UNIVERSIDAD DE GUANAJUATO

The 19th International Electronic Conference on Synthetic Organic Chemistry

Synthesis of novel Ylides via a cascade process: Ugi 4CR/Ylide initiated Michael/ring opening chromone.

Submission ID: sciforum-005801

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WHY MCR

Readily Available Starting Materials

Better yields

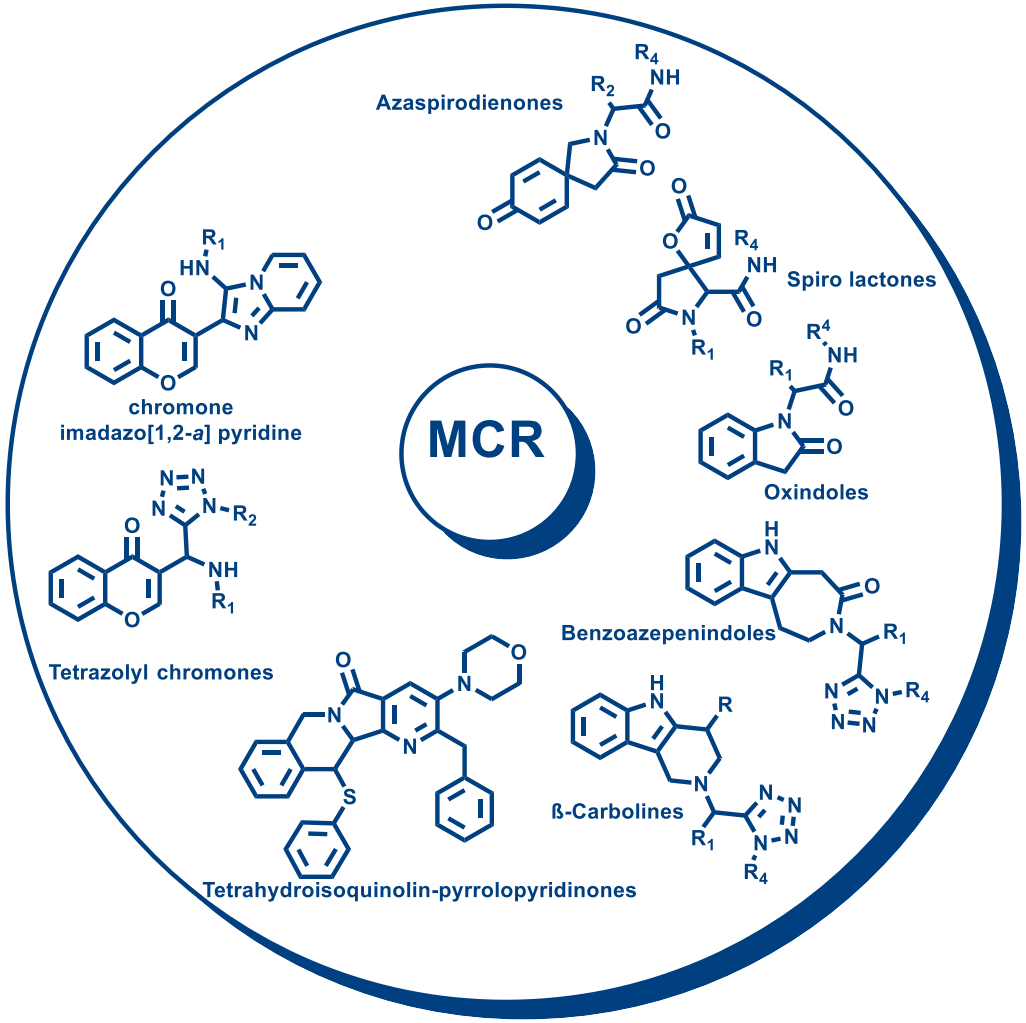
Simple

One Pot

Domling, A. *Chem. Rev*. **2006**, *106,* 17-89.
Ugi, I. *et al*. Angew. *Chem. Int. Ed.* **2000**, *39*, 3168-3210.
Zhu, J. *et al. Eur. J. Org. Chem*. **2003**, 1133-1144.

Dra. Gámez research group investigation in synthesis of heterocycles using multicomponent reactions

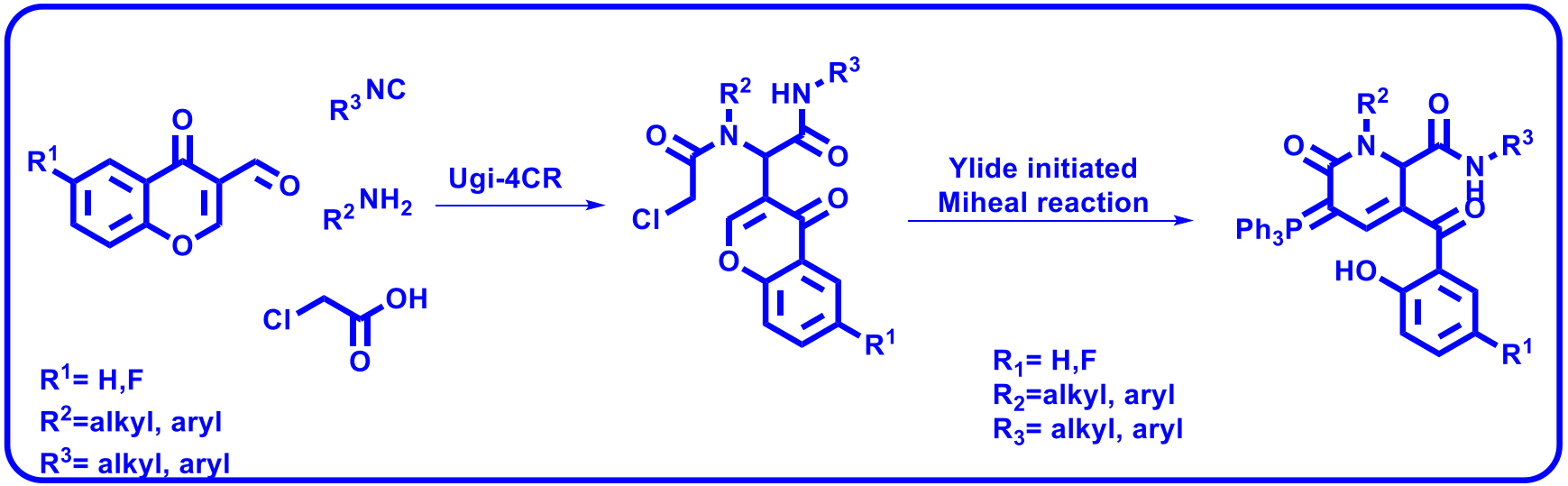
Past targets



a) Unnamatla M. Basavanag, Aurelie dos Santos, Laurent el Kaim*, Rocío Gámez-Montaño,* Laurence Grimaud.* *Angewandte Chemie Int Ed.* **2013**, 52, 7194-7197. b) Luis E. Cárdenas-Galindo, Alejandro Islas-Jácome, Carlos J. Cortes-García, Laurent El Kaim* and Rocío Gámez-Montaño* *J. Mex. Chem. Soc.* **2013**, *57 (4)*, 283-289. c) Kranti Kishore, Unnamatla M. Basavanag, Alejandro Islas-Jácome and Rocío Gámez-Montaño* *Tetrahedron Lett* 56 (1) 155-158 **2015**. d) *Raul E. Gordillo Cruz*, Angel Rentería-Gómez, Alejandro Islas-Jácome, Carlos J. Cortes-Garcia, Erick Díaz-Cervantes, Juvencio Robles, Rocío Gámez-Montaño* *Org. Biomol. Chem.*, **2013**, 11 (38), 6470 – 6476.

Synthesis of novel stable Ylides via Ugi 4CR/Ylide initiated Michael sequence.

