Literature Review

Combined Amino/Metal Catalysis

Becky Greenaway

16th December 2011

Literature Review

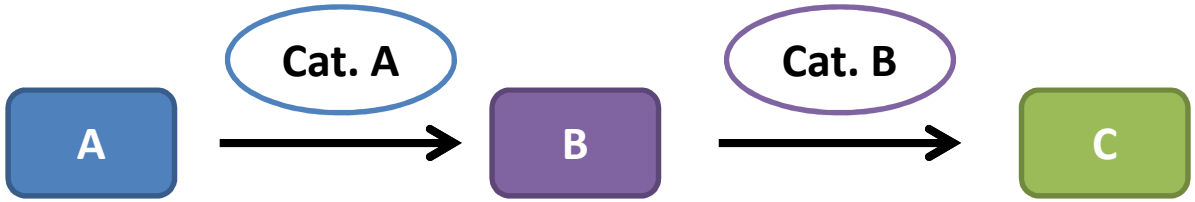
Combined Amino/Metal Catalysis

1. **Introduction**
2. **Aminocatalysis with metal catalysis**
   i. **Enamine Addition to Transition Metal-Activated Electrophiles**
   ii. **Enamines and Rhodium-Catalysed Hydroformylation**
   iii. **Enamines and SOMO Catalysis**
   iv. **Transition Metal-Activated Nucleophiles with Iminium Catalysis**
3. **Natural Product Applications**
4. **Summary**

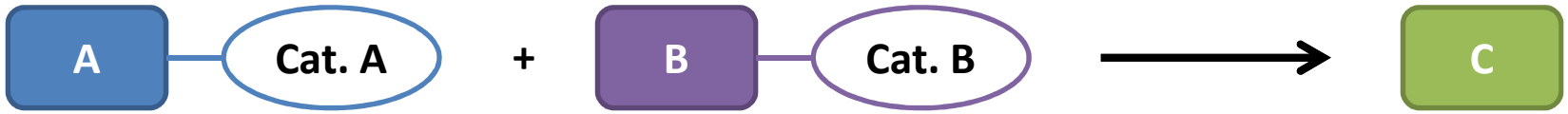
Literature Review

Combined Amino/Metal Catalysis

Co-operative Catalysis



Dual Catalysis



Literature Review

Combined Amino/Metal Catalysis

Combined Catalysis

Two different catalysts functioning co-operatively

Advantages

- Enables unprecedented transformations not currently possible by the use of each catalytic system alone
- One pot approach – reducing waste and time

Disadvantages

- Catalyst compatibility – catalyst poisoning
- Functional group tolerance
- Aminocatalysts are confined to aldehyde and ketone functionality

Jacobsen, E. N.; Danjo, H.; Sammis, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 9928

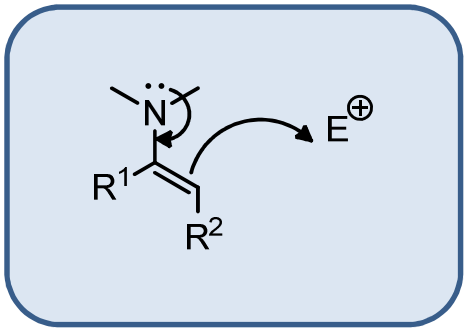
Literature Review

Combined Amino/Metal Catalysis

Literature Review

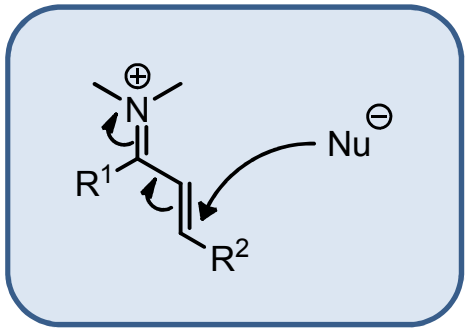
Combined Amino/Metal Catalysis

Enamine Catalysis



o HOMO-raising addition of enamine nucleophile to transition metal activated electrophile

Iminium Catalysis



o LUMO-lowering activation of α,β-unsaturated aldehydes and ketones as improved electrophile

o Only one example of direct iminium catalysis and transition metal catalysis has been reported

Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999; Shao, Z.; Zhang, H.; *Chem. Soc. Rev.* **2009**, *38*, 245; MacMillan, D. W. C. *Nature*, **2008**, *455*, 304

Literature Review

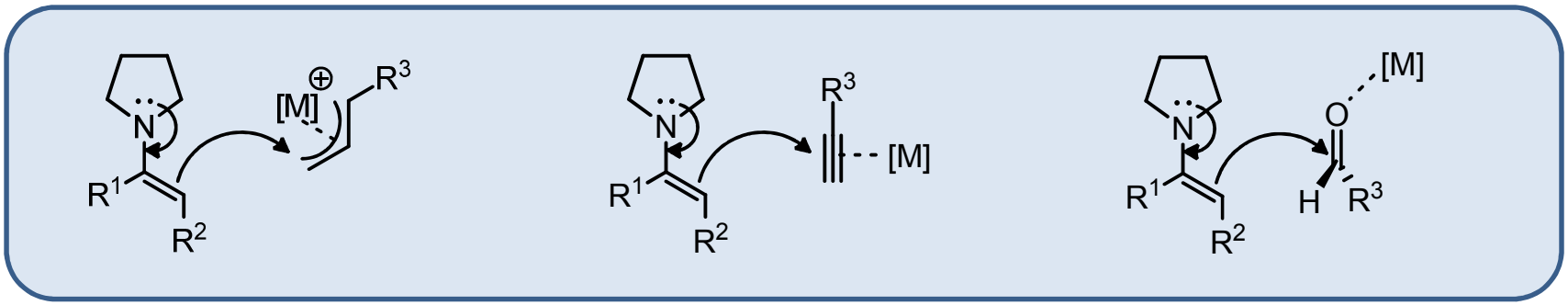
Combined Amino/Metal Catalysis

1. Introduction
2. Aminocatalysis and metal catalysis
   i. Enamine Addition to Transition Metal-Activated Electrophiles
   ii. Enamines and Rhodium-Catalysed Hydroformylation
   iii. Enamines and SOMO Photoredox Catalysis
   iv. Transition Metal-Activated Nucleophiles with Iminium Catalysis
3. Natural Product Applications
4. Summary

Literature Review

Combined Amino/Metal Catalysis

Enamine Addition to Transition Metal-Activated Electrophiles



Enamine Nucleophilic Addition to π-Allyl Electrophiles

Enamine Addition to π-Acid-Activated Alkynes

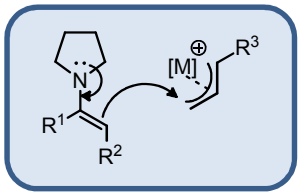
Enamine Addition to Metal Lewis Acid activated carbonyls

Zhong, C.; Shi, X. *Eur. J. Org. Chem.* **2010**, 2999

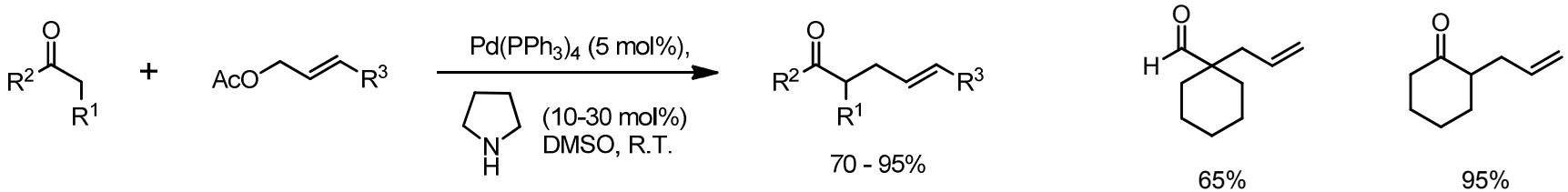
Literature Review

Combined Amino/Metal Catalysis

Enamine Nucleophilic Addition to π-Allyl Electrophiles

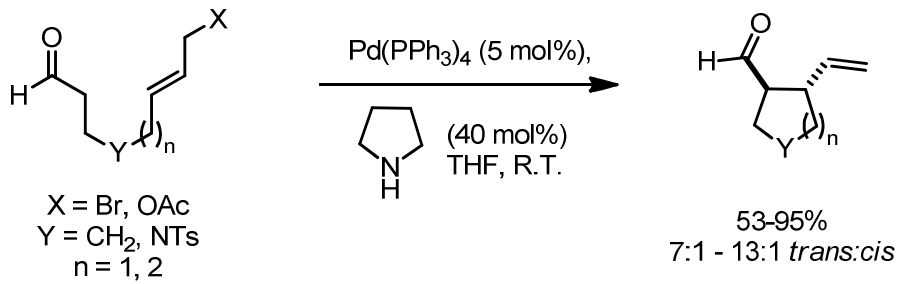


o In 2006 Córdova's group reported the **first catalytic system** combining **enamine nucleophiles** derived from both aldehydes and ketones with **Tsuji-Trost palladium π-allyl electrophiles**



o Of particular note is the suitability of this route for both **primary and secondary aldehydes**, as well as **cyclic ketones**

o Utilising similar conditions an **intramolecular route to 5- and 6-membered cyclic species** was reported by Saicic's group



o Enolates pregenerated with LDA and KHMDS were also tested but did not give the desired products in good yields.

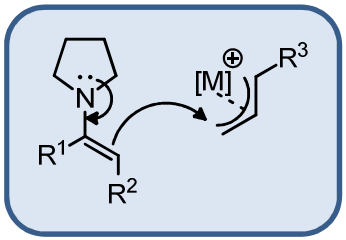
o Other ring sizes were attempted (3, 4 and 7) but all failed under similar conditions.

