# SILVER CATALYSED INTRAMOLECULAR CYCLISATION OF 2-ALKYNYL-ACETOPHENONES AND 3-ACETYL-2-ALKYNYLPYRIDINES IN THE PRESENCE OF AMMONIA

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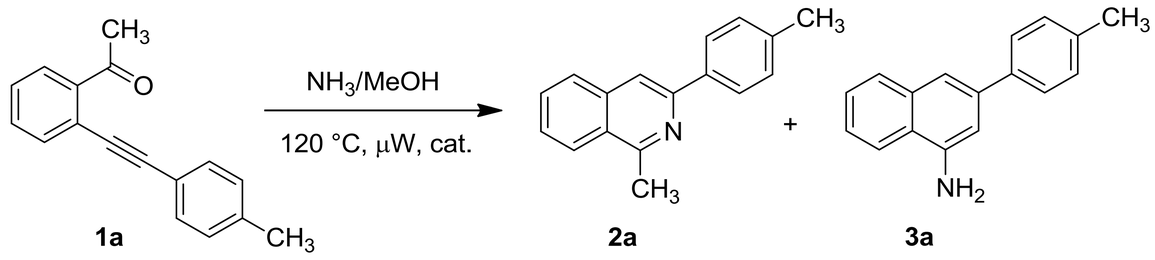
## Introduction

In our laboratories, many efforts have been devoted to the synthesis of nitrogen containing rings by sequential addition/annulation reaction of γ– or δ–ketoalkynes in the presence of ammonia. Some years ago, we reported an in-depth investigation on the synthesis of the pyrazino[1,2-*a*]indole nucleus through the sequential imination/annulation of 2-carbonyl-1-propargylindoles in the presence of ammonia in methanol.[1] This valuable approach has been very recently applied to the synthesis of pyrrolo[1,2-*a*]pyrazines and isoquinolines starting from 2-acetyl-*N*-propargyl pyrroles and 2-alkynyl-benzaldehydes, respectively,[2] and the approach to isoquinolines was also successfully transformed in a multicomponent process.[3] But, unexpectedly, when we tried to react 2-alkynylacetophenone derivatives under optimized conditions for the domino process the reaction failed. This result prompted us to investigate the reaction of alynyl ketones more in depth.

These are our results…

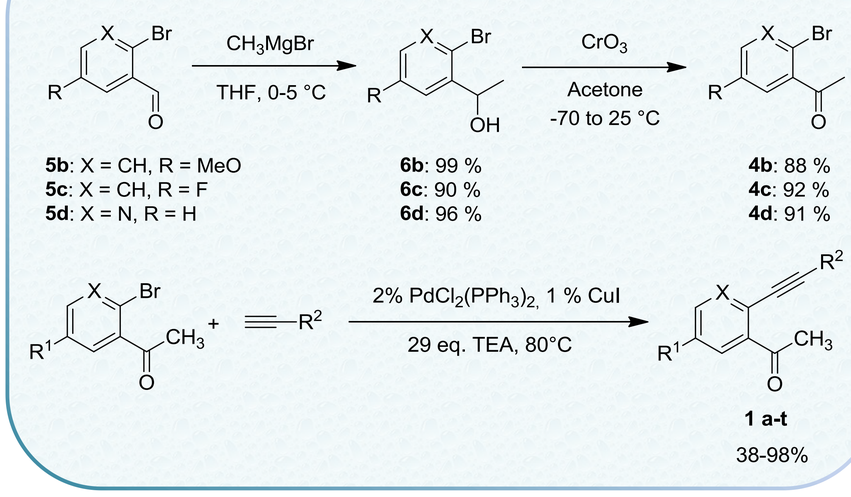
## Screening of reaction conditions for domino addition/annulation



