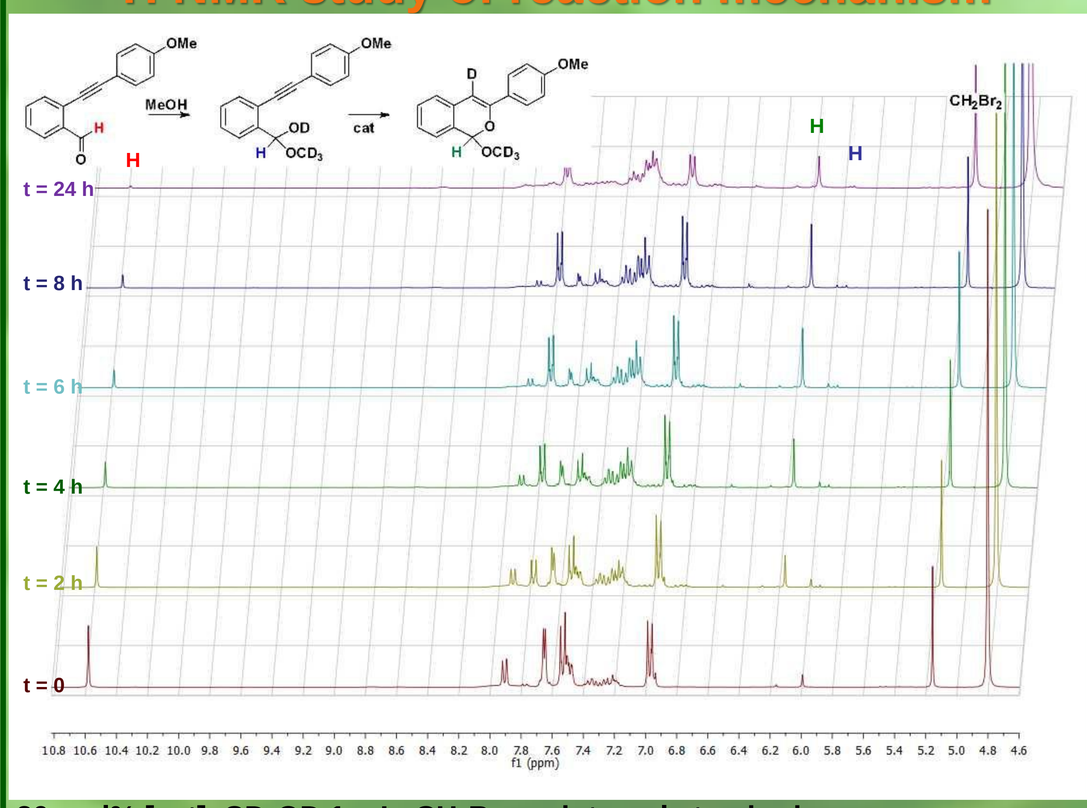
[a]Reaction conditions: 30 C, 5 mol% [cat], [substrate] = 0.25 M; [b]isolated yield, chromatography unnecessary.

NMR of the silver complex 2d



^{1}H NMR, 300 MHz, T = 25 °C, $CDCl_3$. In the insert, ^{13}C NMR, 75 MHz of complex 2d compared with free ligand 1d.

^{1}H NMR study of reaction mechanism



20 mol% [cat], CD_3OD 1 mL, CH_2Br_2 as internal standard.

References

1. (a) Wang, W.; Li, T.; Milburn, R.; Yates, J.; Hinnant, E.; Luzzio, M. J.; Noble, S. A.; Attardo, G. Bioorg. *Med. Chem. Lett.* 1998, *8*, 1579. (b) Attardo, G.; Wang, W.; Breining, T.; Li, T.; St-Denis, Y.; Kraus, J.-L. Int. Patent WO 9512588, 1995.
2. Ankisetty, S.; Amsler, C. D.; Clintock, J. B.; Baker, B. J. *J. Nat. Prod*. 2004, *67*, 1172.
3. Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* 2002, *124*, 764.
4. Handa, S.; Slaughter, L. M. *Angew. Chem. Int. Ed.* 2012, *51*, 2912.
5. (a) Caselli, A.; Cesana, F.; Gallo, E.; Casati, N.; Macchi, P.; Sisti, M.; Celentano, G.; Cenini, S. *Dalton Trans.* 2008, 4202. (b) Castano, B.; Pedrazzini, T.; Sisti, M.; Gallo, E.; Ragaini, F.; Casati, N.; Caselli, A. *App. Organometal. Chem.* 2011, *25*, 824.