Presentation of Methodology



Introduction

General objectives

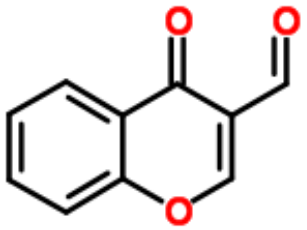
- Building Novel Phosphorus containing compounds using Ugi MCR followed by ylide initiated Michael reaction
- Study of the nucleophilic based ring opening reactions of chromone moiety.
- Synthesis and characterization of compounds using NMR, MASS, HRMS, IR, etc

STABLE YLIDES

- Ylides are nucleophiles, Ylides are reactive intermediates
- Ylides are used in C-C bond forming reactions via Wittig reaction and small ring formations .
- Researchers have also widely used ylides for the synthesis of small ring compounds such as epoxides, cyclopropanes, and aziridines.

Sun, X.-L.; Tang, Y. *Accounts of Chemical Research* **2008**, *41*, 937.

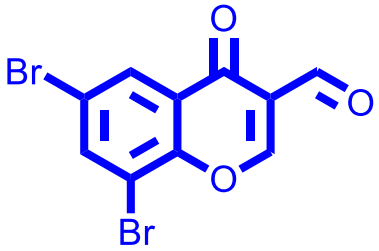
Structure and Activity Relationship of 4-oxo-4H-chromene-3-carbaldehyde



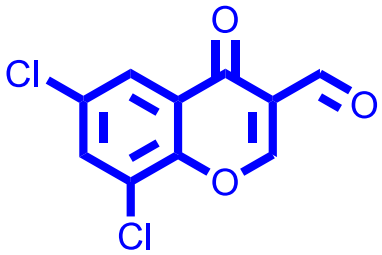
•*Several 3-formylchromone derivatives were examined for their tumor cell-cytotoxic, anti-Helicobacter pylori, urease inhibitory and anti-HIV activity.*

cytotoxic activities

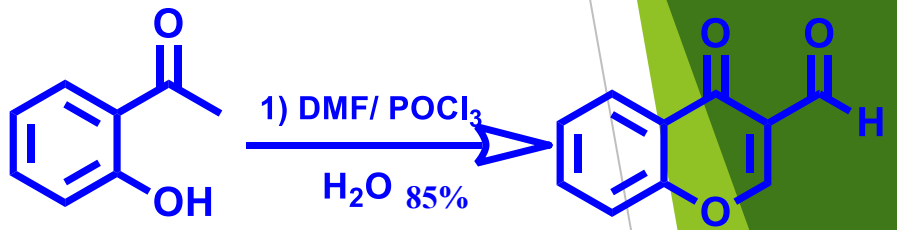
Anti proliferative activity

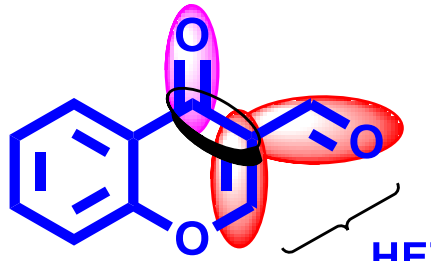


***urease** inhibitory*



anti-Heliobacter. pylori activity





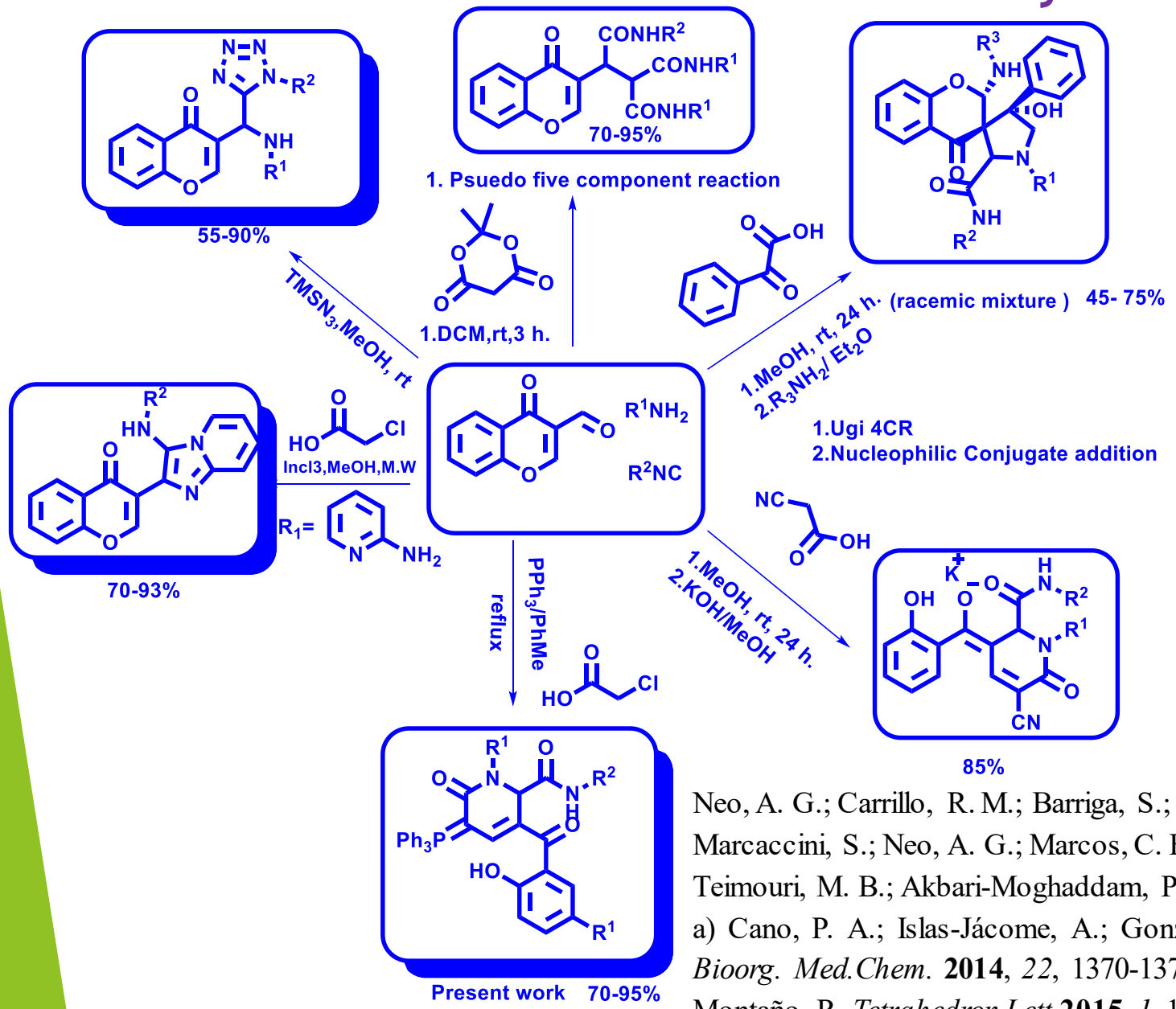
HETERODIENE

Michael Acceptor

Reactive electrophilic center

1.Kawase et al, *in vivo* , **2007,** 21,829-834.
2.Nohara, A. ; Umetani, T.; Sanno, Y. *Tetrahedron Lett.* **1973**, 22, 1995.
3.Nohara, A. ; Umetani, T.; Sanno, Y. *Tetrahedron*, **1974,** 30, 3553.