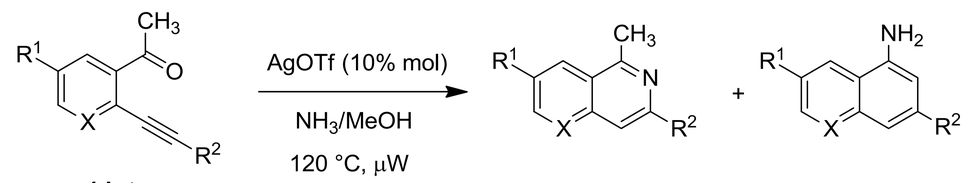

| Entry | t (min) | Catalyst | 2a yield % | 3a yield % | 1a (rec.) yield % | Overall yield % | Ratio 2a/3a |
|---|---|---|---|---|---|---|---|
| 1 | 120 | - | 11[a] | - | 72 | 11 | - |
| 2 | 120 | 4Å molecular sieve | 4 | - | 45 | 4 | - |
| 3 | 30 | $TiCl_4$ (3 eq.) | traces | - | - | - | - |
| 4 | 15 | $TiCl_4$[b] | traces | - | - | - | - |
| 5 | 80 | $TiCl_4 \cdot 2$ THF[b] | 11 | - | 18 | 11 | - |
| 6 | 100 | $Pd(OAc)_2$[b] | 46 | 25 | - | 71 | 1.8 |
| 7 | 60 | $PdCl_2$[b] | 23 | 19 | 7 | 42 | 1.2 |
| 8 | 120 | $Cu(OTf)_2$[b] | 23 | 13 | 8 | 36 | 1.8 |
| 9 | 120 | CuI[b] | 38 | 20 | - | 58 | 1.9 |
| 10 | 120 | AgF[b] | 15 | 14 | 17 | 29 | 1.1 |
| 11 | 120 | $Ag_2O$[b] | 10 | 10 | 18 | 20 | 1.0 |
| 12 | 60 | $AgSbF_6$[b] | 26 | 17 | 4 | 43 | 1.5 |
| 13 | 60 | $AgNO_3$[b] | 46 | 36 | 9 | 82 | 1.3 |
| **14** | **45** | **AgOTf[b]** | **58** | **40** | - | **98** | 1.5 |
| 15 | 120 | $NaAuCl_4 \cdot 2\ H_2O$[b] | 11 | 6 | 31 | 17 | 1.8 |
| 16 | 30 | $PPh_3AuCl$[b] | 41 | 34 | 10 | 75 | 1.2 |
| 17 | 60 | $PPh_3AuCl$ (7.5 mol%) AgOTf[b] | 27 | 43 | - | 70 | 0.6 |
| 18 | 120 | $InCl_3$[b] | 5 | - | 18 | 5 | - |
| 19 | 120 | $In(OTf)_3$[b] | Traces | - | - | - | - |

[a] The reaction performed under conventional heating at 110 °C overnight gave only traces of isoquinoline **2a**.
[b] 10 mol%.