Ibrahem, I.; Córdova, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 1952; Bihelovic, F.; Matovic, R.; Vulovic, B.; Saicic, R. N. *Org. Lett.* **2007**, *9*, 5063

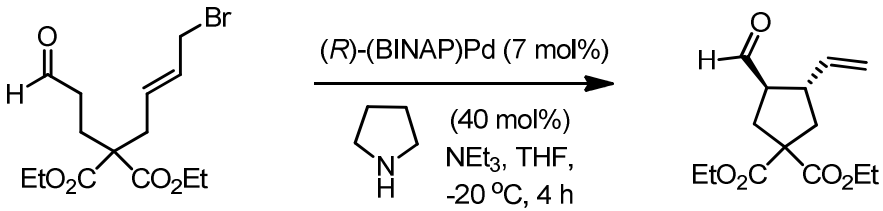
Literature Review

Combined Amino/Metal Catalysis

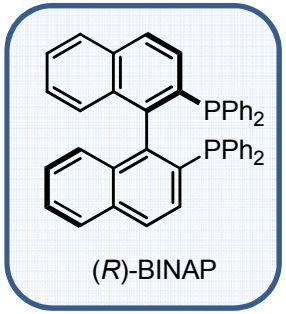
Enamine Nucleophilic Addition to π-Allyl Electrophiles



- Investigations into whether the cyclisation could be performed as a **catalytic asymmetric reaction** were conducted and whilst good *ee*'s were obtained, poor yields were common

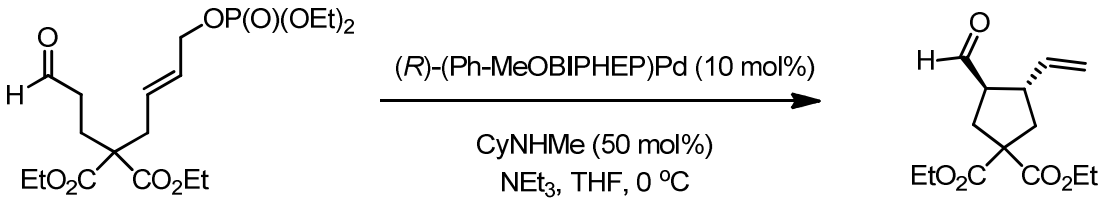


40%, 91% ee

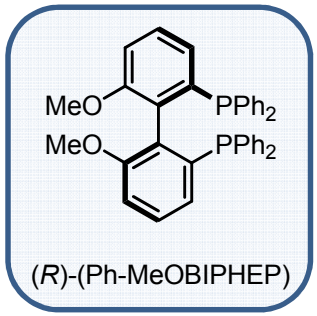


MacMillan's catalyst, (*S*)-proline and (*S*)-2- diphenylprolinol all failed

- In 2009 the same group reported an **alternative catalyst system** that greatly improved the yield and enantioselectivity



76%, *trans:cis* 7.4:1, 98% *ee*

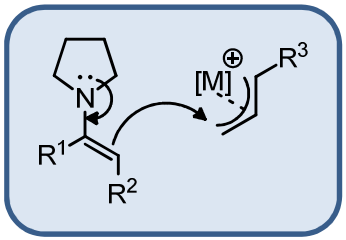


Bihelovic, F.; Matovic, R.; Vulovic, B.; Saicic, R. N. *Org. Lett.* **2007**, *9*, 5063; Vulovic, B.; Bihelovic, F.; Matovic, R.; Saicic, R. N. *Tetrahedron Lett.* **2009**, *65*, 10485

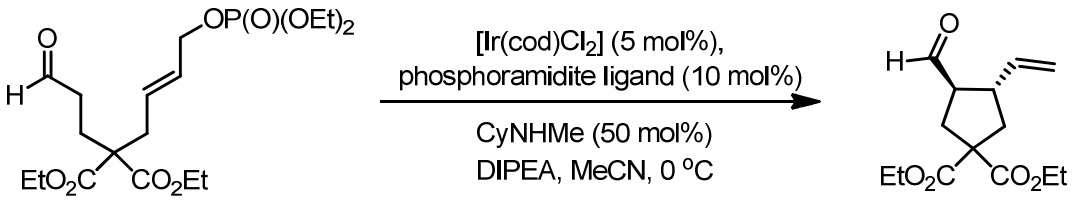
Literature Review

Combined Amino/Metal Catalysis

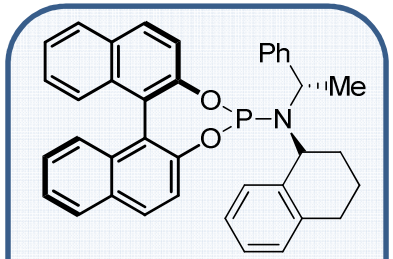
Enamine Nucleophilic Addition to π-Allyl Electrophiles



o Alongside the Pd-catalyst system the **allylation** was also tested with an **iridium complex** previously reported by Hartwig

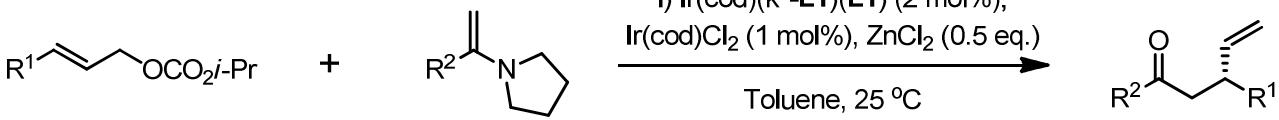


98%
very poor *dr* and *ee*



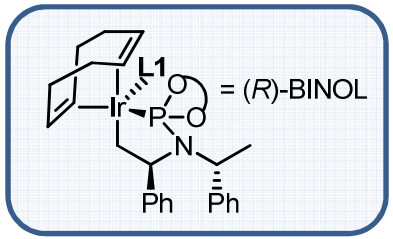
phosphoramidite ligand

o Initially these conditions were used for the **intermolecular allylation of enamines derived from ketones**



R^1 and R^2 = Ar, alkyl

64-91%
77-97% *ee*

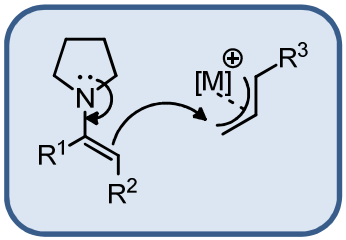


Vulovic, B.; Bihelovic, F.; Matovic, R.; Saicic, R. N. *Tetrahedron Lett.* **2009**, *65*, 10485; Weix, D. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7720

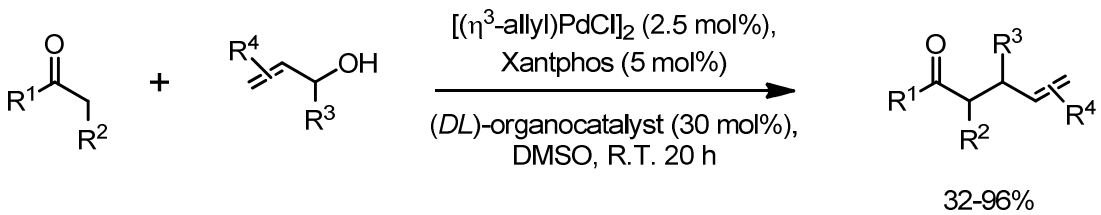
Literature Review

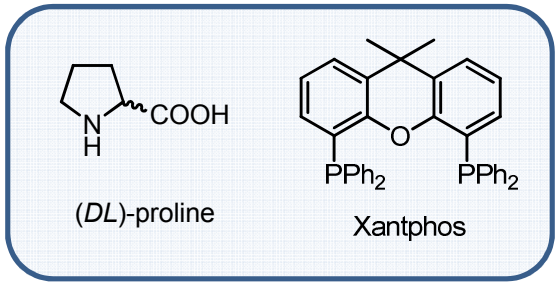
Combined Amino/Metal Catalysis

Enamine Nucleophilic Addition to π-Allyl Electrophiles

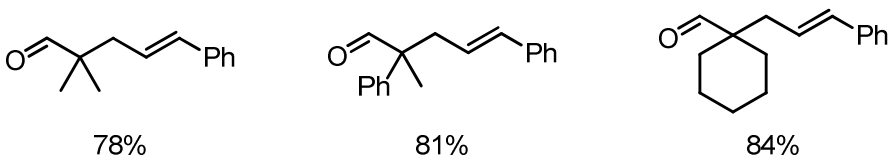


o In 2009 Breit's group reported an **intermolecular enamine addition to a palladium π-allyl complex** using an **allyl alcohol** directly instead of of an allyl bromide, allyl acetate or allyl phosphate





o Unfortunately the yield drops to around 44% when an acyclic ketone was used even though aldehydes turned out to be excellent substrates (73-84%) and also allowed access to quarternary carbon centers