Reported Isocyanide based multicomponent reactions based 3-formyl chromone



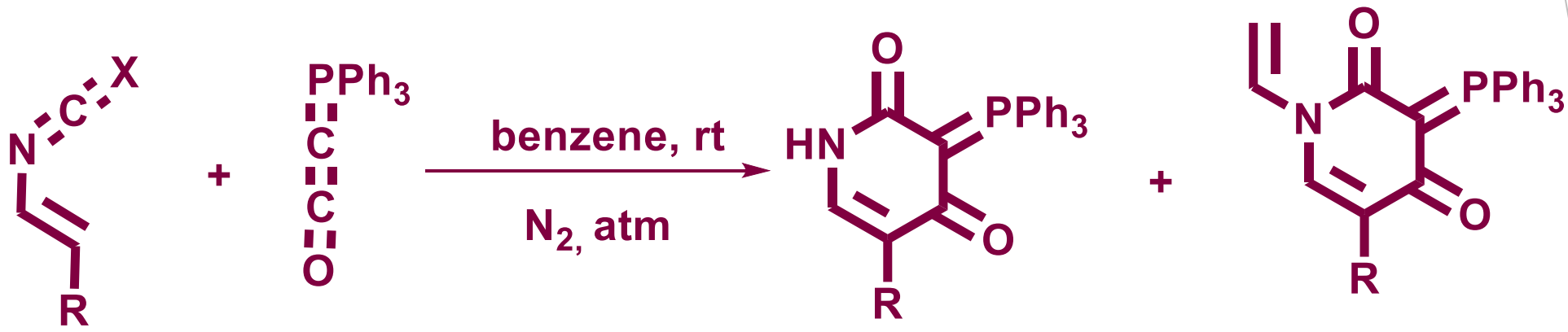
Neo, A. G.; Carrillo, R. M.; Barriga, S.; Momán, E.; Marcaccini, S.; Marcos, C. F. *Synlett* **2007**, *2*, 0327-0329.

Marcaccini, S.; Neo, A. G.; Marcos, C. F. *J. Org. Chem.* **2009**, *74*, 6888-6890.

Teimouri, M. B.; Akbari-Moghaddam, P.; Golbaghi, G. *ACS Combinatorial Science* **2011**, *13*, 659-666.

a) Cano, P. A.; Islas-Jácome, A.; González-Marrero, J.; Yépez-Mulia, L.; Calzada, F.; Gámez-Montaño, R. *Bioorg. Med.Chem.* **2014**, *22*, 1370-1376.b) Kishore, K. G.; Basavanag, U. M. V.; Islas-Jácome, A.; Gámez-Montaño, R. *Tetrahedron Lett* **2015,** *1,* 155-158 .

Stable ylides by [4+2] cycloaddition reactions



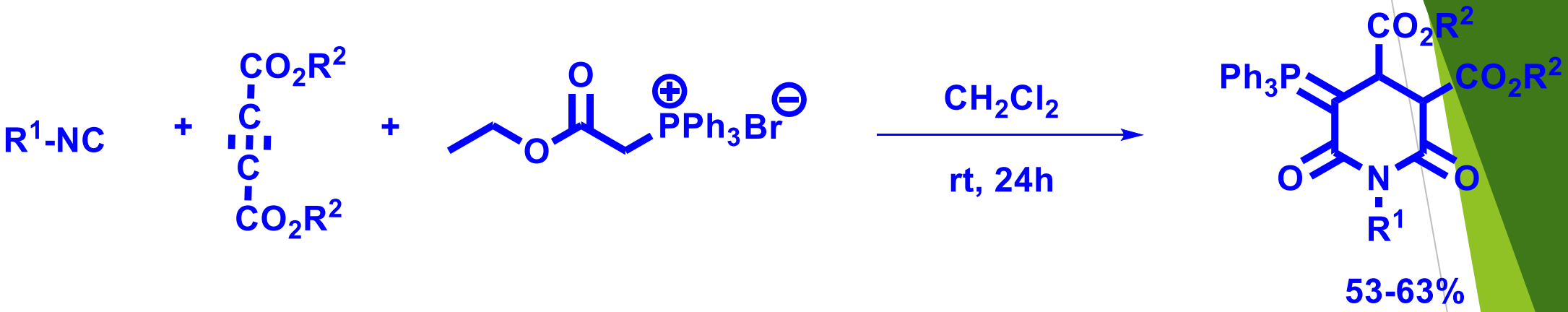
98% overal yield

X = O, R = H
X = S, R = H
X = S, R = Ph

X = O, R = H
X = S, R = H
X = S, R = Ph

1. Kniežo, L.; Kristian, P.; Imrich, J.; Ugozzoli, F.; Andreetti, G. D. *Tetrahedron* **1988**, *44*, 543-556.

Stable ylides from Isocyanide base multicomponent reaction.

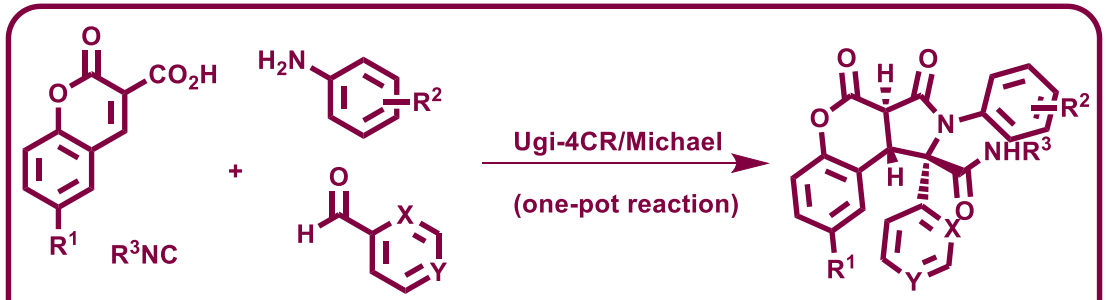


Product	R^1	R^2	Yield (%)
a	Cyclohexyl	Me	63
b	Cyclohexyl	Et	61
c	Cyclohexyl	t-Bu	56
d	t-Bu	Et	51

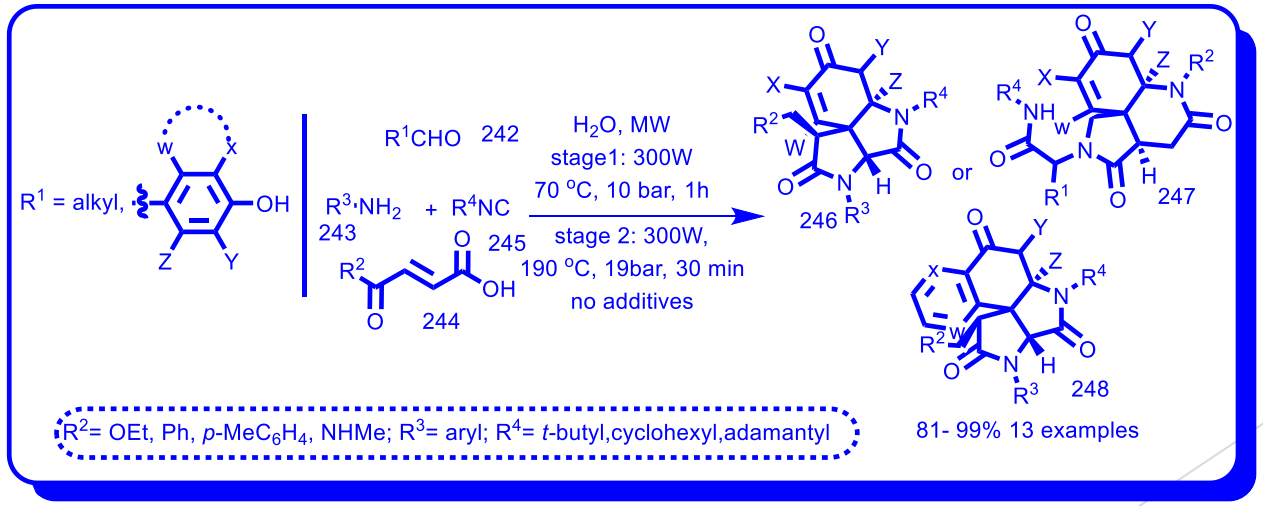
Shaabani, A.; Soleimani, E.; Khavasi, H. R.; Hoffmann, R.-D.; Rodewald, U. C.; Pöttgen, R. *Tetrahedron Lett.* **2006**, *47*, 5493-5496.