## Synthesis of starting compounds




## AgOTf catalysed domino addition/cyclisation reaction

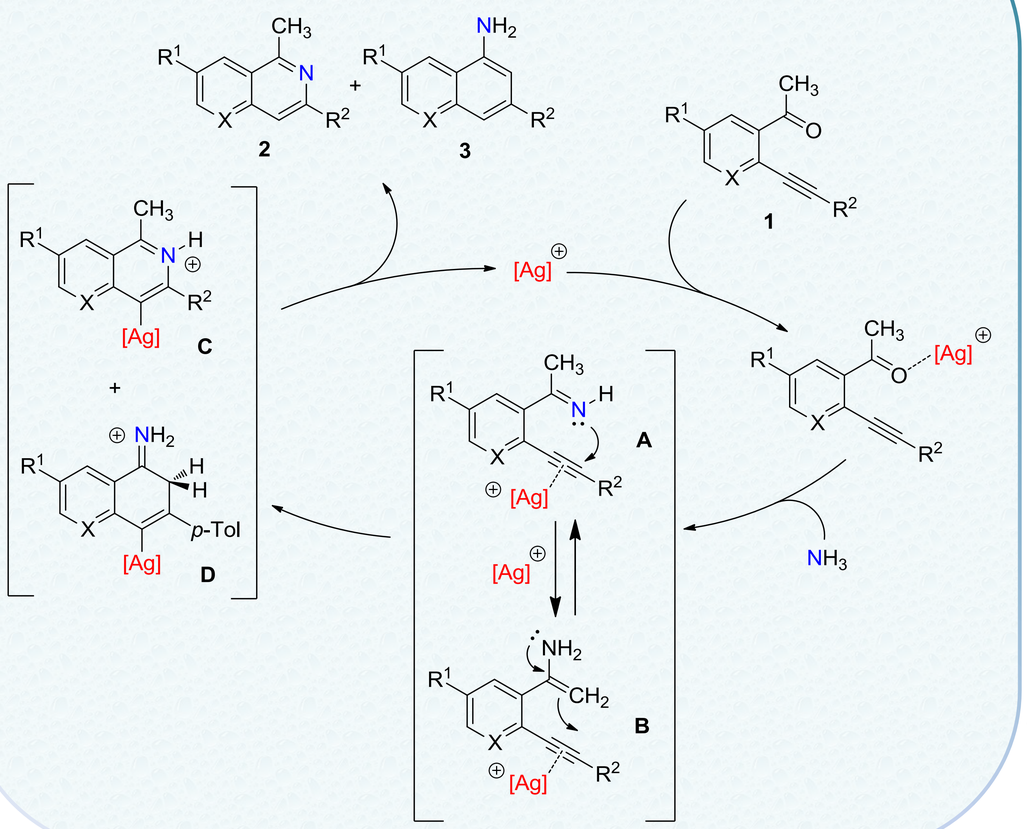



| Entry | 1,2,3 | X | $R^1$ | $R^2$ | t (min) | 2 yield % | 3 yield % |
|---|---|---|---|---|---|---|---|
| 1 | b | CH | H |  | 120 | 36 | 44 |
| 2 | c | CH | H |  | 90 | 32 | 41 |
| 3 | d | CH | H |  | 90 | 35 | 40 |
| 4 | e | CH | H |  | 120 | 23 | 39 |
| 5 | f | CH | H |  | 210 | traces | traces |
| 6 | g | CH | H |  | 90 | traces | - |
| 7 | h | CH | H | $CH_3(CH_2)_4$— | 90[a] | 63 | 15 |
| 8 | i | CH | H | $CH_3(CH_2)_5$— | 90 | 61 | 20 |
| 9 | j | CH | H | $CH_3(CH_2)_7$— | 90[b] | 44 | 14 |
| 10 | k | CH | H |  | 120 | 25 | - |
| 11 | l | CH | MeO | $CH_3(CH_2)_2$— | 150 | 71 | 17 |
| 12 | m | CH | F | $CH_3(CH_2)_2$— | 150 | 55 | 15 |
| 13 | n | N | H |  | 60 | 41 | 25 |
| 14 | o | N | H |  | 30 | 48 | 19 |
| 15 | p | N | H |  | 105 | - | - |
| 16 | q | N | H | $CH_3(CH_2)_4$— | 60 | 57 | 25 |
| 17 | r | N | H | $CH_3(CH_2)_5$— | 60 | 75 | - |
| 18 | s | N | H |  | 60 | 20 | 7 |
| 19 | t | N | H |  | 60 | ($R^2$=H) 37[c] | traces[c] |

[a] The reaction, performed without catalyst under conventional heating at 110 °C overnight gave only the isoquinoline **2h** in 35% yield.
[b] Catalysed with $AgNO_3$ (10 mol%).
[c] Desilylated product.