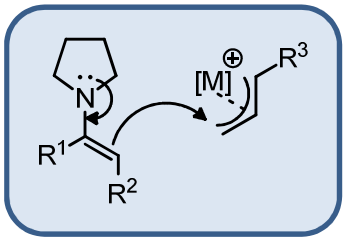


Usui, I.; Schmidt, S.; Breit, B. *Org. Lett.* **2009**, *11*, 1453

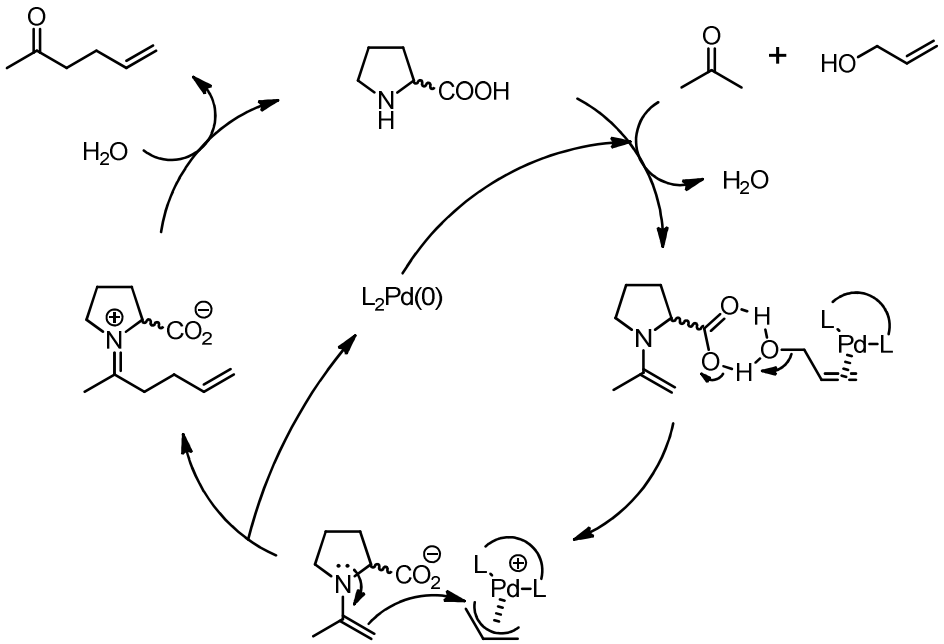
Literature Review

Combined Amino/Metal Catalysis

Enamine Nucleophilic Addition to π-Allyl Electrophiles



- By a series of control experiments it was determined that the **carboxylic acid functionality was required** in order for the reaction to occur

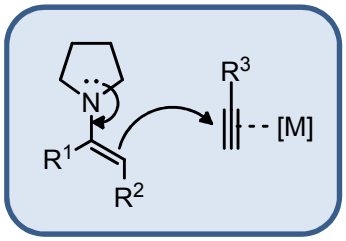


Usui, I.; Schmidt, S.; Breit, B. *Org. Lett.* **2009**, *11*, 1453

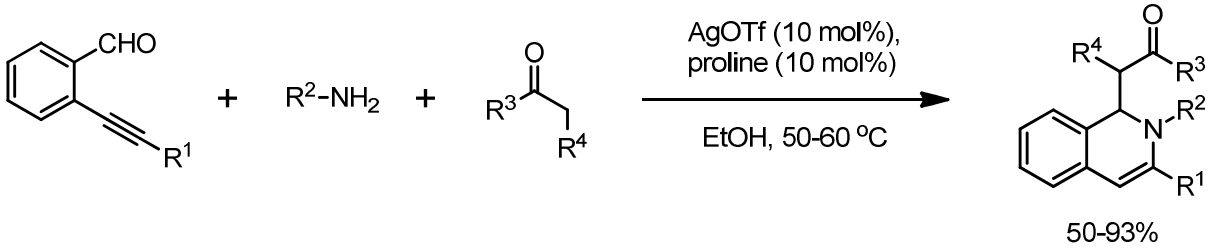
Literature Review

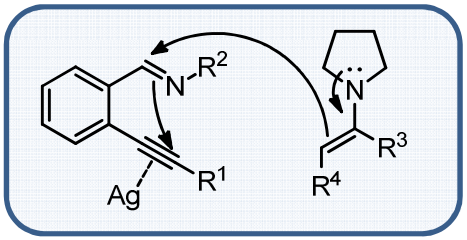
Combined Amino/Metal Catalysis

Enamine Addition to π-Acid-Activated Alkynes

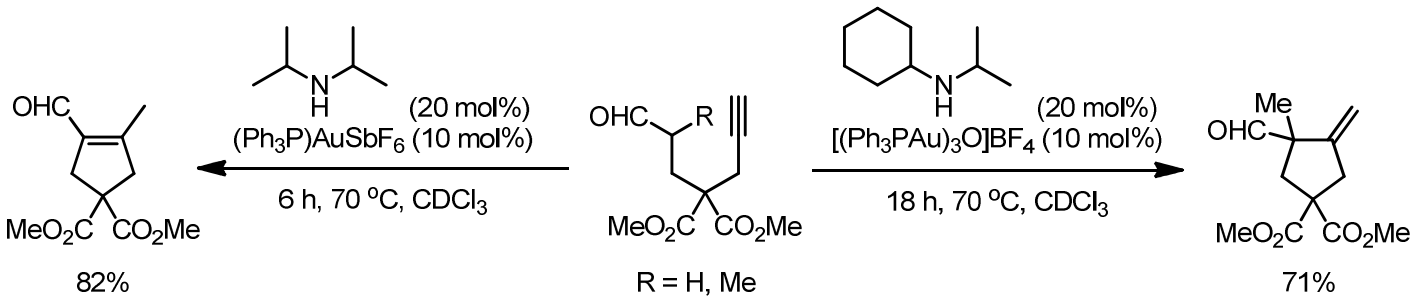


o In 2007 Wu and co-workers reported the **first example** of a **cascade** reaction involving a combination of **enamine catalysts and π-acid catalysts** through the use of proline and AgOTf





o More recently **cationic gold complexes** have been studied as effective catalysts for electrophilic activation and in 2008 Kirsch and co-workers demonstrated successful **5-*exo-dig* cyclisations on both aldehydes and ketones**



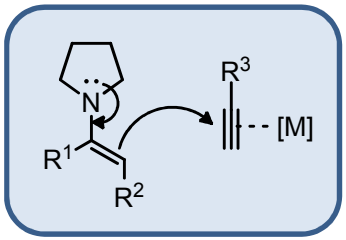
When R = H double bond migration occurs

Ding, Q.; Wu, J. *Org. Lett.* **2007**, *9*, 4959; Binder, J. T.; Crone, B.; Haug, T. T.; Menz, H.; Kirsch S. F. *Org. Lett.* **2008**, *10*, 1025

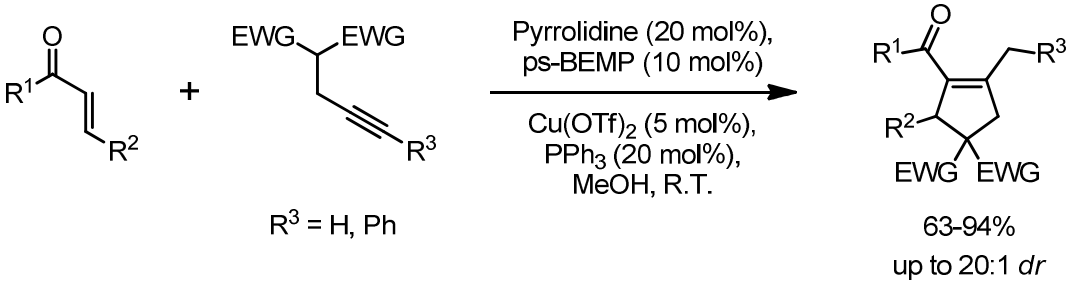
Literature Review

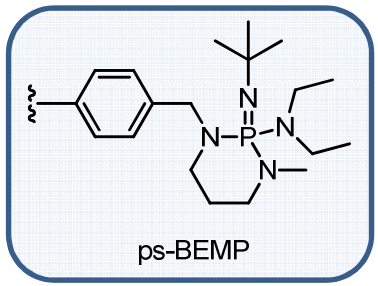
Combined Amino/Metal Catalysis

Enamine Addition to π-Acid-Activated Alkynes



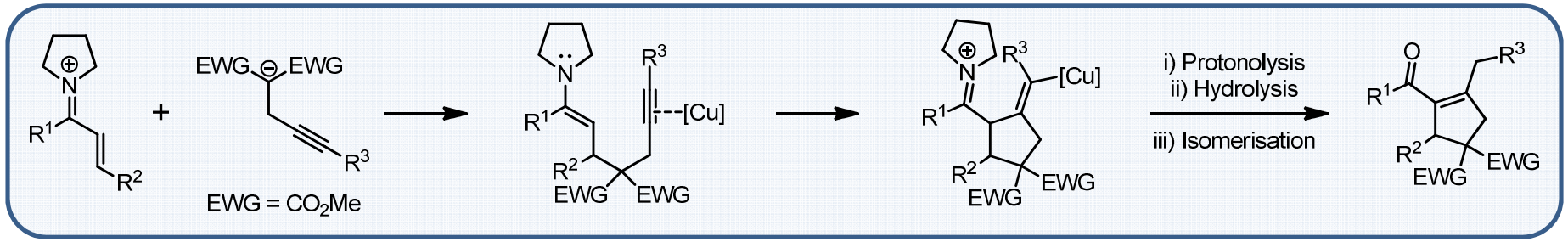
o This strategy was further extended by Dixon's group who reported a **cascade** involving the ***in-situ* generation of enamine-alkyne intermediates *via* an iminium species**





Added to quench any residuel protic acids present in the metal ion salts

o This route proved to be successful on **both cyclic and acyclic α,β-unsaturated ketones** initiated through a Michael addition to the iminium activated enone

