Mild AgOTf Catalyzed Synthesis of 1-Carbosubstituted-isochromenes

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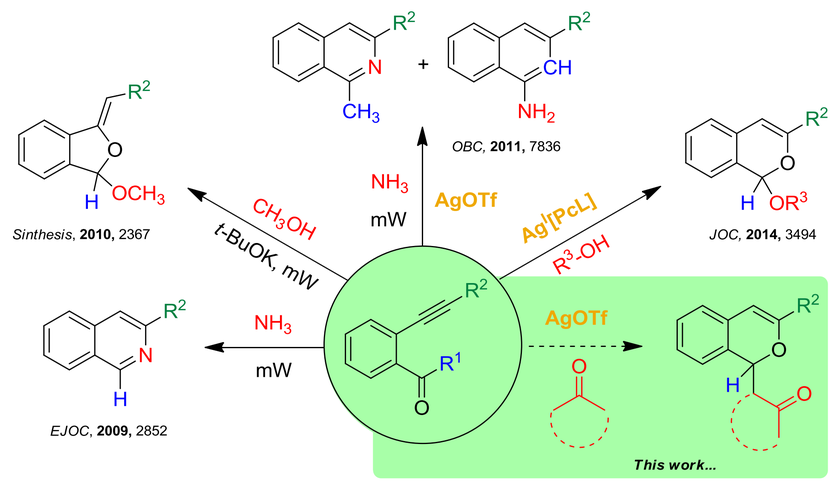
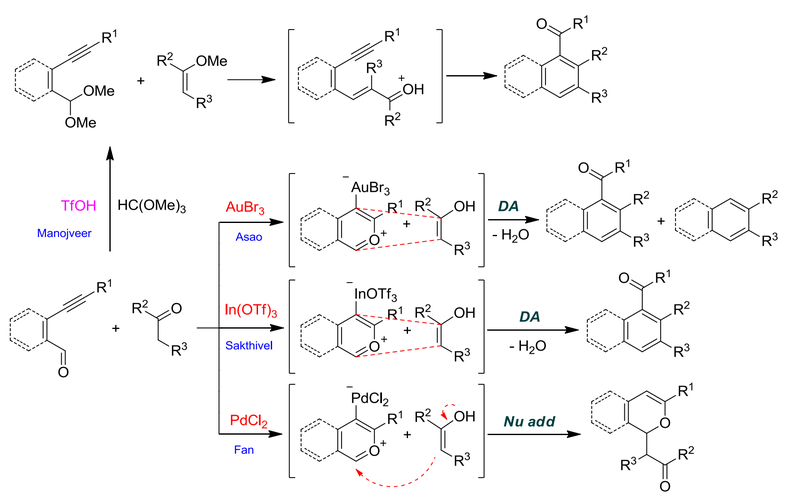
INTRODUCTION

One of the most efficient methods for the construction of 1-substituted isochromenes (and related heteroaryl compounds such as pyrano[4,3-b]pyridines) is the metal catalyzed regioselective domino cycloisomerization/nucleophilic addition reaction of a properly substituted 2-alkynyl(hetero)arylaldehyde in the presence of a suitable nucleophile.[1] The reaction with oxygen nucleophiles is the most studied and several metal catalyst, i.e., Pd(II),[2] Cu(I),[3] Ag(I),[4] Au(I)[5] and In(III),[6] demonstrated to be effective for synthesis of 1-alkoxyisochromenes. Conversely, the reaction with carbon nucleophiles,[7] and in particular with enolizable carbonyl compounds, is relatively less investigated.[8] In connection with our ongoing interest in the development domino addition/annulation reactions starting from 1-acyl-2-alkynylarene derivatives, we present here a silver(I) catalyzed synthesis of isochromenes starting from 2-alkynyl(hetero)arylcarbaldehydes and enolizable carbonyl compounds.

