Iminium–Allenamine Cascade Catalysis: One-Pot Access to Chiral 4*H*-Chromenes by a Highly Enantioselective Michael–Michael Sequence

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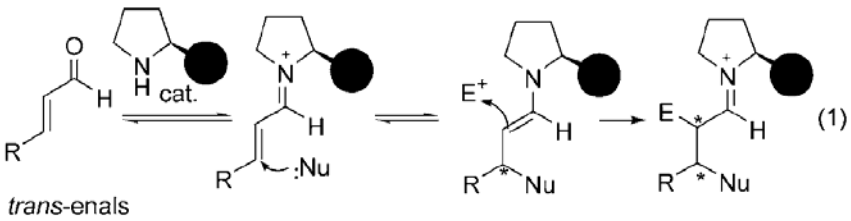
Angew. Chem. Int. Ed., **2010**, Early view

Christophe Allais

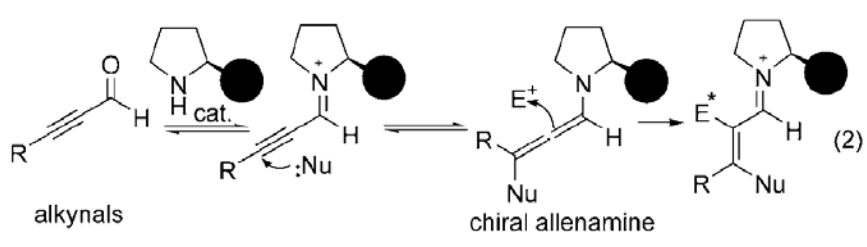
RCC 28.10.2010

A new activation mode…

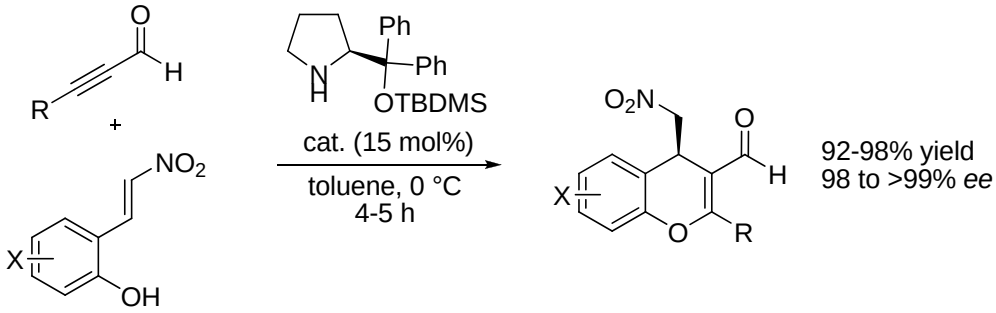
Well-known catalysis *via* iminium-enamine activation of enals



This work: unprecedented iminium-allenamine activation of alkynals

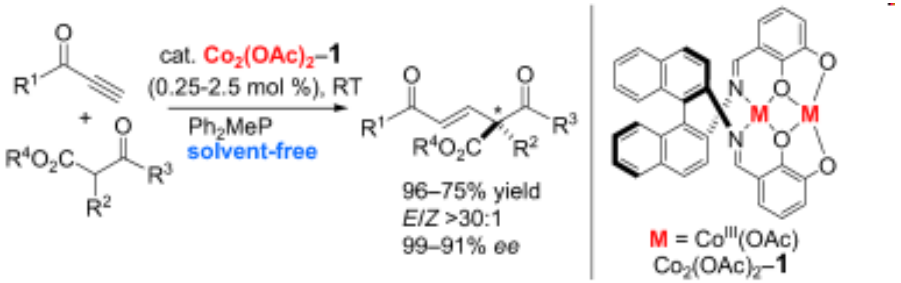


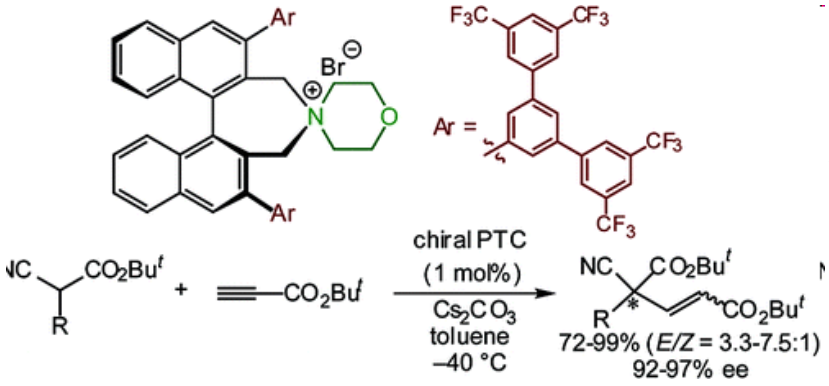
Application to the synthesis of chiral 4*H*-chromene derivatives