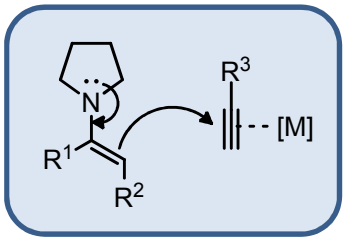


Yang, T.; Ferrali, A.; Campbell, L.; Dixon, D. J. *Chem. Commun*. **2008**, 2923

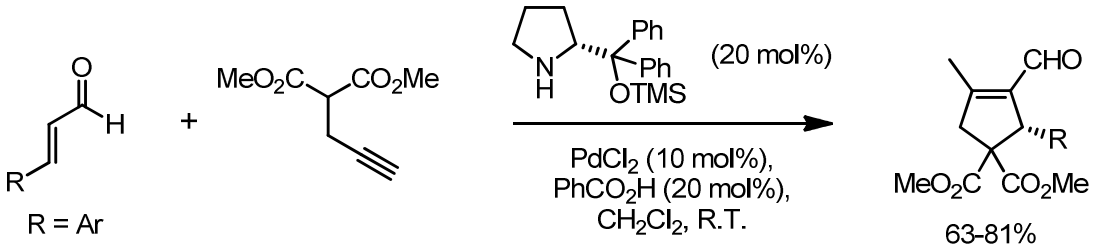
Literature Review

Combined Amino/Metal Catalysis

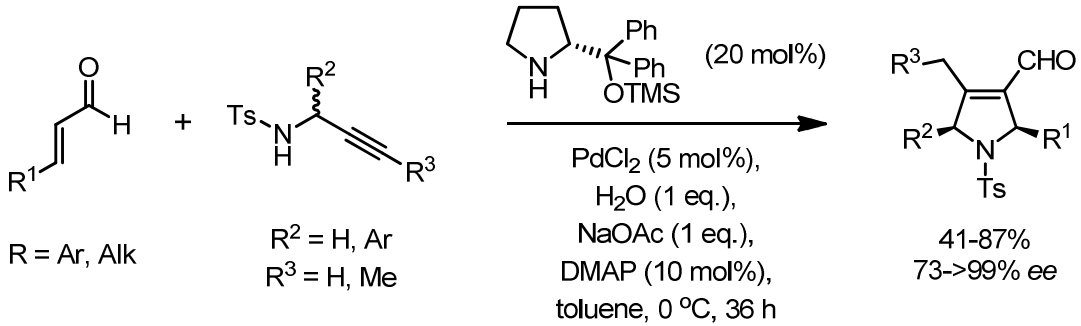
Enamine Addition to π-Acid-Activated Alkynes



o In 2009 Wang and co-workers reported a similar **enantioselective Michael-cyclisation cascade** but *via* the use of a **palladium-activated alkyne** producing highly **enantioenriched cyclopentenes** in good yield



o In 2010 another Wang group used similar methodology to allow access to **chiral 2,5-dihydropyrroles**. However when the less reactive aliphatic enals were used both the yield and the *ee* suffered

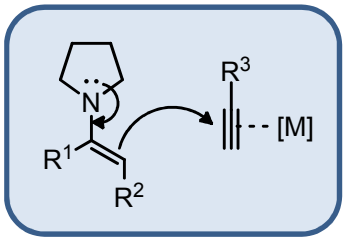


Chenguang, Y.; Zhang, Y.; Zhang, S.; He, J.; Wang, W. *Tetrahedron Lett.* **2010**, *51*, 1742; Sun, W.; Zhu, G.; Hong, L.; Wang, R. *Chem. Eur. J.* **2011**, *ASAP*

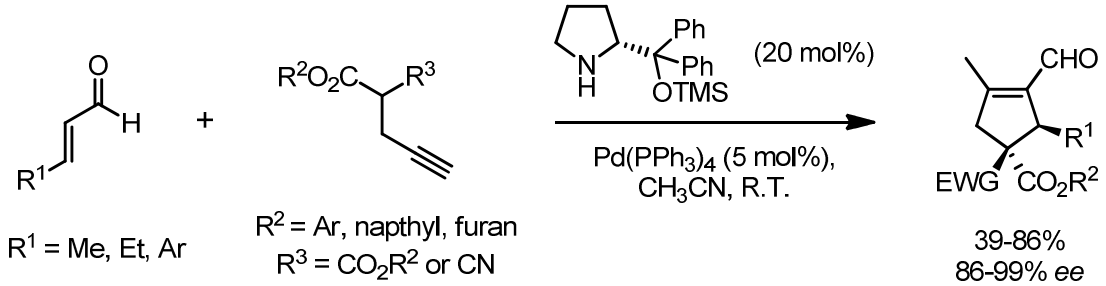
Literature Review

Combined Amino/Metal Catalysis

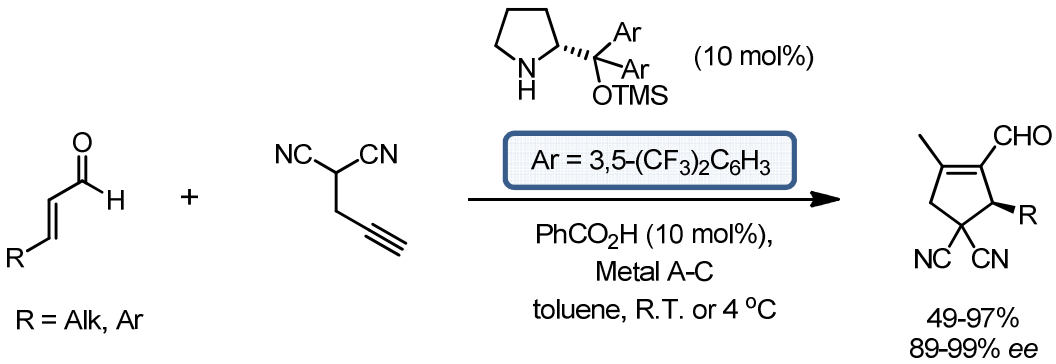
Enamine Addition to π-Acid-Activated Alkynes



o Around the same time there were other similar reports of the same type of reaction by other independent groups



o The group of Jørgensen reported three different catalyst systems that all worked efficiently



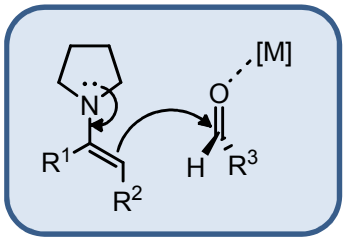
Metal:
A: $Cu(OTf)_2$ (5 mol%), PPh_3 (20 mol%)
B: CuOTf (5 mol%), PPh_3 (20 mol%)
C: $[Au(NTf_2)(PPh_3)]$ (5 mol%)

Zhao, G-L.; Ullah, F.; Deiana, L.; Lin, S.; Zhang, Q.; Sun, J.; Ibrahem, I.; Dziedzic, P.; Córdova, A. *Chem. Eur. J.* **2010**, *16*, 1585; Jensen, K. L.; Franke, P. T.; Arróniz, C.; Kobbelgaard, S.; Jørgensen, K. A. *Chem. Eur. J.* **2010**, *16*, 1750

Literature Review

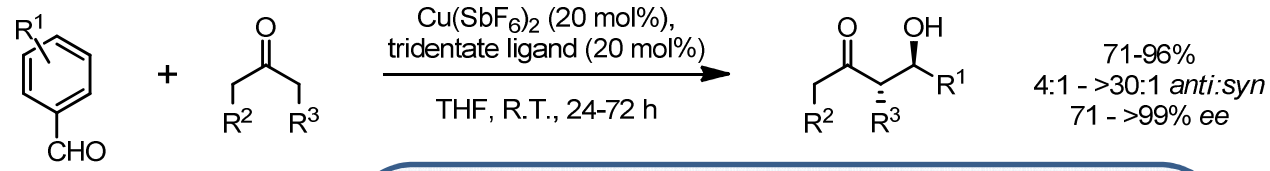
Combined Amino/Metal Catalysis

Enamine-Metal Lewis Acid Bifunctional Catalysis

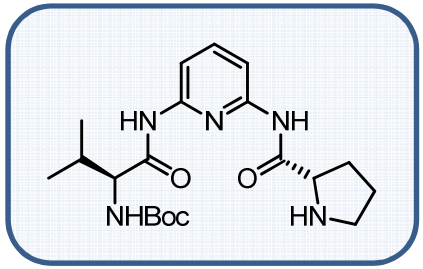


- In 2009 Wang and co-workers reported the **first combination** of an **enamine and a metal lewis acid** for an **asymmetric direct aldol reaction**

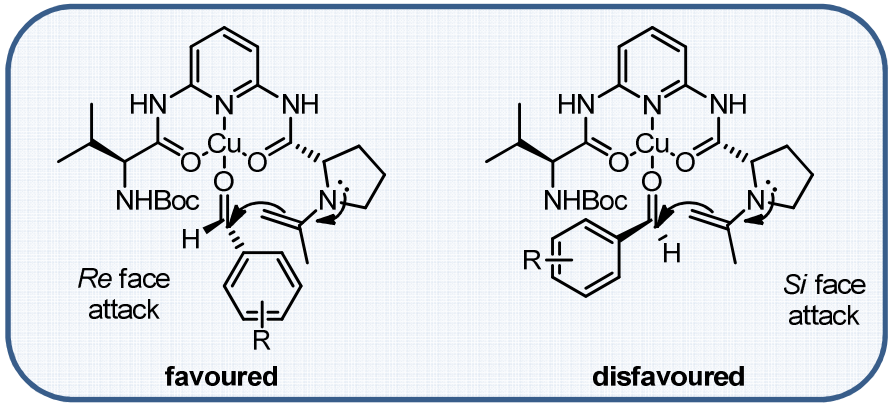
- They developed a tridentate-ligand-tethered secondary amine as a **bifunctional catalyst** to maximise the compatibility of of a lewis basic secondary amine and a lewis acidic transition metal



R^1 = NO_2, CN, CO_2Me, Cl, napthyl, Me



- Enamine attack from the *Re* face of the aldehyde gives the (*R*)-aldol product



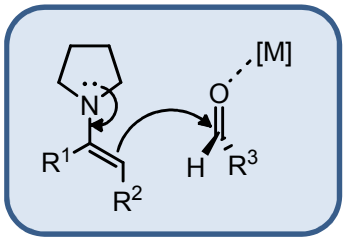
- Mechanism needs further investigation but Cu^{II} is speculated to act as a lewis acid and the pyrrolidine ring as a lewis base

Xu, Z.; Daka, P.; Budik, I.; Wang, H.; Bai, F-Q.; Zhang, H-X. *Eur. J. Org. Chem.* **2009**, 4581