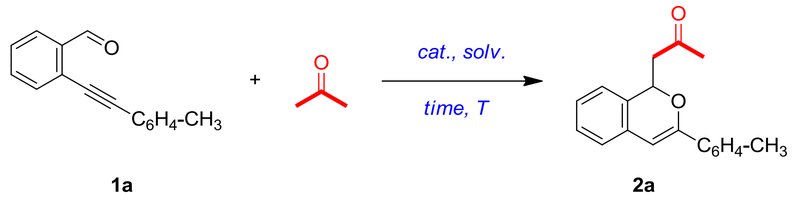
OUR PREVIOUS WORKS on 1-ACYL-2-ALKYNYLARENES and THIS WORK



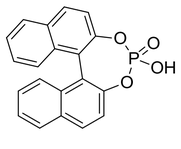
STATE of the ART: 1-ACYL-2-ALKYNYLARENES + ENOLIZABLE CARBONYL COMPOUNDS[7]



SCREENING of REACTION CONDITIONS (selected)

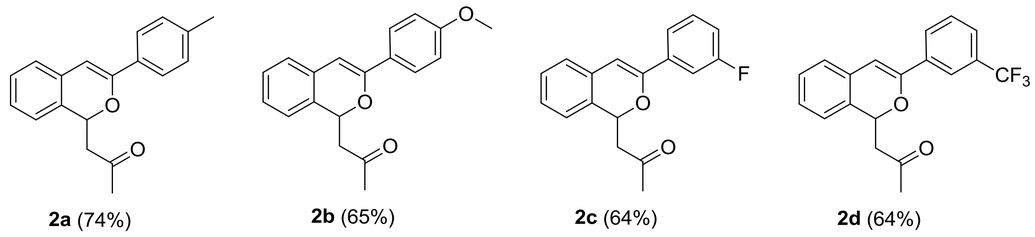


1a 2a

Catalyst (10 mol%)	Solvent	T (°C)	t (h)	2a (yield %)	1a rec. (yield %)
AgOTf	Acetone (68 eq.)	60	12	45	-
AgOTf	Toluene:Acetone 9:1 (~6 eq.)	60	25	10	-
AgOTf	DCE:Acetone 9:1 (~6 eq.)	60	25	-	-
AgOTf	DMF:Acetone 9:1 (~6 eq.)	60	25	15	30
AgOTf	Acetone (68 eq.)	80	7	**74**	
AgOTf	Acetone (68 eq.)	r.t.	24	34[a]	
AgOTf	Acetone (68 eq.)	100 mW	0.5	35[a]	5[a]
$AgNTf_2$	Acetone (68 eq.)	80	7	42[a]	56[a]
$AgNO_3$	Acetone (68 eq.)	80	3	-	-
CuI	Acetone (68 eq.)	60	22	-	quant.[b]
$FeCl_3$	Acetone (68 eq.)	60	29	-	20[a]
	Acetone (68 eq.)	60	24	-	30[a]

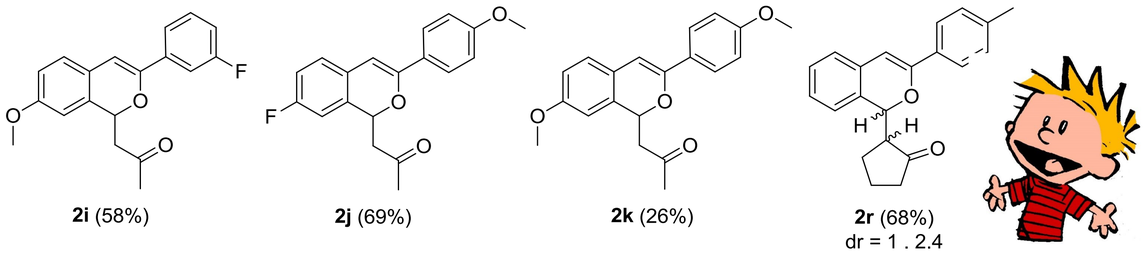
[a] Yields calculated via ^1H NMR using dimethyl terephthalate (DMT) as internal standard. [b] Determined by TLC-analysis.

SUCCESSFUL REACTIONS



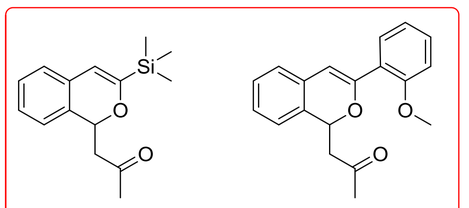
2a (74%) **2b** (65%) **2c** (64%) **2d** (64%)

2e (70%) **2f** (45%) **2g** (79%) **2h** (29%)



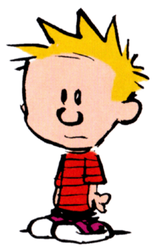
2i (58%) **2j** (69%) **2k** (26%) **2r** (68%) dr = 1 . 2.4