About the literature…

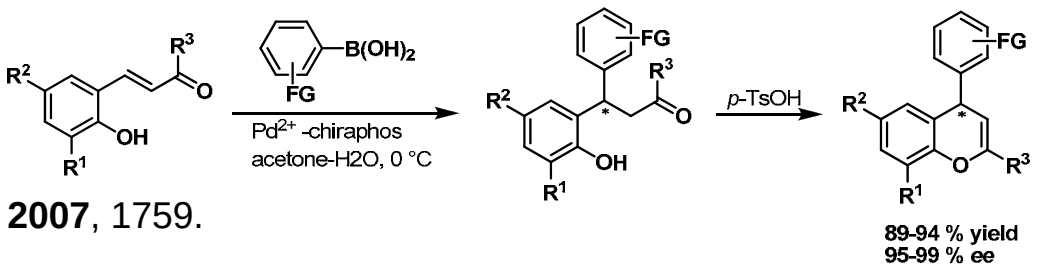
Single-step conjugate addition with alkynones
M. Shibasaki *and co-workers*, *ACIEE*, **2009**, 2218.





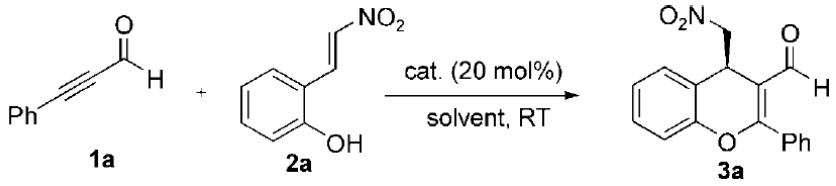
Single-step conjugate addition with acetylenic esters
K. Maruoka *and co-workers*, *JACS*, **2007**, 1038.

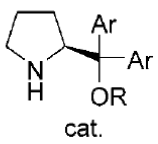
Only one example of asymmetric
Synthesis of 4*H*-chromene derivatives
N. Miyaura *and co-workers*, *Adv. Synth. Catal.* **2007**, 1759.