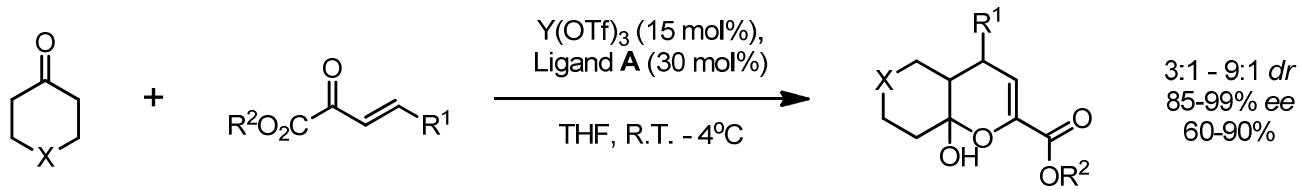
Literature Review

Combined Amino/Metal Catalysis

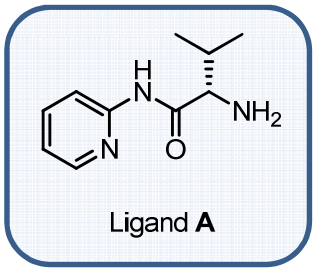
Enamine-Metal Lewis Acid Bifunctional Catalysis



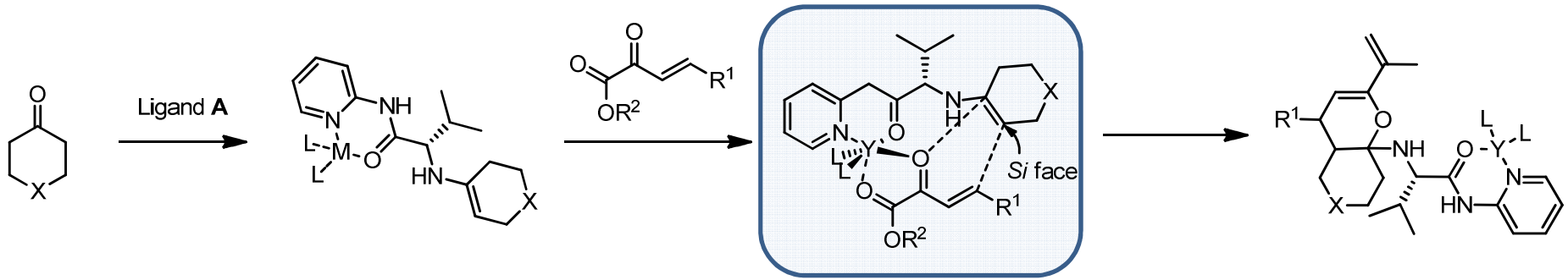
o In 2011 the same group reported an **inverse-electron-demand Hetero-Diels-Alder reaction** of six-membered cyclic ketones *via* the use of a **bifunctional catalyst**



3:1 - 9:1 *dr*
85-99% *ee*
60-90%



o The bifunctional nature of the catalysts was revealed by the fact that neither the metal or the ligand alone could catalyse the reaction – *Si* facial attack occurs due to the bulky *i*Pr group shielding the *Re* face of the enamine



Xu, Z.; Lui, L.; Wheeler, K.; Wang, H. *Angew. Chem. Int. Ed.* **2011**, *50*, 3484

Literature Review

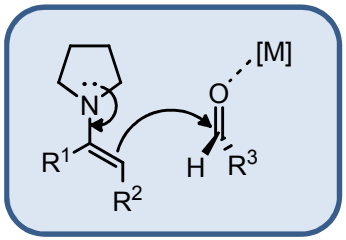
Combined Amino/Metal Catalysis

1. Introduction
2. Aminocatalysis and metal catalysis
   i. Enamine Addition to Transition Metal-Activated Electrophiles
   ii. **Enamines and Rhodium-Catalysed Hydroformylation**
   iii. Enamines and SOMO Catalysis
   iv. Transition Metal-Activated Nucleophiles with Iminium Catalysis
3. Natural Product Applications
4. Summary

Literature Review

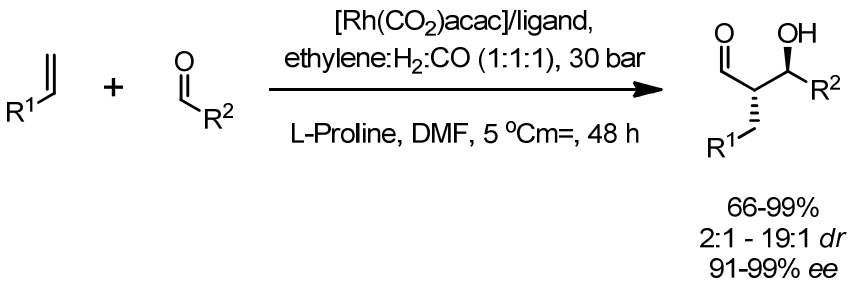
Combined Amino/Metal Catalysis

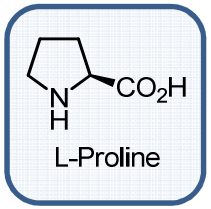
Enamines and Rhodium-Catalysed Hydroformylation

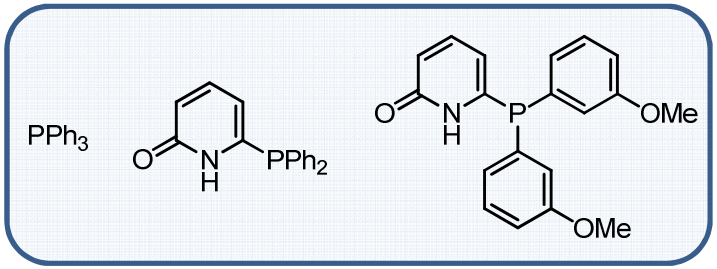


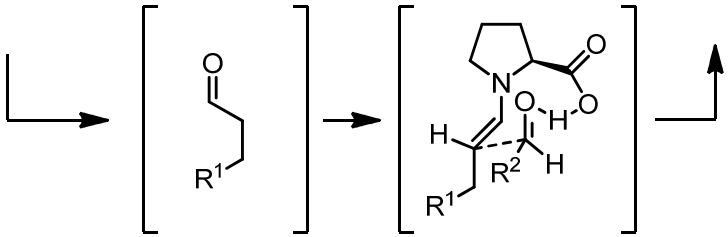
o In 2007 **two domino hydroformylation-enantioselective aldol reactions** were independently reported by Breit's group and Eilbracht's group where hydroformylation occurred *in situ* to produce the aldehydes for the following cross-aldol reaction

o Breit's work used **aldehydes as the aldol reaction acceptors**









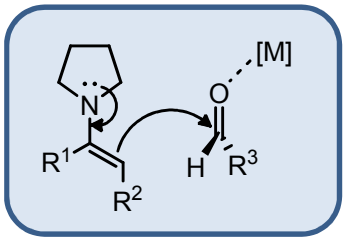
o The influence of the catalyst and the effects of different pressures, combinations of CO and H_2 gases and different rhodium ligands were investigated

Abillard, O.; Breit, B. *Adv. Synth. Catal.* **2007**, *349*, 1891; Chercheja, S.; Eilbracht, P. *Adv. Synth. Catal.* **2007**, *349*, 1897

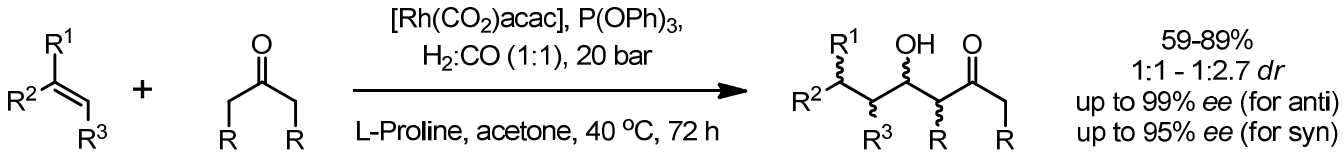
Literature Review

Combined Amino/Metal Catalysis

Enamines and Rhodium-Catalysed Hydroformylation



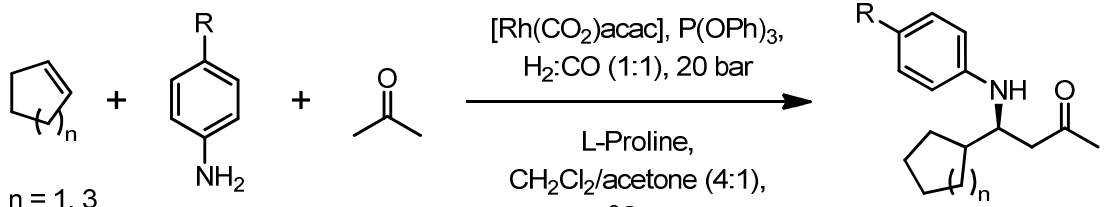
o In Eilbracht's work **ketones, which were considered more challenging, were used as the aldol acceptors**



59-89%
1:1 - 1:2.7 *dr*
up to 99% *ee* (for anti)
up to 95% *ee* (for syn)

R = Me, cyclic

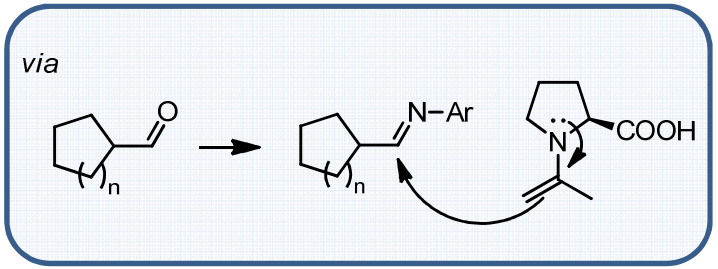
o The same group further extended this strategy reporting **sequential hydroformylation and enantioselective multi-component Mannich reactions** albeit with only moderate yields and enantioselectivities – of particular note is when R = OMe the *ee* suffers, but when R = Cl or F the yield appears to suffer



n = 1, 3

R = OMe, Cl, F

25-53%
32-74% *ee*



Chercheja, S.; Eilbracht, P. *Adv. Synth. Catal.* **2007**, *349*, 1897; Chercheja, S.; Rothenbücher, T.; Eilbracht, P. *Adv. Synth. Catal.* **2009**, *351*, 339

