

Domino Addition/Cycloisomerization Reactions of 2-Alkynyl-Arylaldehydes: Silver Catalyzed Synthesis of 1,3-Dicarbo-Substituted Isochromenes

Giorgio Abbiati, Valentina Pirovano, Elisabetta Rossi

Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "Alessandro Marchesini"
Università degli Studi di Milano, Via Venezian 21, 20133 Milano, Italy

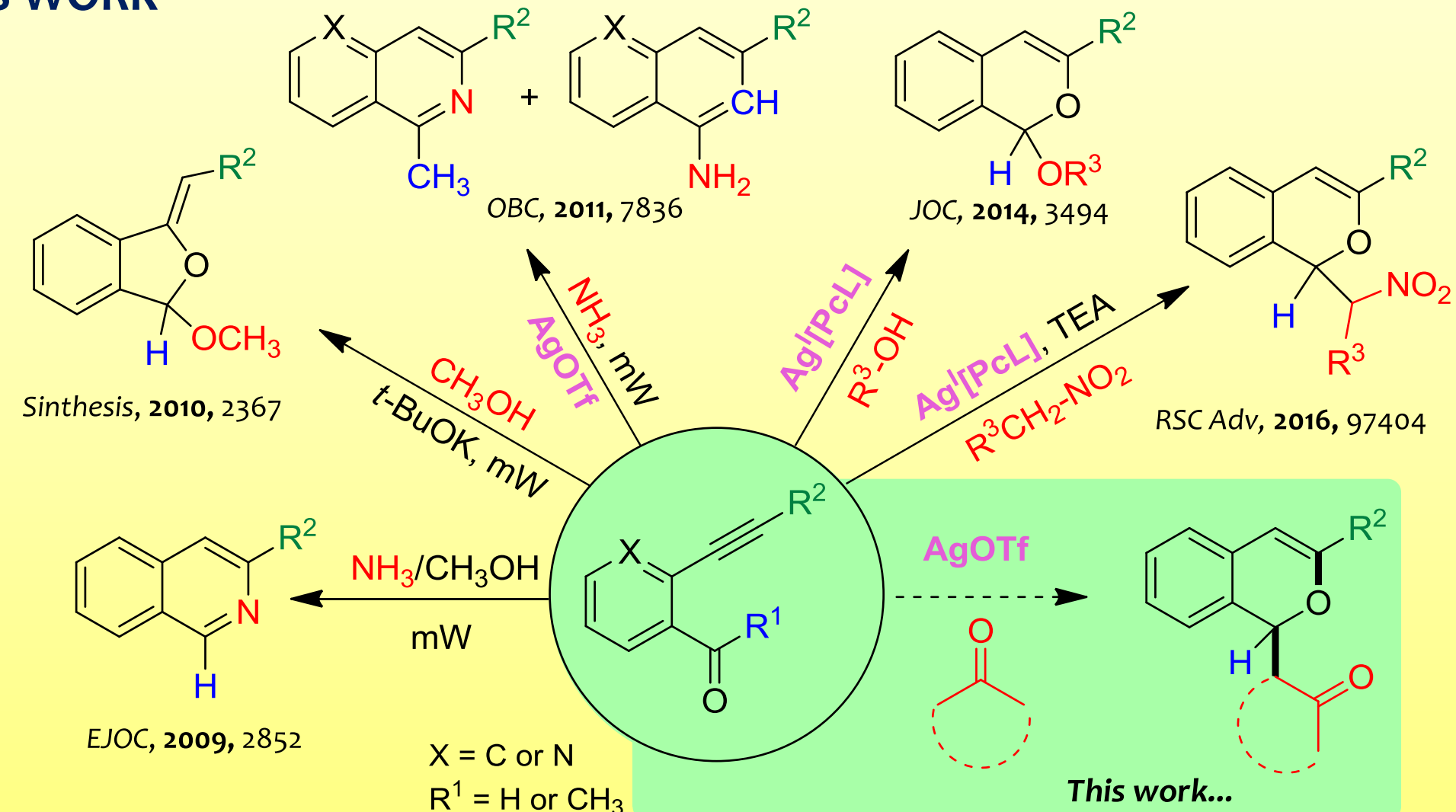
e-mail: giorgio.abbiati@unimi.it



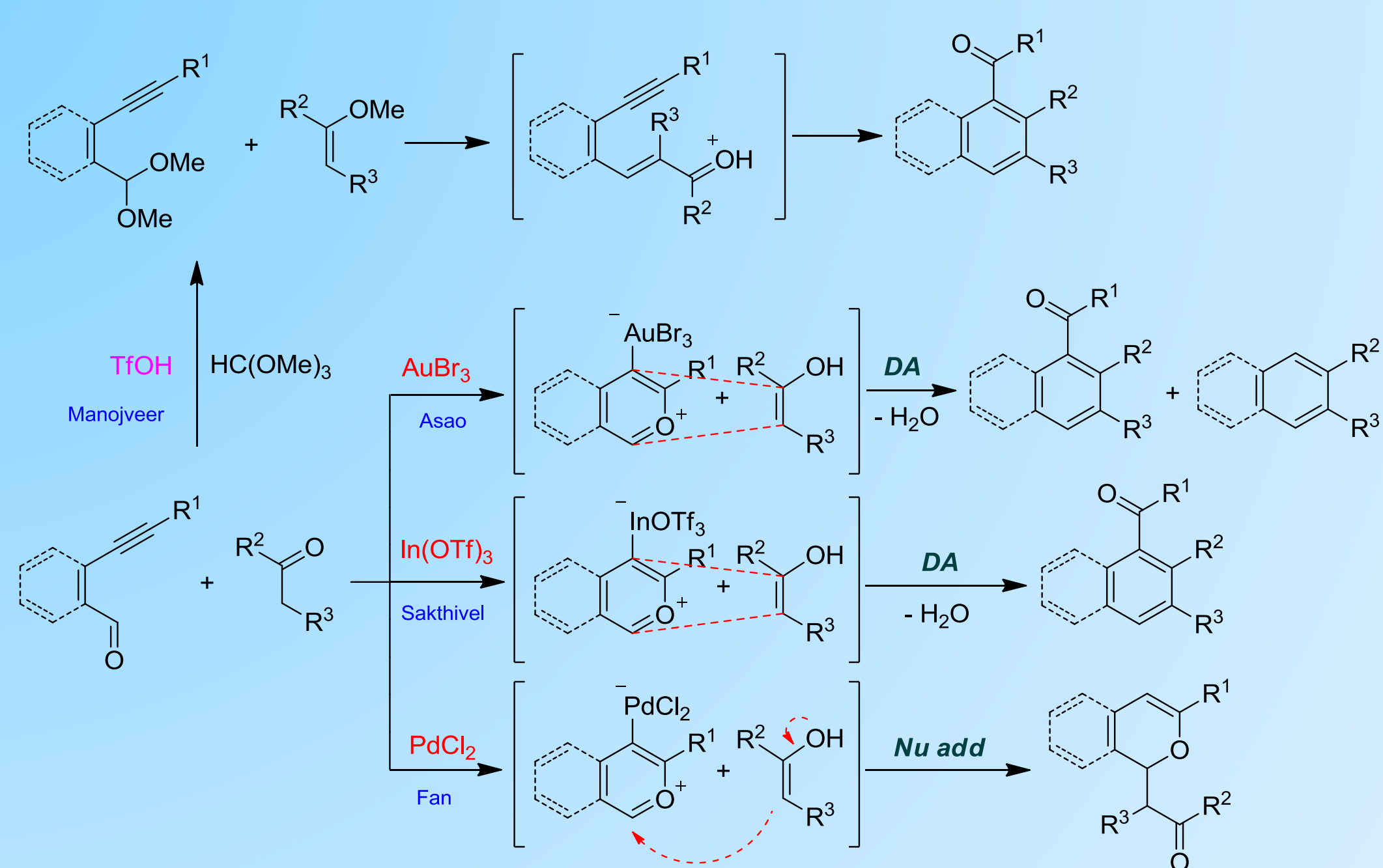
INTRODUCTION

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 one, whereas the reaction with carbon nucleophiles is relatively less investigated. Several different metal catalysts have been used to prepare these heterocycles by this way, and our group provided some recent contributions in the field of silver catalyzed² synthesis of isochromenes. To the best of our knowledge, in the literature there are only few examples on the reaction of 2-alkynyl(hetero)arylaldehydes with enolizable carbonyl compounds.³ In connection with our ongoing interest in the development domino addition/cyclization reactions starting from 1-acyl-2-alkynylarene derivatives, we describe here a silver(I) catalyzed synthesis of isochromenes starting from 2-alkynyl(hetero)arylaldehydes and enolizable carbonyl compounds.⁴