Reported methodologies of Ugi-4CR/Michael reactions

Zhen yang et al. in **2010** reported Synthesis of chromeno[3,4-*c*]pyrrole-3,4-diones derivatives via Ugi-4CR/Michael.

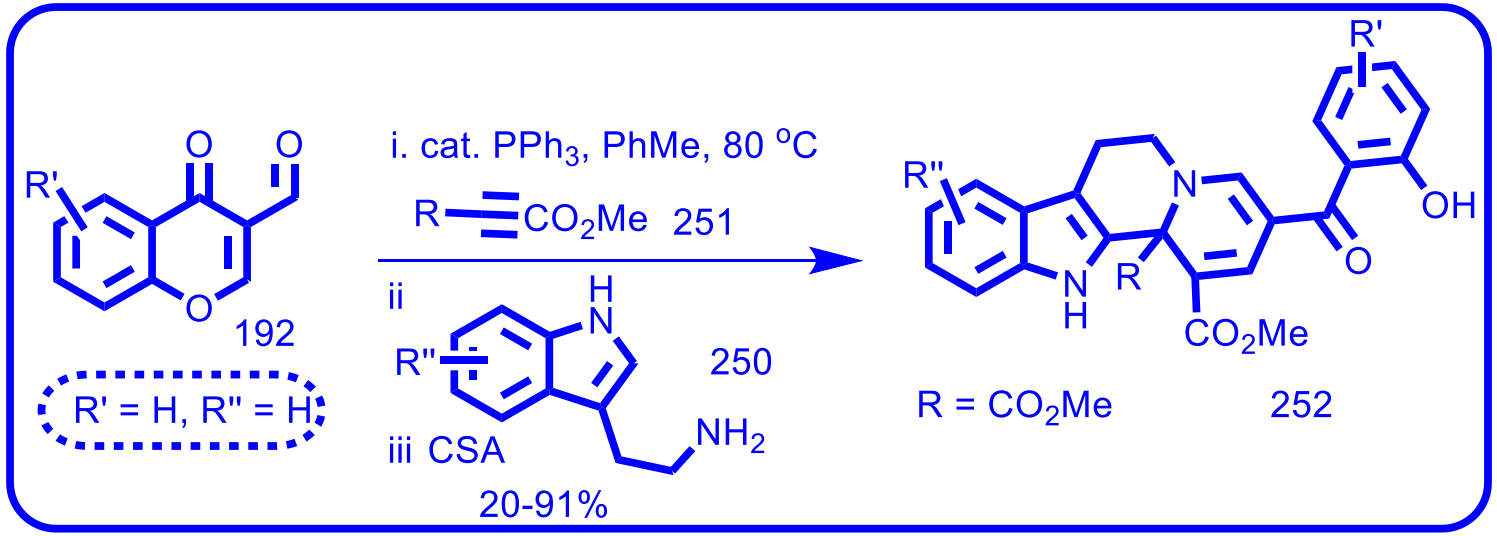


Later in **2011** *Santra et al.* reported Ugi/Michael/Aza-Michael Cascade Reaction.



Che, C.; Li, S.; Jiang, X.; Quan, J.; Lin, S.; Yang, Z. *Org. Lett.* **2010**, *12*, 4682-4685.
Santra, S.; Andreana, P. R. *Angew. Chem. Int. Ed.* **2011**, *50*, 9418-9422.

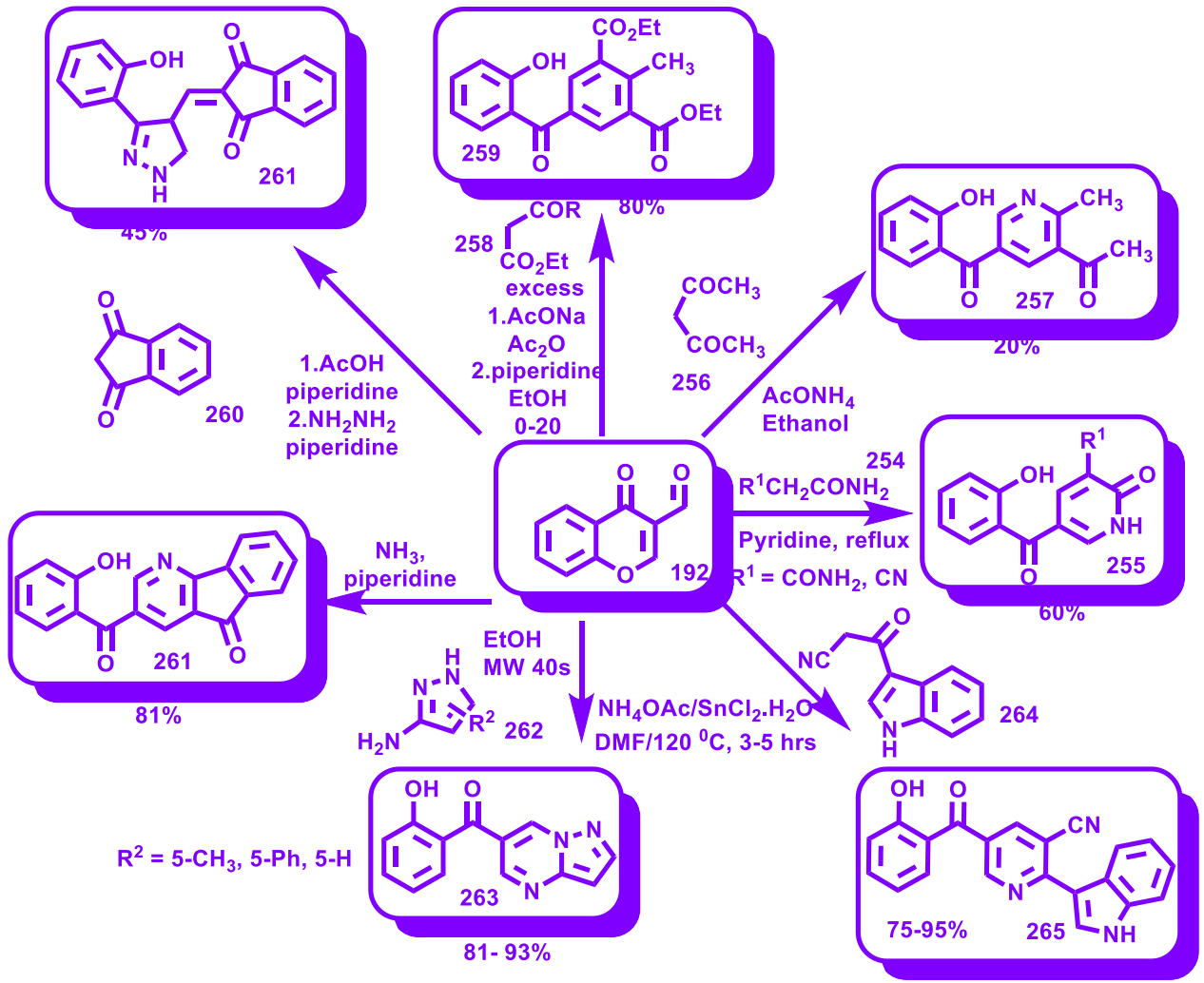
Heiko dückert et al. in 2012 report the development of a one-pot, twelve-step cascade reaction sequence that includes nine different reactions and two opposing kinds of organo catalysis.



Dückert, H.; Pries, V.; Khedkar, V.; Menninger, S.; Bruss, H.; Bird, A. W.; Maliga, Z.; Brockmeyer, A.; Janning, P.; Hyman, A.; Grimme, S.; Schürmann, M.; Preut, H.; Hübel, K.; Ziegler, S.; Kumar, K.; Waldmann, H. *Nat. Chem. Biol.* **2012**, 8, 179-184.