Literature Review

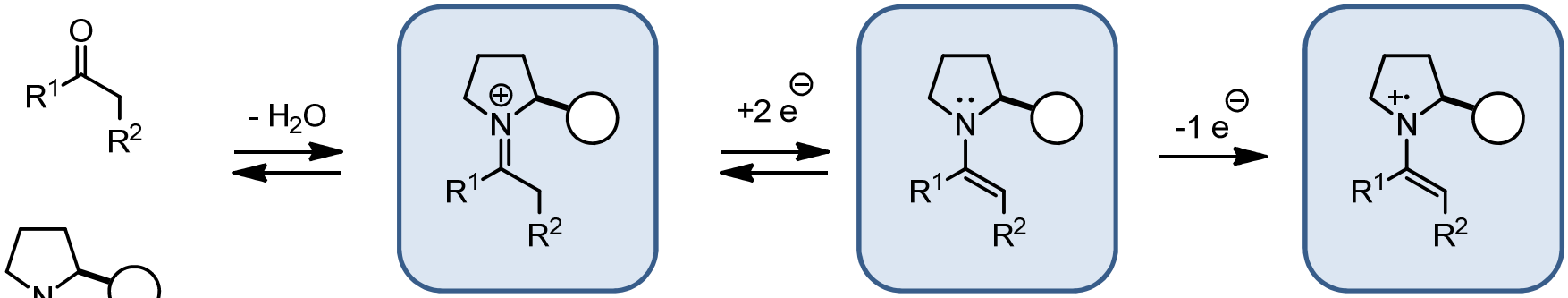
Combined Amino/Metal Catalysis

1. Introduction
2. Aminocatalysis and metal catalysis
   i. Enamine Addition to Transition Metal-Activated Electrophiles
   ii. Enamines and Rhodium-Catalysed Hydroformylation
   iii. Enamines and SOMO Catalysis
   iv. Transition Metal-Activated Nucleophiles with Iminium Catalysis
3. Natural Product Applications
4. Summary

Literature Review

Combined Amino/Metal Catalysis

Enamines and SOMO Catalysis



Iminium Catalysis

LUMO activation

Enamine Catalysis

HOMO activation

SOMO Catalysis

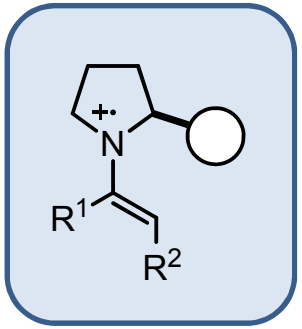
SOMO activation

Beeson, T. D.; Mastracchio, A.; Hong, J-B.; Ashton, K.; MacMillan, D. W. C. *Science*, **2007** *316*, 582

Literature Review

Combined Amino/Metal Catalysis

Enamines and SOMO Catalysis



SOMO Catalysis

SOMO activation

- Based on the idea that one-electron oxidation of an electron-rich enamine selectively generates a reactive radical cation with 3 π-electrons

- This SOMO of this intermediate allows it to react readily with a variety of weakly nucleophilic carbon-based SOMOphiles at the α-carbon of the enamine

MacMillan, D. W. C. *Nature*, **2008**, *455*, 304

Literature Review

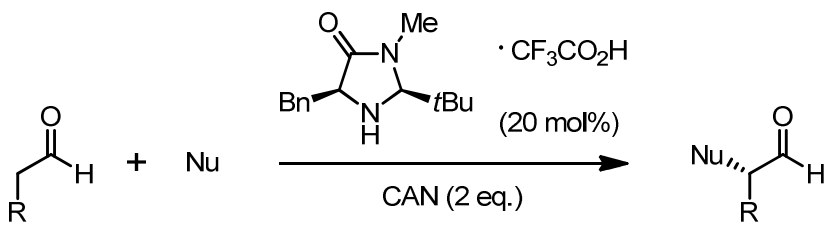
Combined Amino/Metal Catalysis

Enamines and SOMO Catalysis

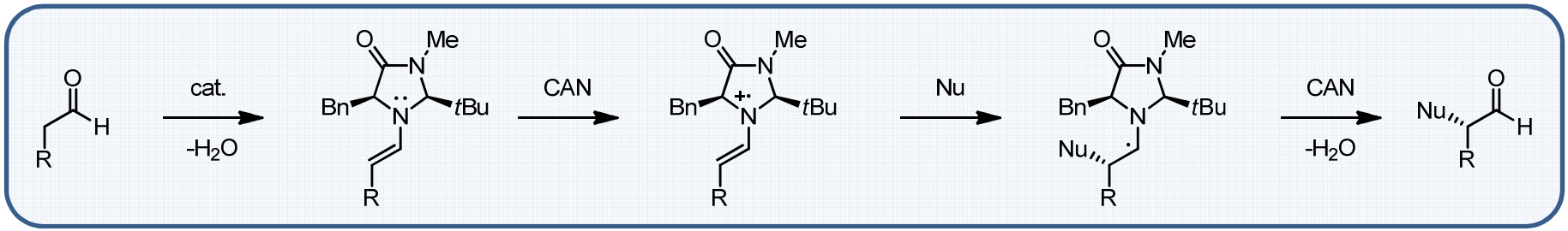
- In 2007 MacMillan's group pioneered enamine **SOMO (single-electron occupied molecular orbital) catalysis**

- Initially single-electron oxidation of a chiral enamine intermediate was achieved on treatment with **metal oxidants**, e.g. CAN (ceric ammonium nitrate), to form a radical cationic electrophile

- Addition of suitable nucleophiles gave the **α-functionalised carbonyl-containing products enantioselectively**



Unfortunately, this methodology was **not successful with ketones**

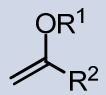
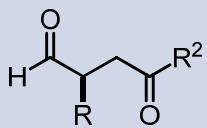
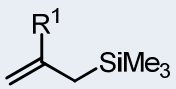
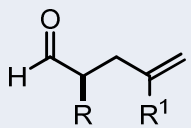
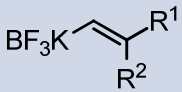
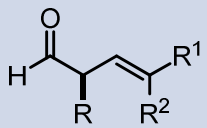
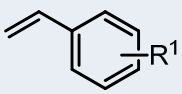
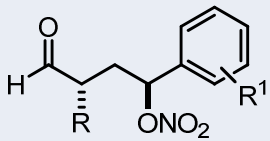


Beeson, T. D.; Mastracchio, A.; Hong, J-B.; Ashton, K.; MacMillan, D. W. C. *Science*, **2007** *316*, 582

Literature Review

Combined Amino/Metal Catalysis

Enamines and SOMO Catalysis

Nucleophile		Product	
	R^1 = TMS, TBS, TBDPS R^2 = Alk, Ar, Het		55-85% 86-96% *ee*
	R^1 = Alk, Ar, CO_2Et		70-88% 87-95% *ee*
	R^1 = Alk, Ar R^2 = H, Me		61-93% 89-95% *ee*
	R^1 = H, F, Cl, Br, NO_2, CF_3, Me		83-95% 89-97% *ee*

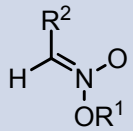
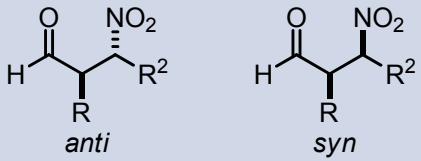
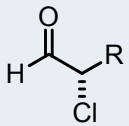
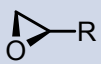
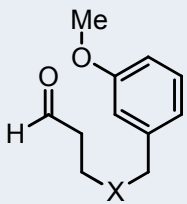
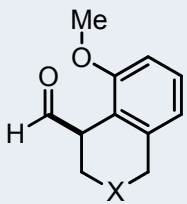
Trapping with nitrate anion from reduction of the Ce(IV) oxidant

Beeson, T. D.; Mastracchio, A.; Hong, J-B.; Ashton, K.; MacMillan, D. W. C. *Science*, **2007** *316*, 582; Jang, H. Y.; Hong, J-B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 704; Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398; Graham, T. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 16494;

Literature Review

Combined Amino/Metal Catalysis

Enamines and SOMO Catalysis

Nucleophile	Product	
 R^1 = TMS, TES, TBDPS, TIPS R^2 = H, Alk	 *anti* *syn*	53-95% 84-97% *ee*
NaCl *or* LiCl + $Cu(TFA)_2$		75-95% 91-96% *ee*
$Cu(TFA)_2$, H_2O, LiCl, $NaBH_4$, KOH		73-92% 93-95% *ee*
 X = C, NTs		61-96% 58-98% *ee*

TIPS favoured *anti*, TBS favoured *syn*

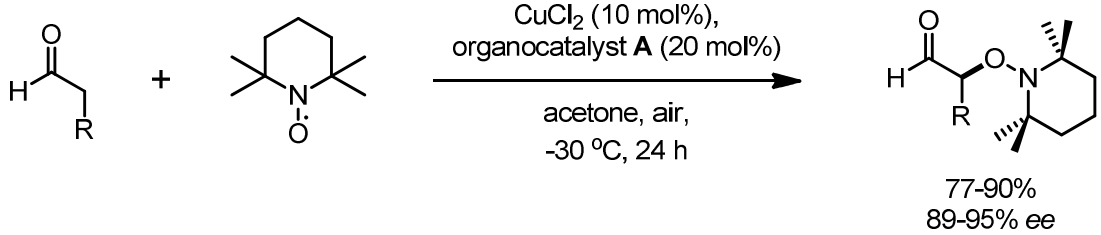
Wilson, J. E.; Casarez, A. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11332; Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 5121; Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640