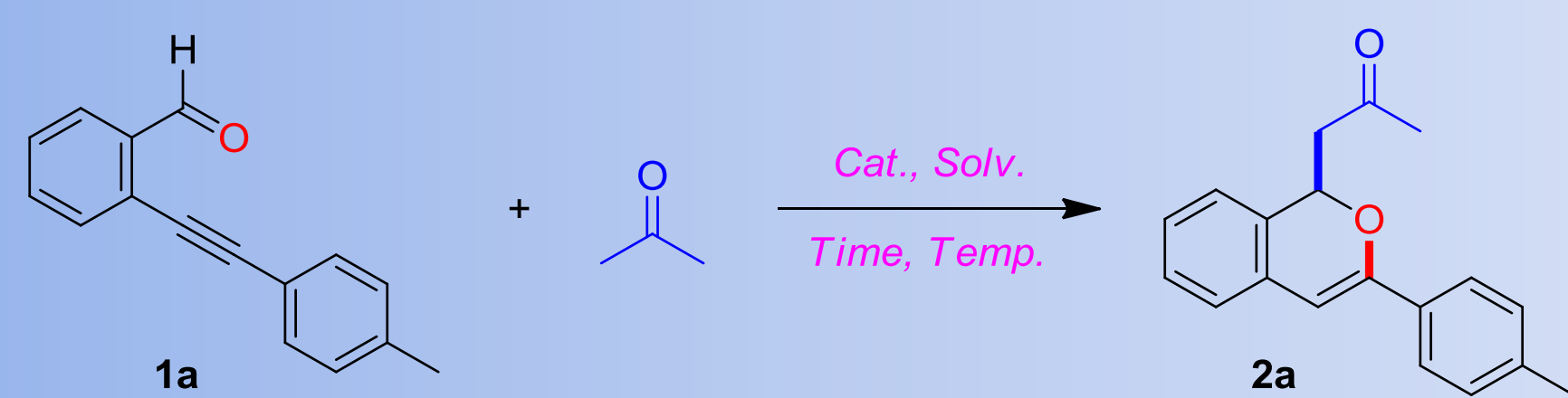
OUR PREVIOUS WORKS on CYCLOISOMERISATION of 1-ACYL-2-ALKYNYLARENES and THIS WORK