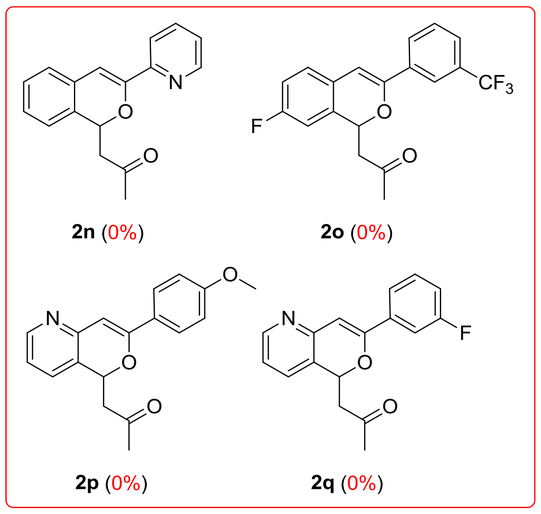
UNSUCCESFUL REACTIONS



2l (0%) **2m** (0%)

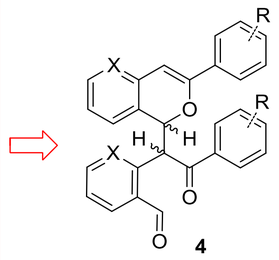
Complex mixture of by-products





2n (0%) **2o** (0%)

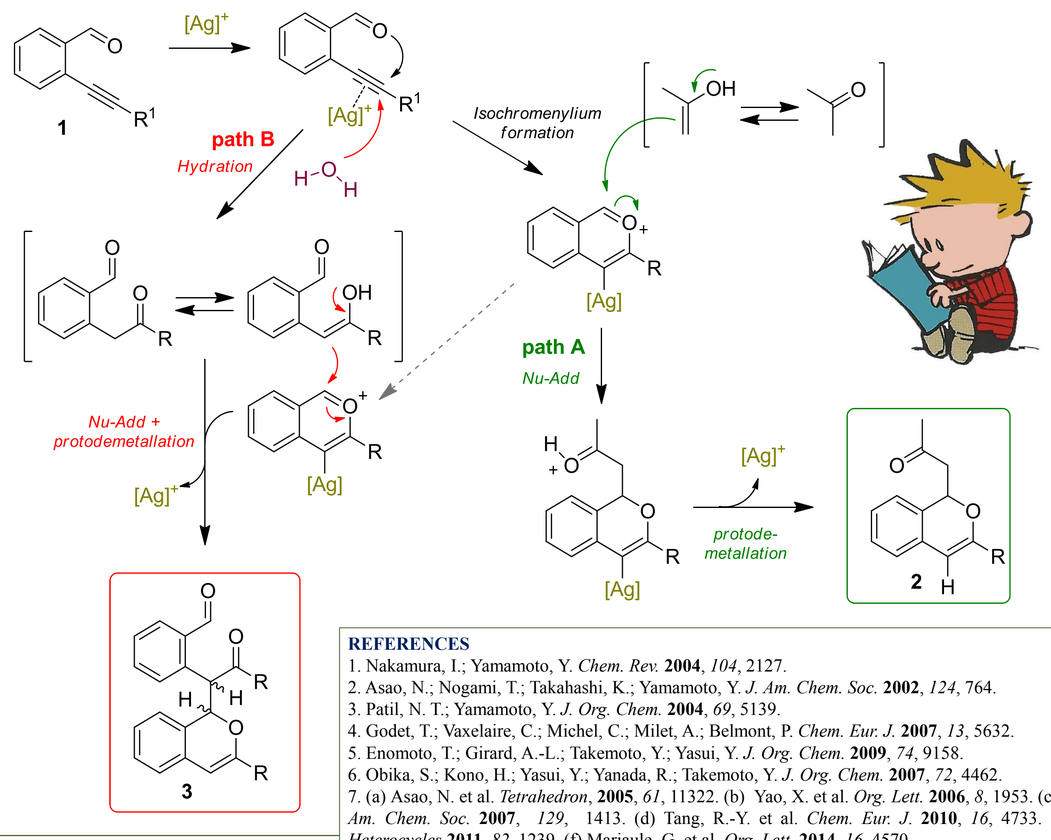
2p (0%) **2q** (0%)



4

Diastereoisomeric mixture of dimeric products
yields: 35-82%
selectivities. 1:1 - 1:5

SUGGESTED MECHANISM



1 **2** **3**

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