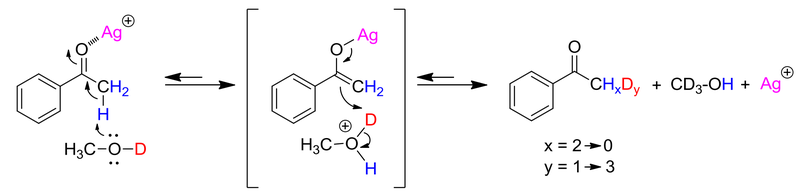
## Proposed mechanism

for the AgOTf catalysed nucleophilic addition/annulation sequence




## Dynamic $^1$H NMR study

The catalyst is able to speed up the tautomeric equilibria

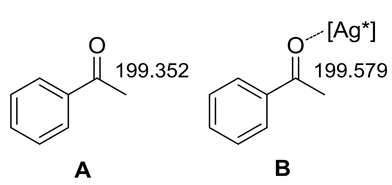


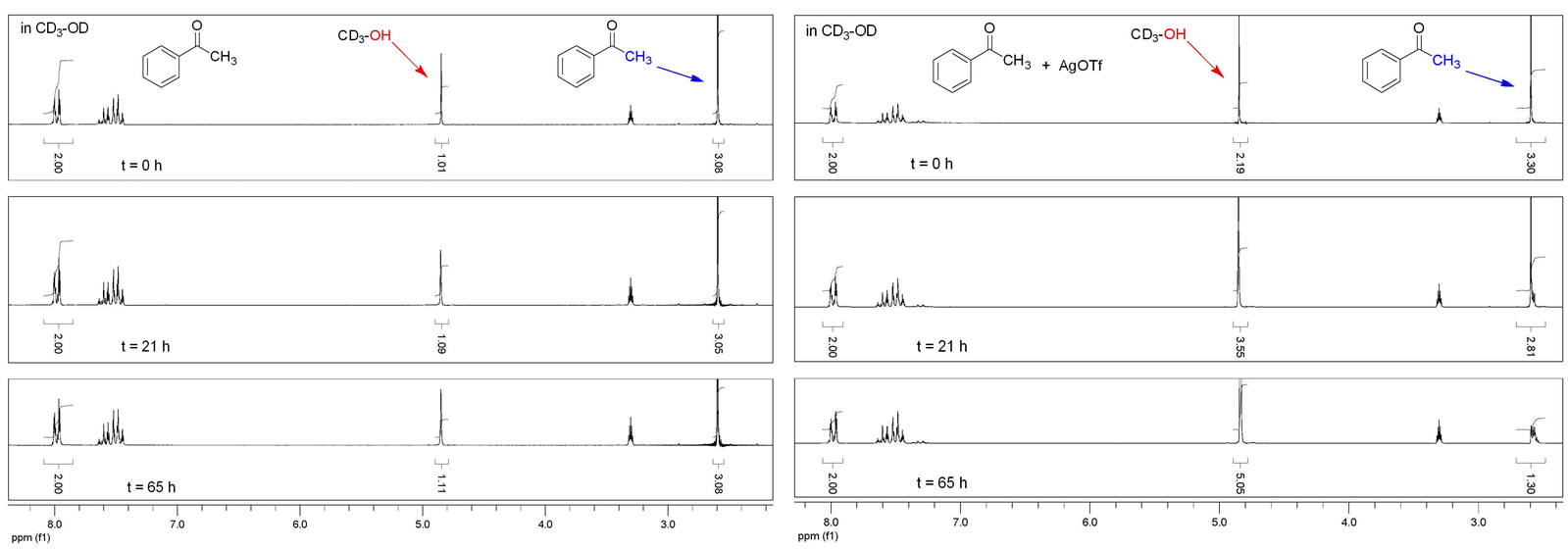

| Time (h) | Acetophenone in $CD_3OD$ | | Acetophenone + AgOTf (50 mol%) in $CD_3OD$ | |
|---|---|---|---|---|
| | Integral (ref. to 2 CH arom.) | | Integral (ref. to 2 CH arom.) | |
| | $CH_3$-CO-Ph | $CD_3OH$ | $CH_3$-CO-Ph | $CD_3OH$ |
| 0 | 3.08 | 1.01 | 3.30 | 2.19 |
| 16 | 3.11 | 1.12 | 2.94 | 2.40 |
| 21 | 3.05 | 1.09 | 2.81 | 3.55 |
| 44 | 3.07 | 1.10 | 1.92 | 4.42 |
| 65 | 3.09 | 1.11 | 1.30 | 5.05 |

## $^{13}$C NMR spectra of acetophenone in $CD_3OD$

in the absence (A) and in the presence (B) of AgOTf (1 eq.)

The metal showed a weak interaction with the carbonyl oxygen: a slight shift of the C carbonyl signal at higher frequencies indicated a deshielding of carbonyl carbon.




**References:**

1. (a) Abbiati, G.; Arcadi, A.; Beccalli, E.; Rossi, E. *Tetrahedron Lett.* **2003**, *44*, 5331. (b) Abbiati, G.; Arcadi, A.; Bellinazzi, A.; Beccalli, E.; Rossi, E.; Zanzola S. J. *Org. Chem.* **2005**, *70*, 4088.Abbiati, G.; Arcadi, A.; Beccalli, E.; Rossi, E. *Tetrahedron Lett.* **2003**, *44*, 5331.
2. Alfonsi, M.; Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2009**, 2852–2862.
3. Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. *Synlett* **2010**, 2672–2676.