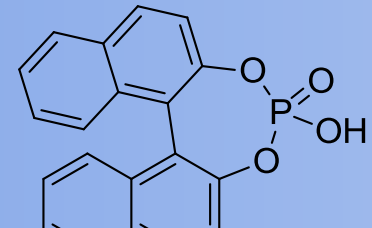


STATE of the ART: 1-ACYL-2-ALKYNYLARENES + ENOLIZABLE CARBONYL COMPOUNDS⁴



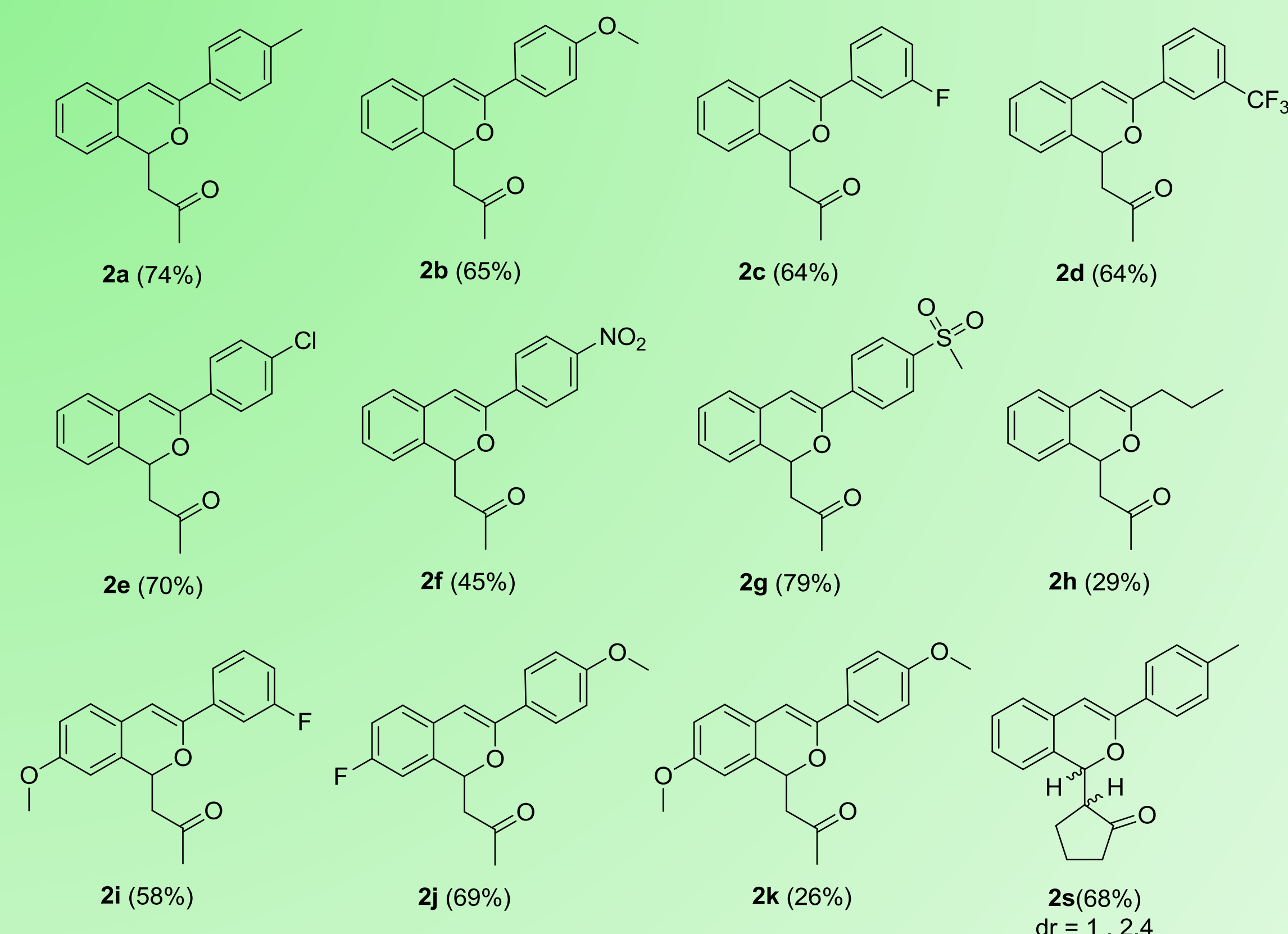
SCREENING of REACTION CONDITIONS (selected)