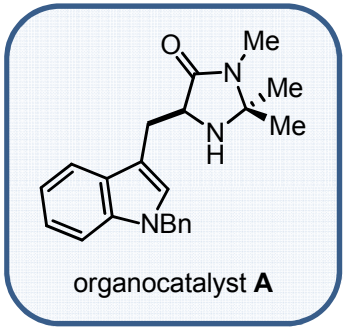
Literature Review

Combined Amino/Metal Catalysis

Enamines and SOMO Catalysis

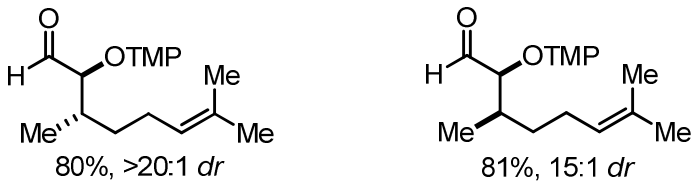
o In 2011 the **α-oxidation** of **aldehydes** with **TEMPO** was published by MacMillan and co-workers





o In terms of the aldehyde scope, ethers, esters, carbamates, phenyl sulfides (without undergoing oxidation at sulfur), aliphatic groups and aromatic groups are tolerated

o Subjection of (*S*)- and (*R*)-citronellal to oxidation yielded the desired *syn* and *anti* products respectively



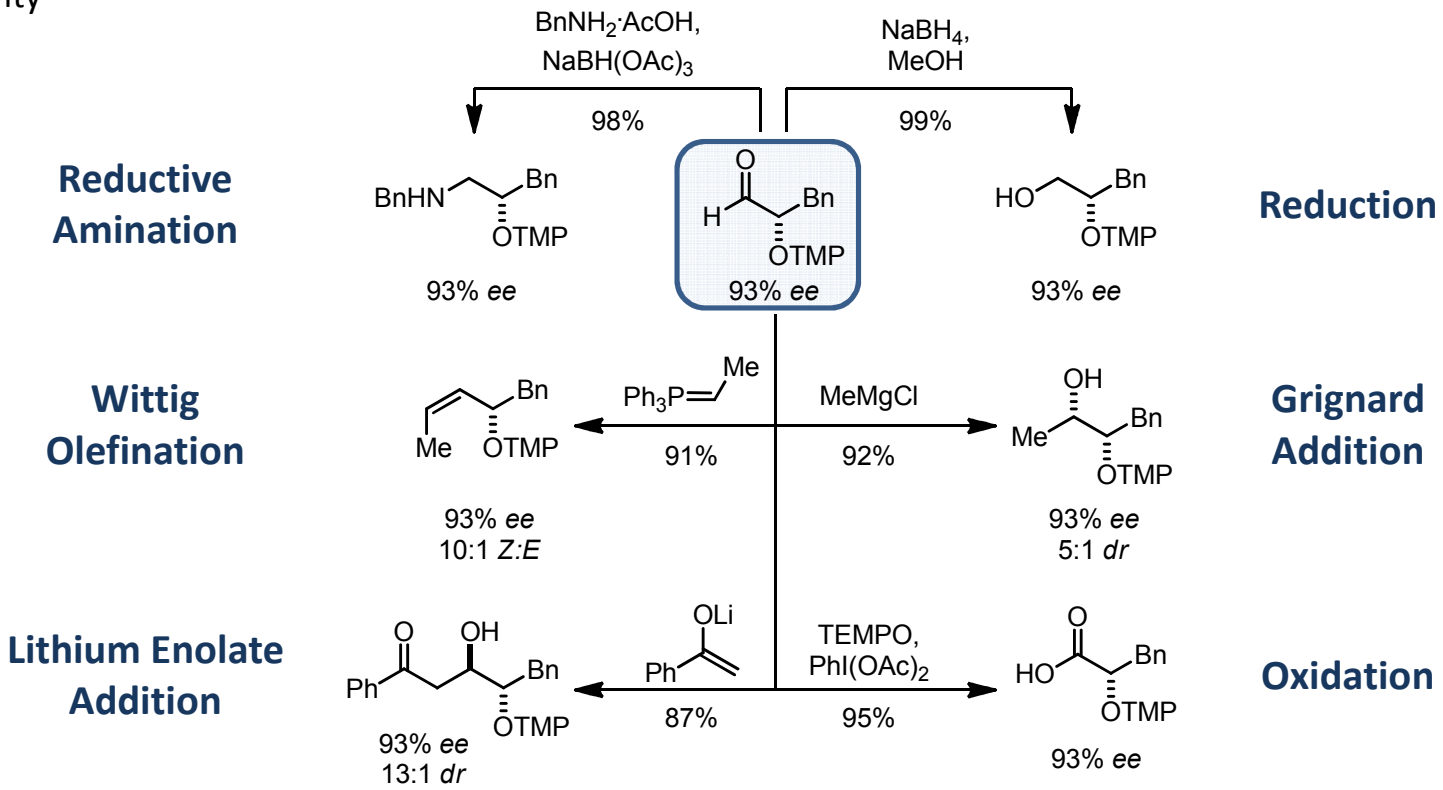
Simonovich, S. P.; Van Humbeck, J. F.; MacMillan, D. W. C. *Chem. Sci.*, **2011**, *ASAP*

Literature Review

Combined Amino/Metal Catalysis

Enamines and SOMO Catalysis

o The synthetic utility of these α-oxyamination products was then demonstrated with no detectable loss in enatiopurity



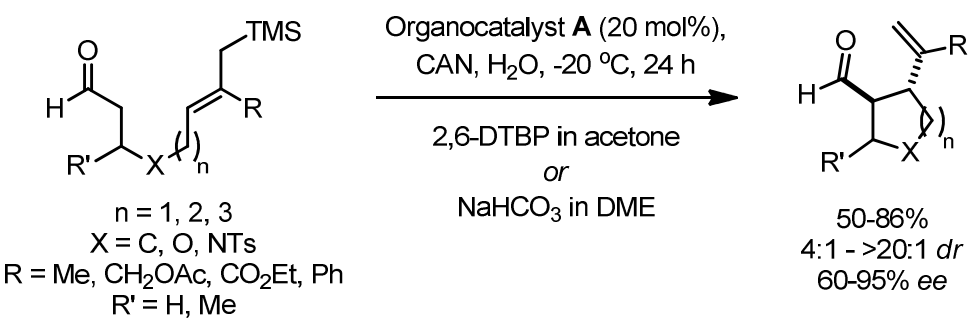
Simonovich, S. P.; Van Humbeck, J. F.; MacMillan, D. W. C. *Chem. Sci.*, **2011**, *ASAP*

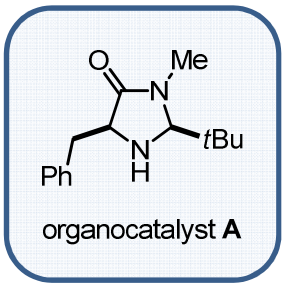
Literature Review

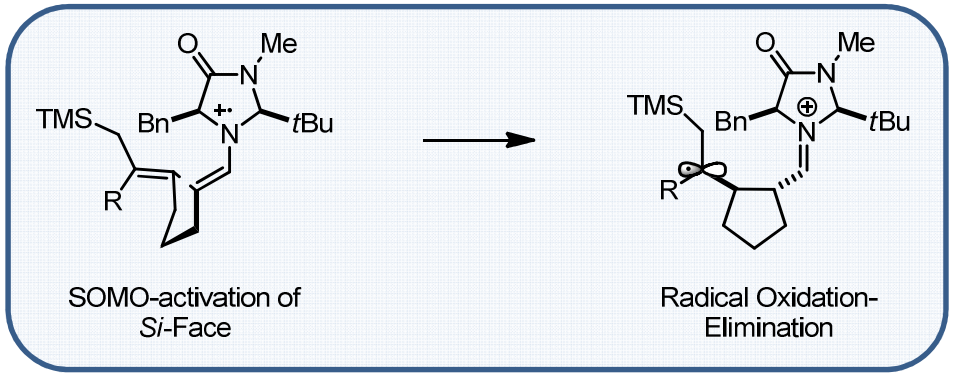
Combined Amino/Metal Catalysis

Enamines and SOMO Catalysis

o In 2011 a novel cyclisation reaction was developed based upon the **enantioselective intramolecular α-allylation of aldehydes** to construct **five-, six- and seven-membered carbocycles** along with **tetrahydropyrans** and **piperidine** motifs







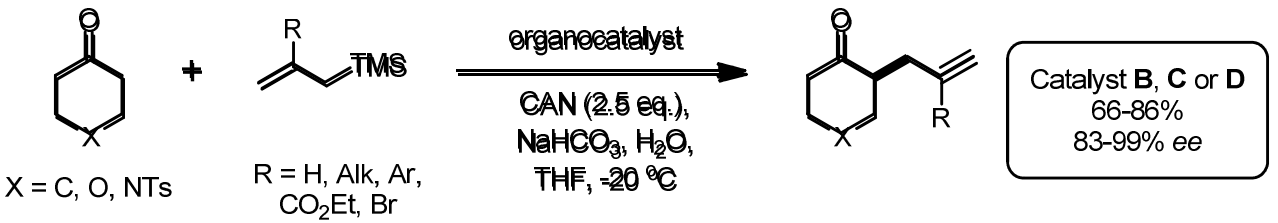
Pham, P. V.; Ashton, K.; MacMillan, D. W. C. *Chem. Sci.*, **2011**, *2*, 1470