Reported methodologies based on ring opening of 3-formychromone

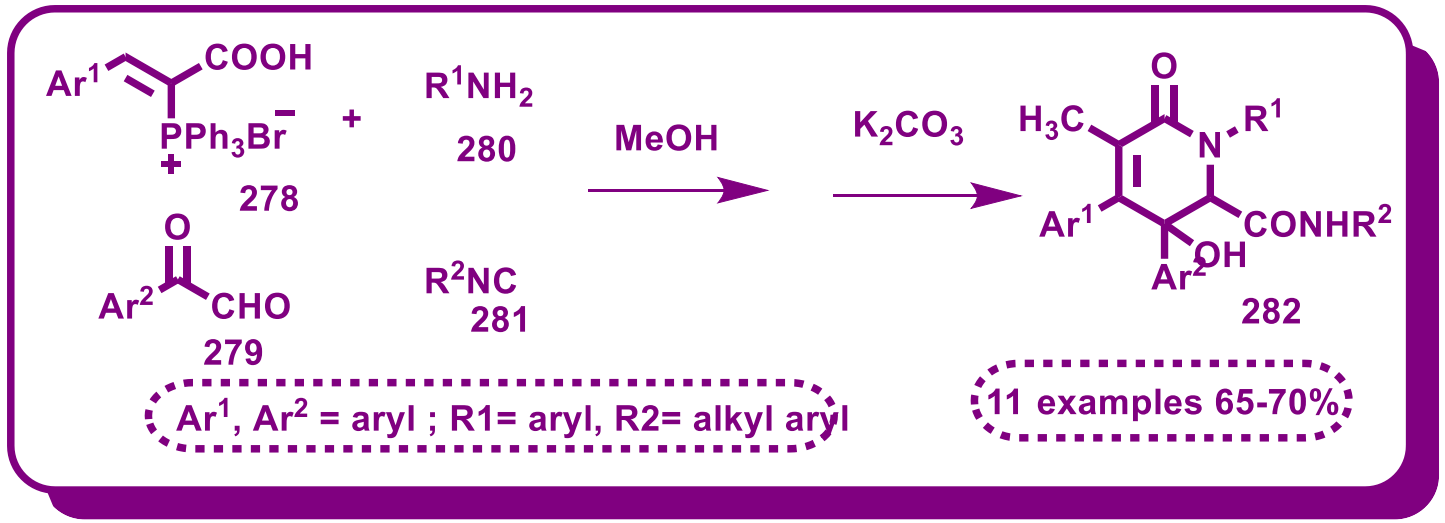
One-Pot Reactions of 3-formylchromone with active methylene and methyl compounds and some subsequent reactions of the resulting condensation products.

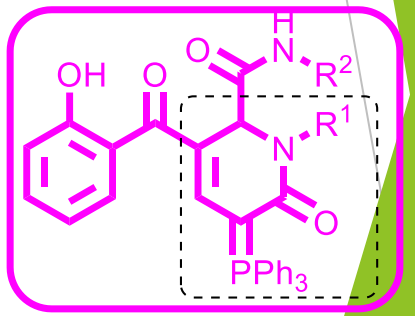


Gasparová, R.; Lácova, M. *Molecules* **2005**, *10*, 937-960.

MCR Approach in synthesis of 5,6-dihydropyridin-2(1H)-ones

Unexpected synthesis of 5,6-dihydropyridin-2(1H)-ones by a domino Ugi/aldol/hydrolysis reaction starting from Baylis–Hillman phosphonium salts

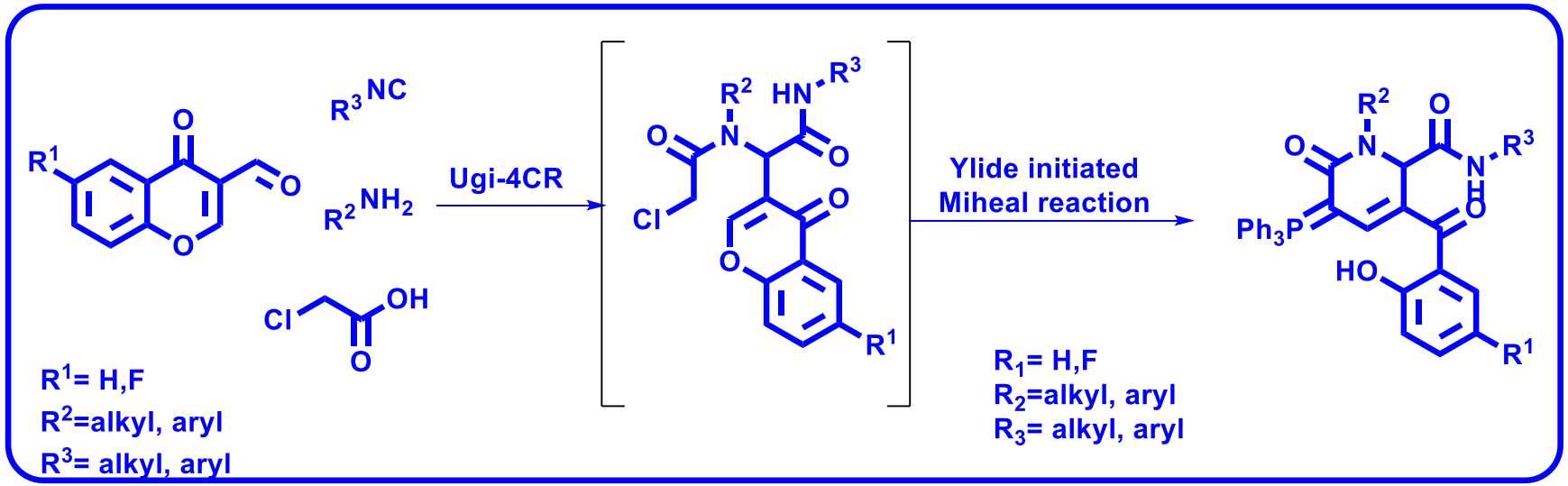




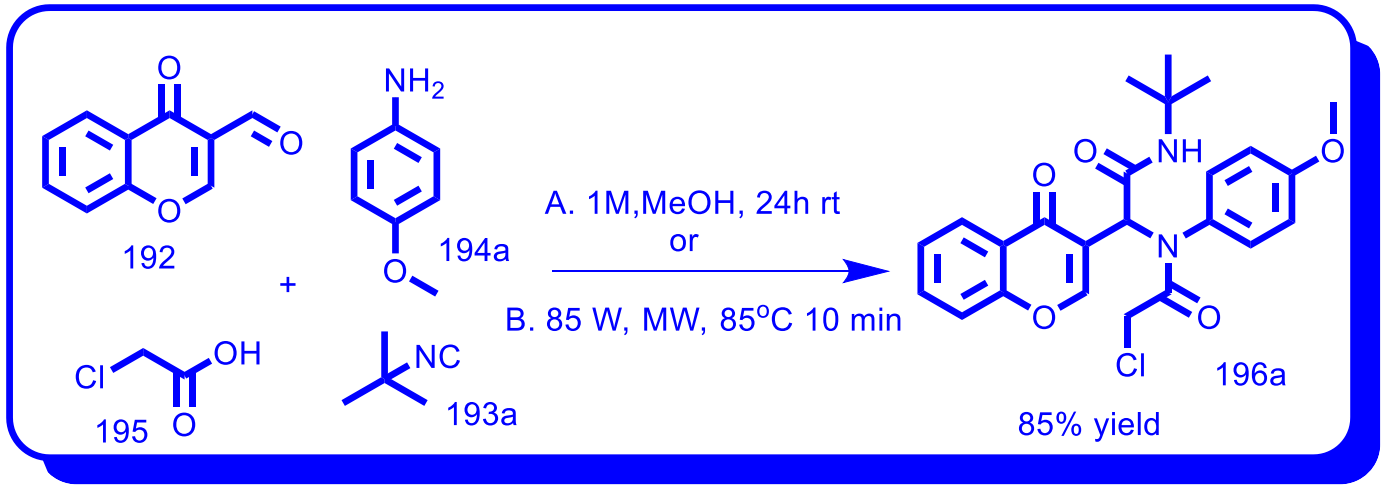
Zeng, X.-H.; Wang, H.-M.; Ding, M.-W. *Org. Lett.* **2015**, *17*, 2234-2237.