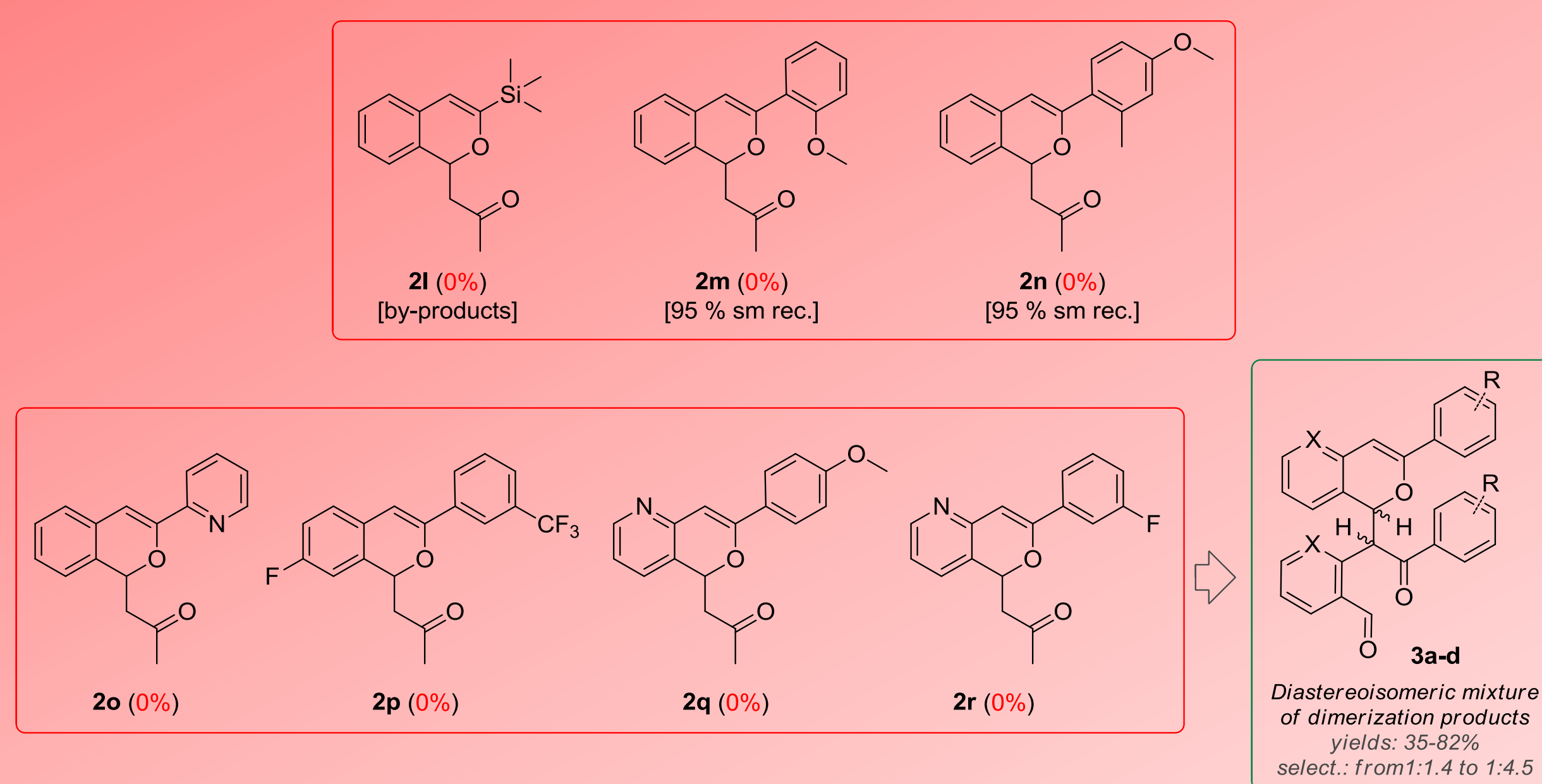
Catalyst (10 mol%)	Solvent	T (°C)	t (h)	2a (yield %)	1a rec. (yield %)
AgOTf	Acetone (68 eq.)	60	12	45	-
AgOTf	Toluene:Acetone 9:1 (~6 eq.)	60	25	10	-
AgOTf	DCE:Acetone 9:1 (~6 eq.)	60	25	-	-
AgOTf	DMF:Acetone 9:1 (~6 eq.)	60	25	15	30
AgOTf	Acetone (68 eq.)	80	7	74	-
AgOTf	Acetone (68 eq.)	r.t.	24	33 ^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	-	30 ^a
	Acetone (68 eq.)	60	24	-	40 ^a