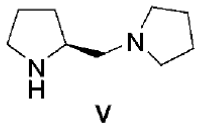
Optimization and mechanism

Jørgensen's catalyst derivatives





I: R = TMS, Ar = Ph
II: R = TES, Ar = Ph
III: R = TBDMS, Ar = Ph
IV: R = TMS, Ar = 3,5-$CF_3C_6H_3$

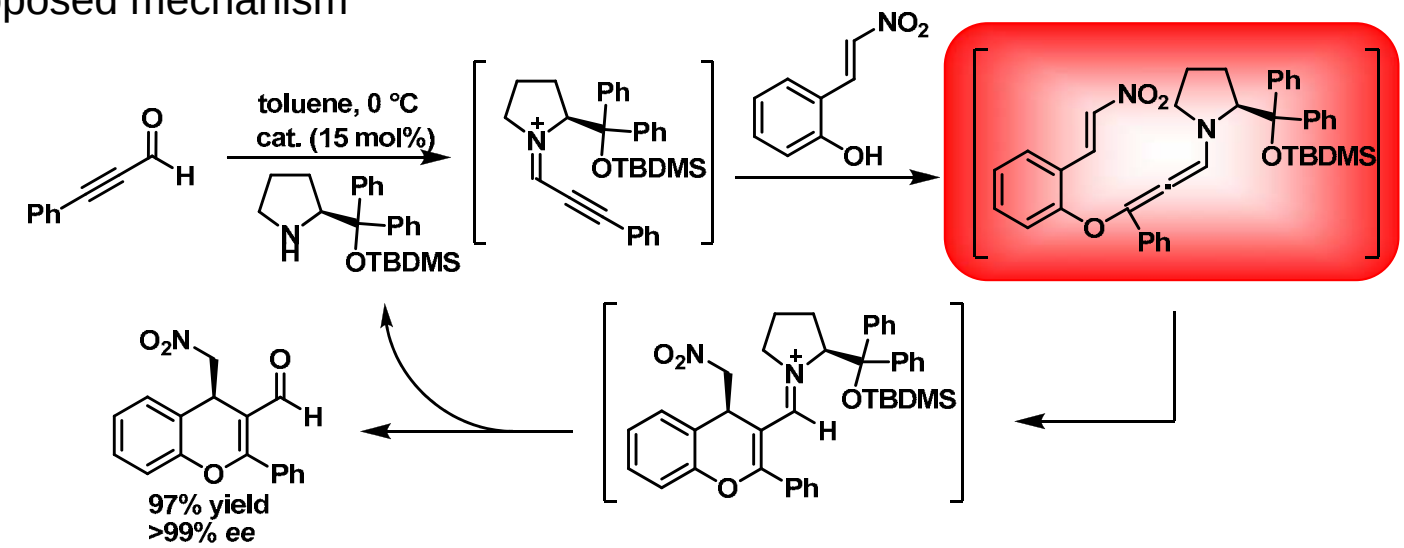


V

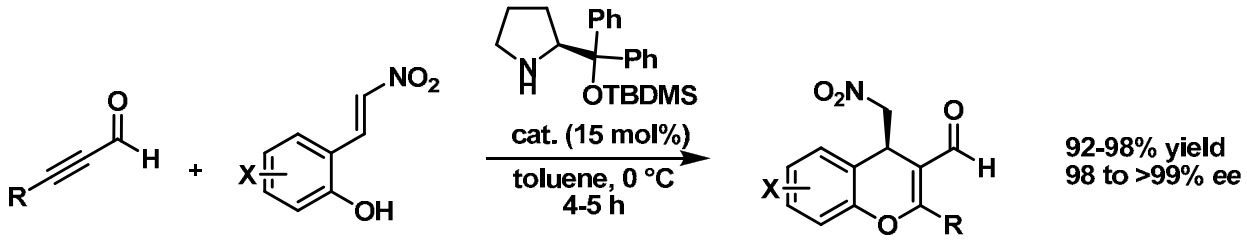
Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	I	CH_2Cl_2	1	95	97
2	II	CH_2Cl_2	1	93	98
3	III	CH_2Cl_2	1	92	98
4	IV	CH_2Cl_2	1	90	96
5	V	CH_2Cl_2	1	91	66
6	III	toluene	1	94	99
7	III	DCE	1	92	98
8[d]	III	toluene	4	97	>99

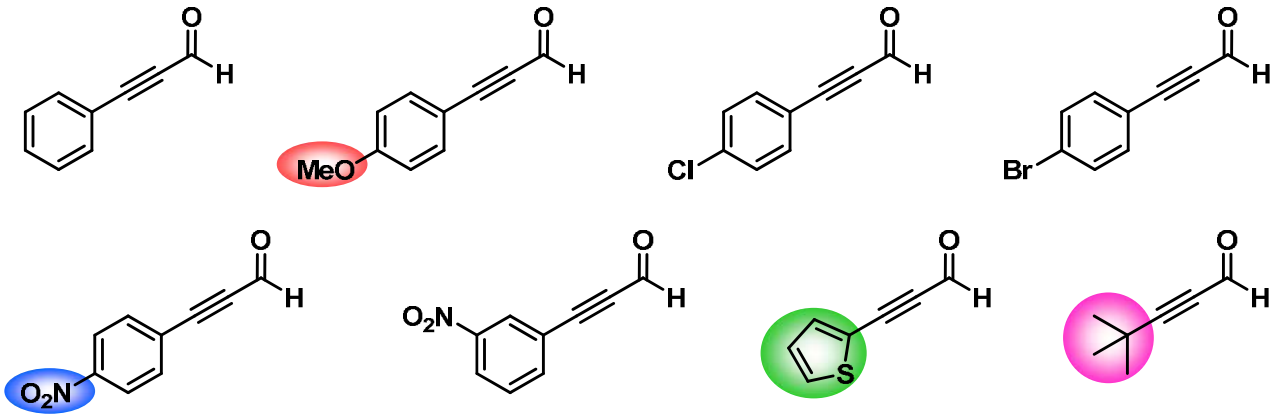
[d] 0 °C, 15 mol% III

Proposed mechanism

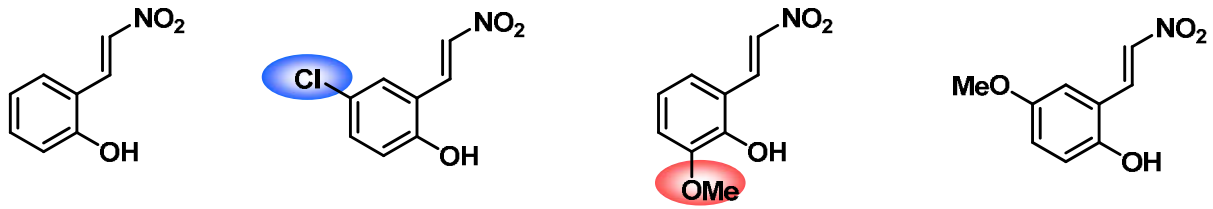


Scope of the reaction





electron donating
electron withdrawing
heteroaryl
aliphatic



electron donating
electron withdrawing

Conclusion

- First chiral iminium-allenamine cascade catalysis: oxa-Michael/Michael process

- Application to the synthesis of biologically interesting 4*H*-chromene derivatives

- High yields and excellent enantioselectivities

- Versatile nitro and aldehyde functionalities (for further elaboration)

- Broad substrate scope successfully employed

- Formation of one C-O bond, one C-C bond and one new stereogenic center

New and original proposed iminium–allenamine activation mode with potent applications in the development of new organocatalytic enantioselective cascade reactions