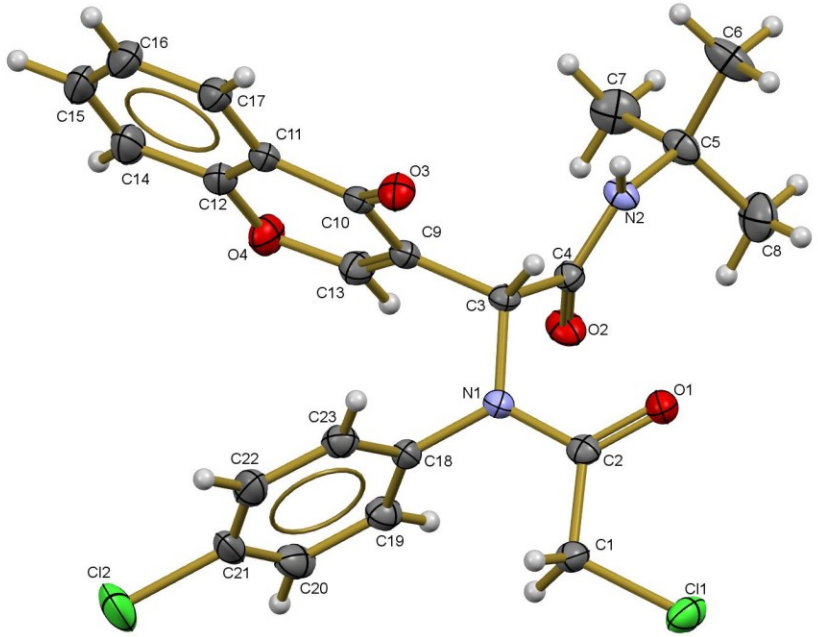
Results and Discussion

Synthesis of novel stable Ylides via Ugi 4CR/Ylide initiated Michael sequence.

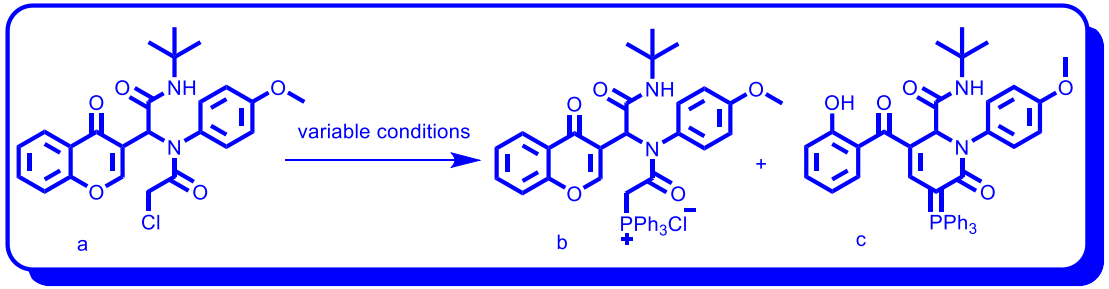


Scope of the Ugi reaction with 3-formyl chromone under microwave irradiation.

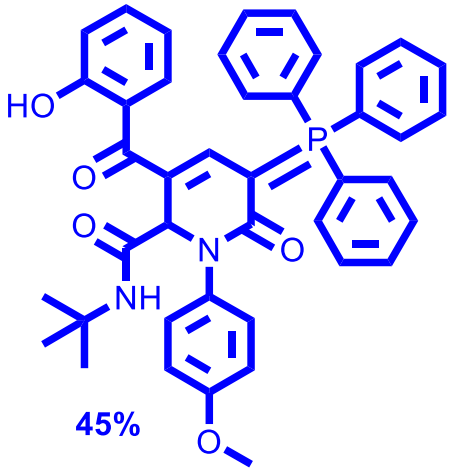




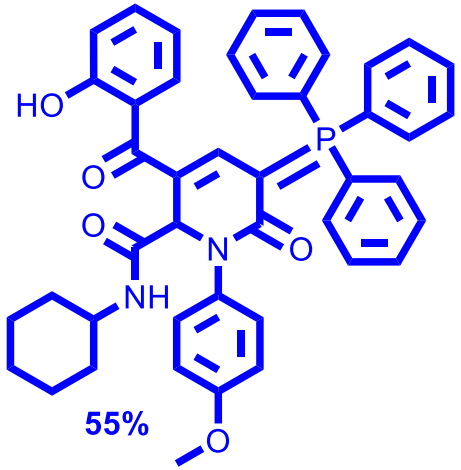
Scope and formation of stable heterocyclic ylide.



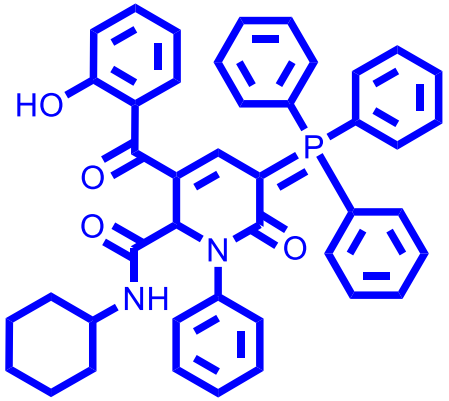
Entry	Condition	Product a	Product b
1	0.5equiv PPh_3,Toluene, 60 °C, 12h	65%	10%
2	1equiv PPh_3,Toluene, 120 °C 12h	55%	27%
3	1.2equiv PPh_3,Toluene, 100W, MW, 120 °C, 60 min	35%	35%
4	1.2equiv PPh_3, MeOH, rt ,24h	44%	0
5	1.2equiv PPh_3, DMF, rt ,24h	65%	5%
6	1.2equiv PPh_3, MeOH, reflux ,12h	60%	17%
7	1.2equiv PPh_3, DMF, reflux ,12h	20%	45%
8	1.2equiv PPh3, DMF, 100W, MW, 120 °C, 30 min	25%	45%