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

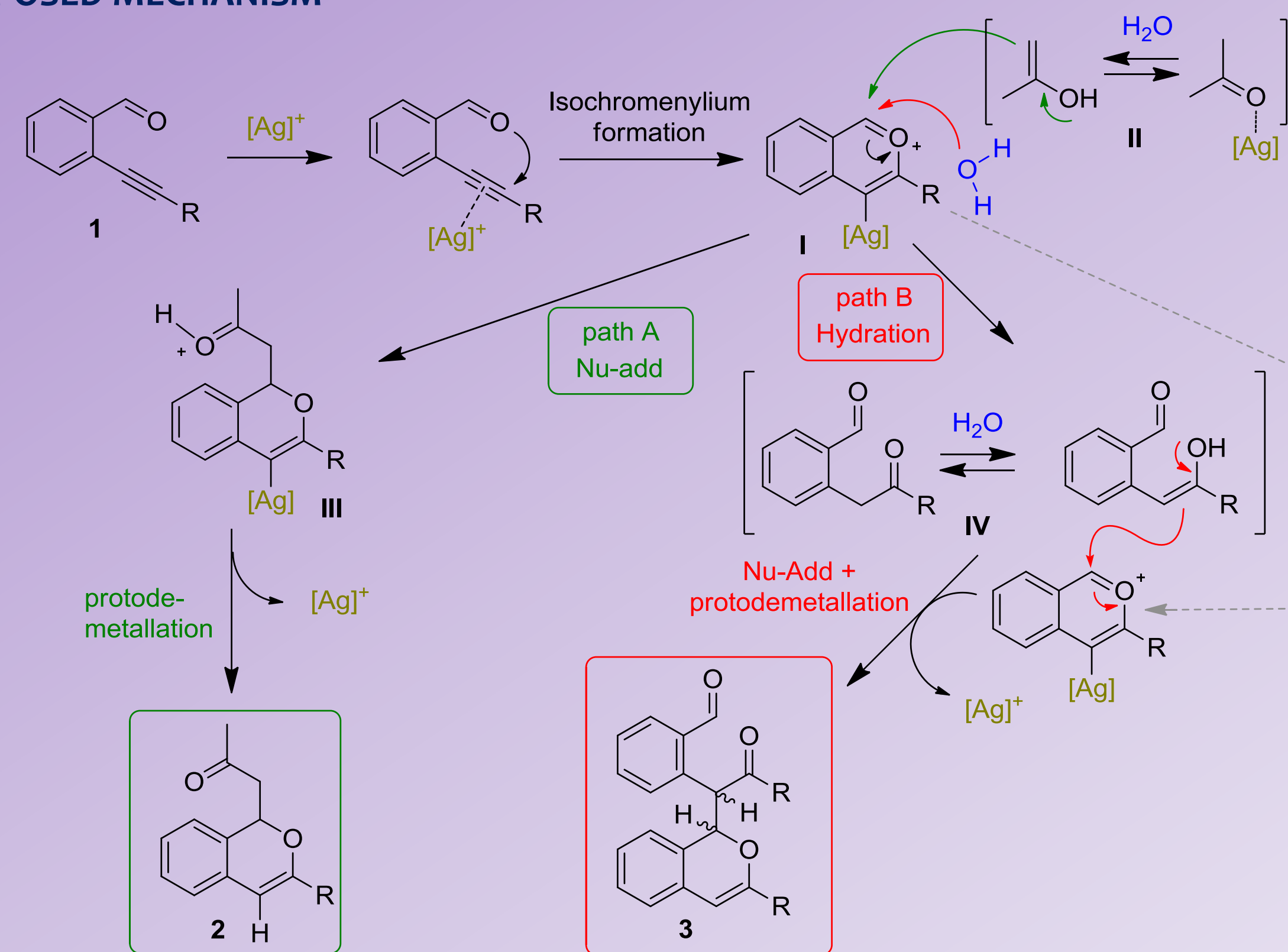
SUCCESSFUL REACTIONS



UNEXPECTED RESULTS

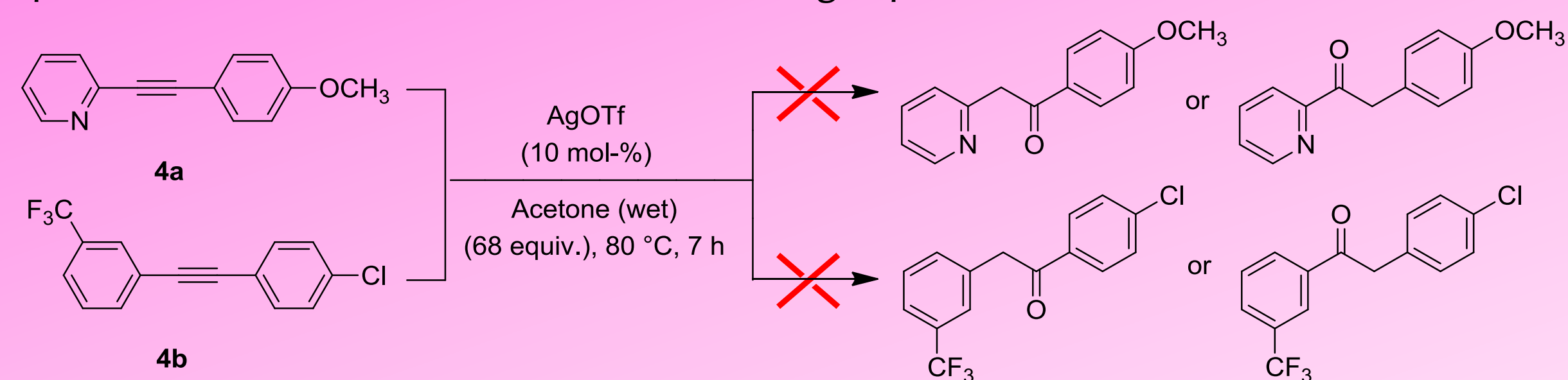


PROPOSED MECHANISM



CONTROL EXPERIMENTS on HYDRATION STEP

The possible formation of intermediate IV by the direct silver-catalyzed hydration of the triple bond was ruled out based on the following experiments.



REFERENCES

- (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (b) Wang, H.; Kuang, Y.; Wu, J. *Asian J. Org. Chem.* **2012**, *1*, 302–312.
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