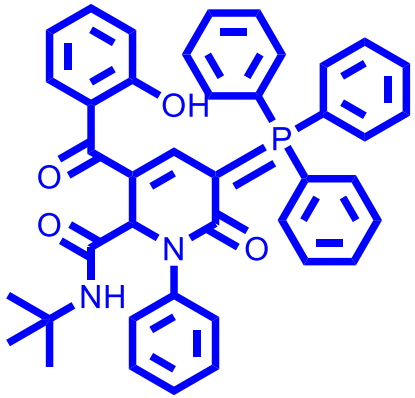
45%



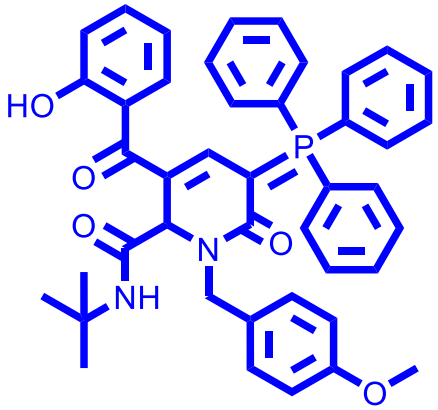
55%



71%

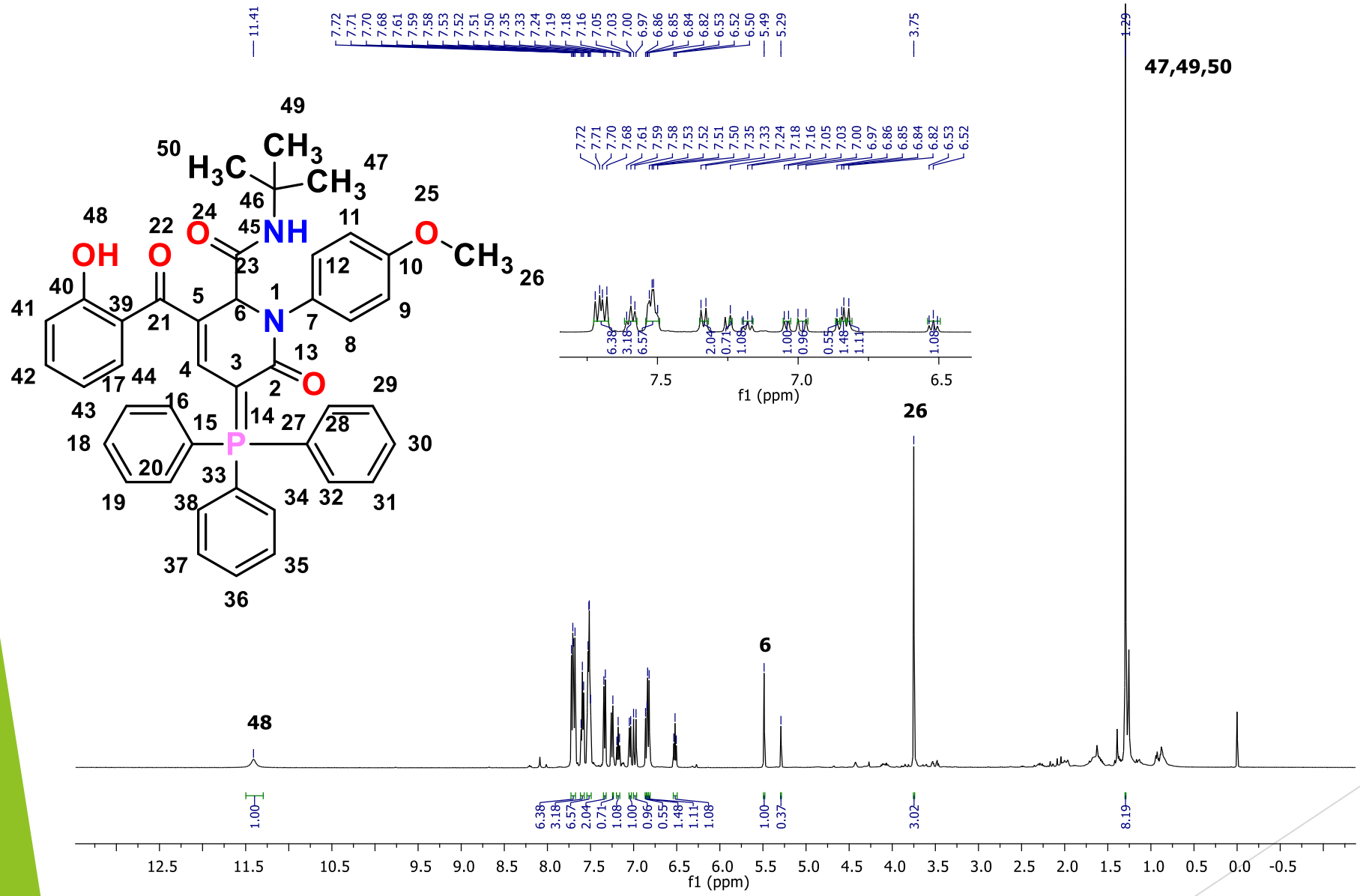


55%

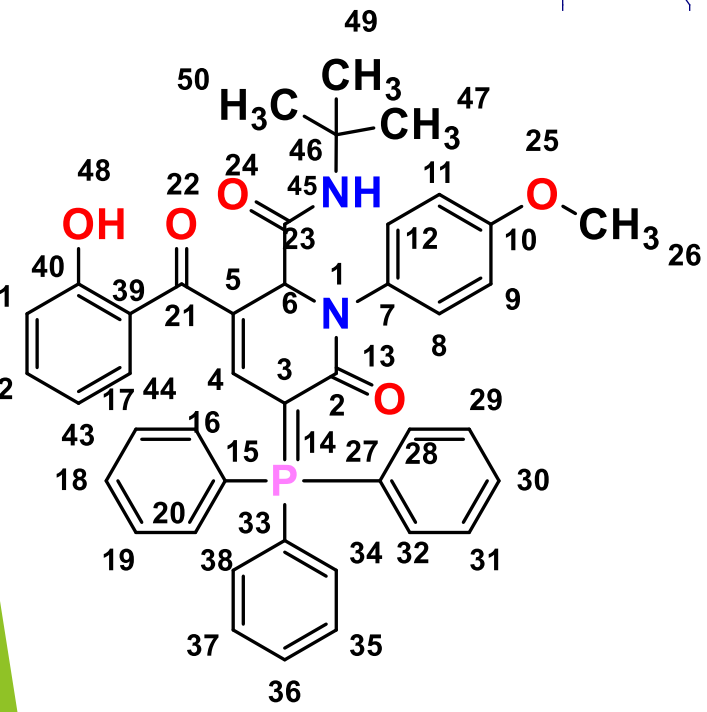


55%

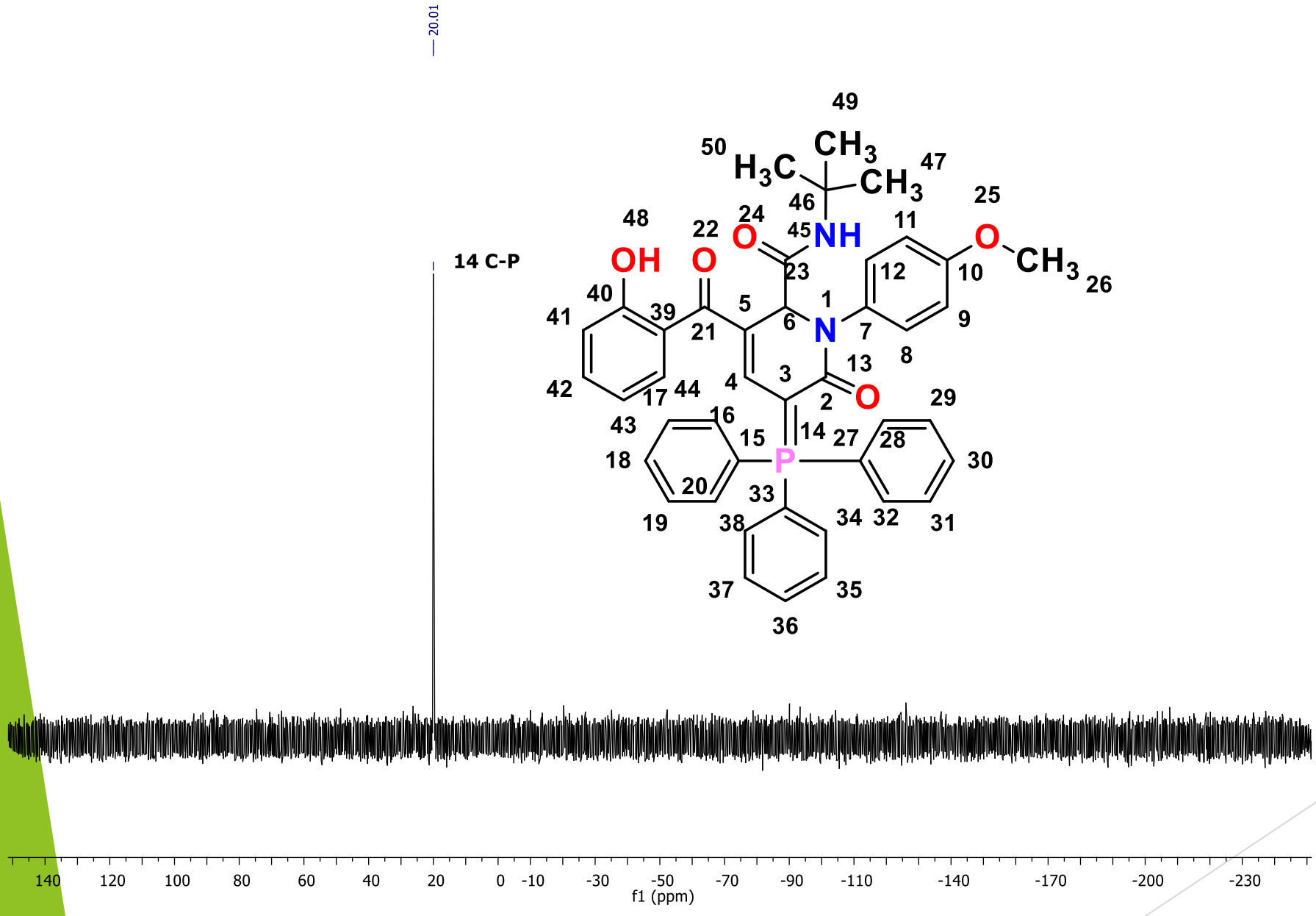
^{1}H NMR of N-(tert-butyl)-3-(2-hydroxybenzoyl)-1-(4-methoxyphenyl)-6-oxo-5-(triphenyl-l5-phosphanylidene)-1,2,5,6-tetrahydropyridine-2-carboxamide



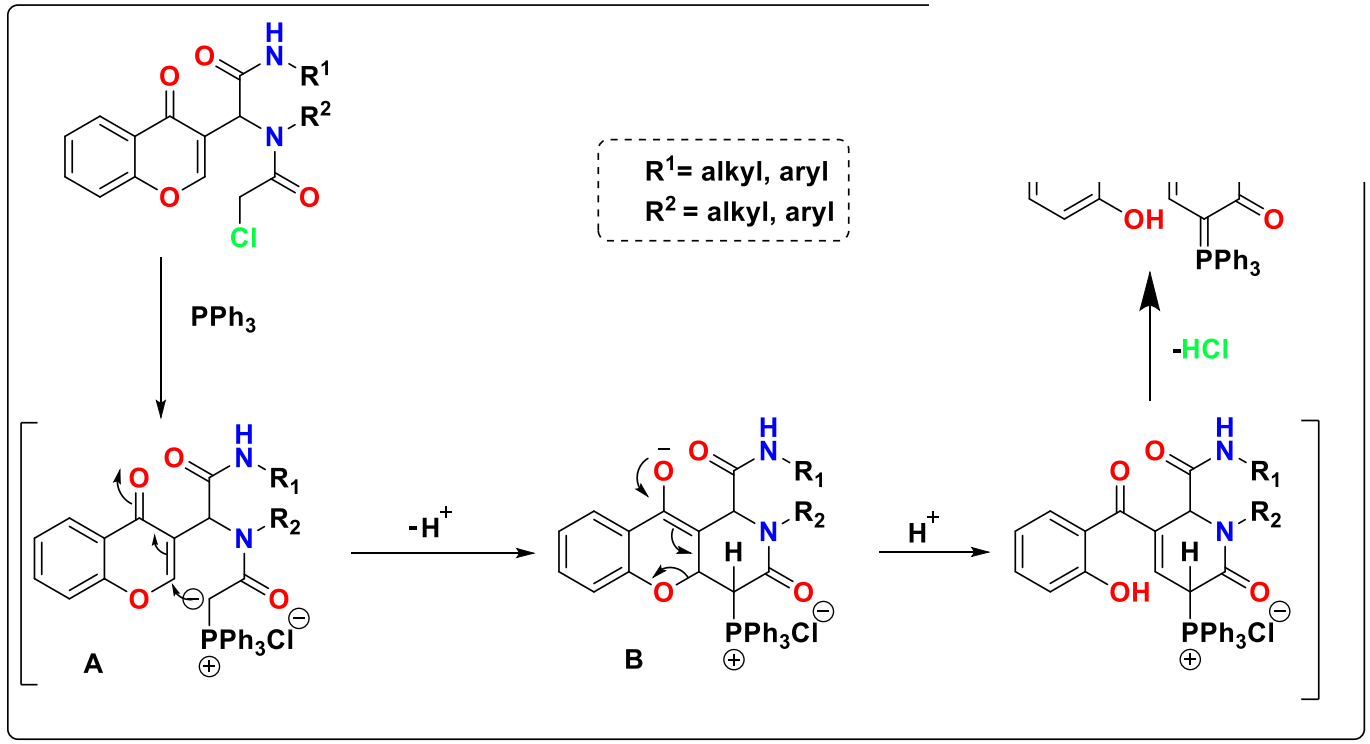
^{13}C NMR of N-(tert-butyl)-3-(2-hydroxybenzoyl)-1-(4-methoxyphenyl)-6-oxo-5-(triphenyl-l5-phosphanylidene)-1,2,5,6-tetrahydropyridine-2-carboxamide



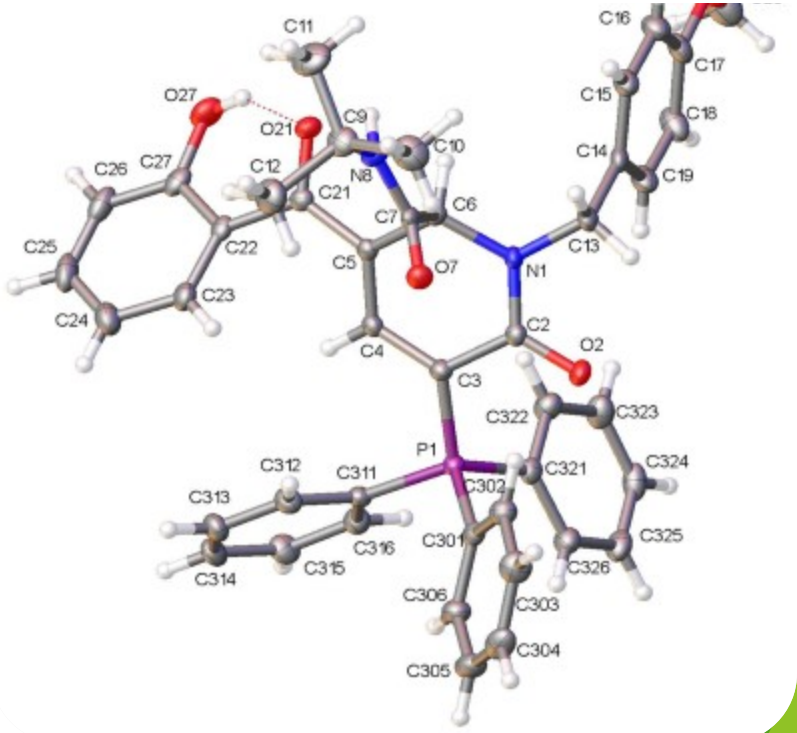
^{31}P NMR of N-(tert-butyl)-3-(2-hydroxybenzoyl)-1-(4-methoxyphenyl)-6-oxo-5-(triphenyl-l5-phosphanylidene)-1,2,5,6-tetrahydropyridine-2-carboxamide



Proposed mechanism of the reaction



X-Ray confirmation of structure



CONCLUSIONS

- We developed a synthesis of novel stable heterocyclic ylides via a cascade process: Ugi/ylide initiated Michael and ring opening reaction of 3-formyl chromone in moderate to good yields.

- The present methodology give a good future scope in generation of novel heterocyclic Wittig reagents.

- This methodology gave scope in ring opening of 3-formyl chromone and that explains the reactivity towards the ylide nucleophile.

CONACYT
Consejo Nacional de Ciencia y Tecnología

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My lab mates