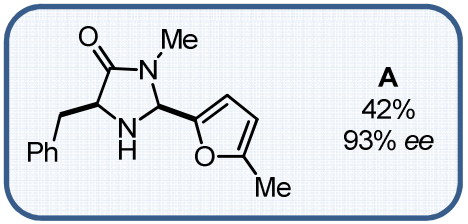
Literature Review

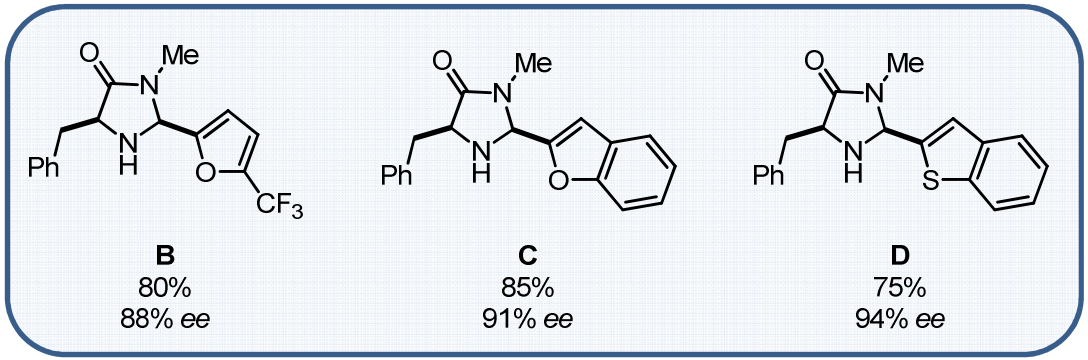
Combined Amino/Metal Catalysis

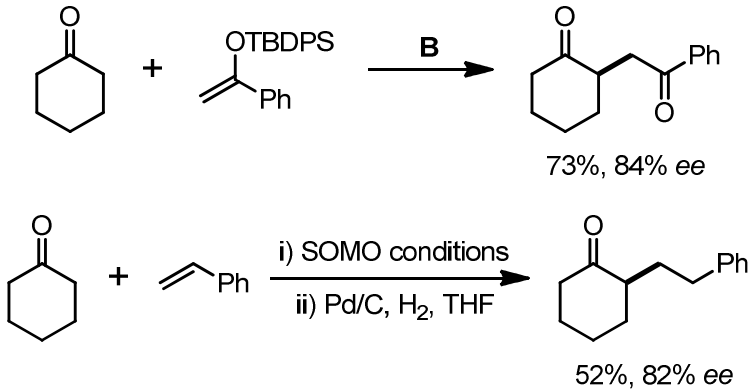
Enamines and SOMO Catalysis

o More recently the MacMillan group have developed a larger family of **oxidatively stable imidazolidinone catalysts** which allow for the methodology to be expanded for the direct **α-allylation, α-enolation** and **α-homobenzylation** of **carbocyclic ketones** (previous catalysts failed to work on ketones)









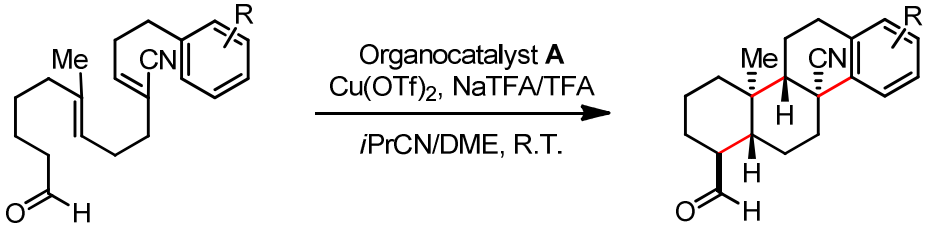
Mastracchio, A.; Warkentin, A. A.; Walji, A. M.; MacMillan, D. W. C. *PNAS*, **2010**, *107*, 20648

Literature Review

Combined Amino/Metal Catalysis

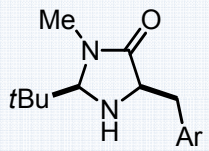
Enamines and SOMO Catalysis

o This SOMO/enamine dual catalysis methodology has been utilised in the **first catalytic enantioselective cyclisation strategy** for the synthesis of **steroidal and terpenoidal frameworks**

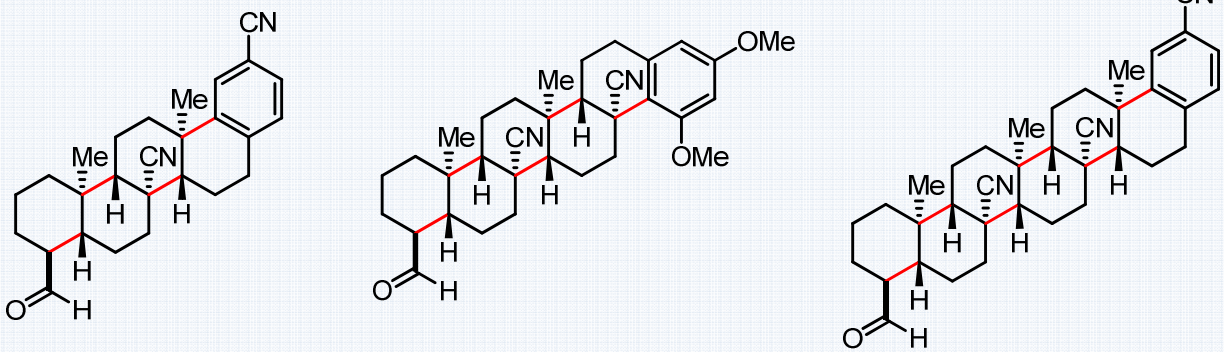


R = F, OMe, CN, CO_2Me, Ph

54-77%
85-93% *ee*



organocatalyst **A**
Ar = Ph, 1-Napthyl



56%, 92% *ee*

63%, 93% *ee*

62%, *ee* n.d.

o Up to 6 new C-C bonds

o Up to 11 contiguous stereocenters

o Up to 5 all-carbon quarternary stereocenters

o ~ 92% per bond formation

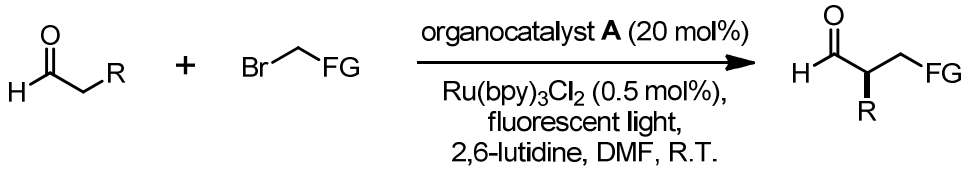
Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.*, **2010**, *132*, 5027

Literature Review

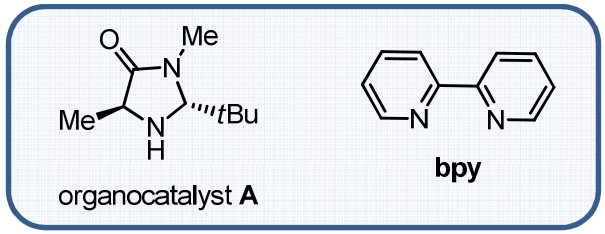
Combined Amino/Metal Catalysis

Enamines and SOMO Photoredox Catalysis

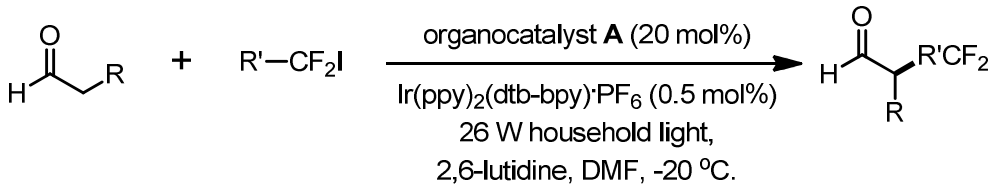
o In 2008 the MacMillan group then combined this methodology with a **photoredox process** as an alternative way of generating the **cationic radicals** required



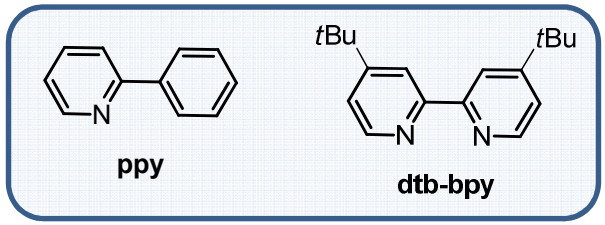
63-93%
90-99% *ee*

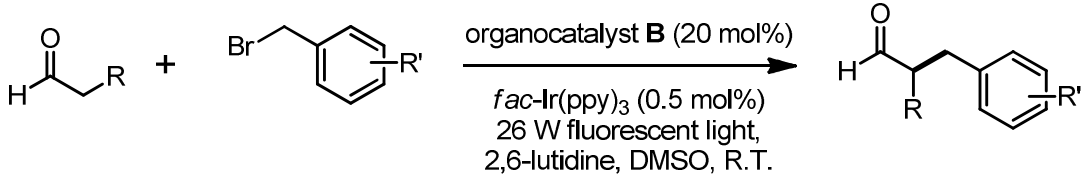


o Later the same group reported both the **α-trifluoromethylation** and **α-benzylation** of aldehydes *via* the combination of **enamine and photoredox catalysis** but with an **Iridium catalyst**

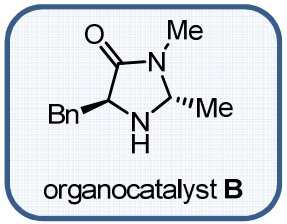


61-89%
90-99% *ee*





68-91%
82-93% *ee*

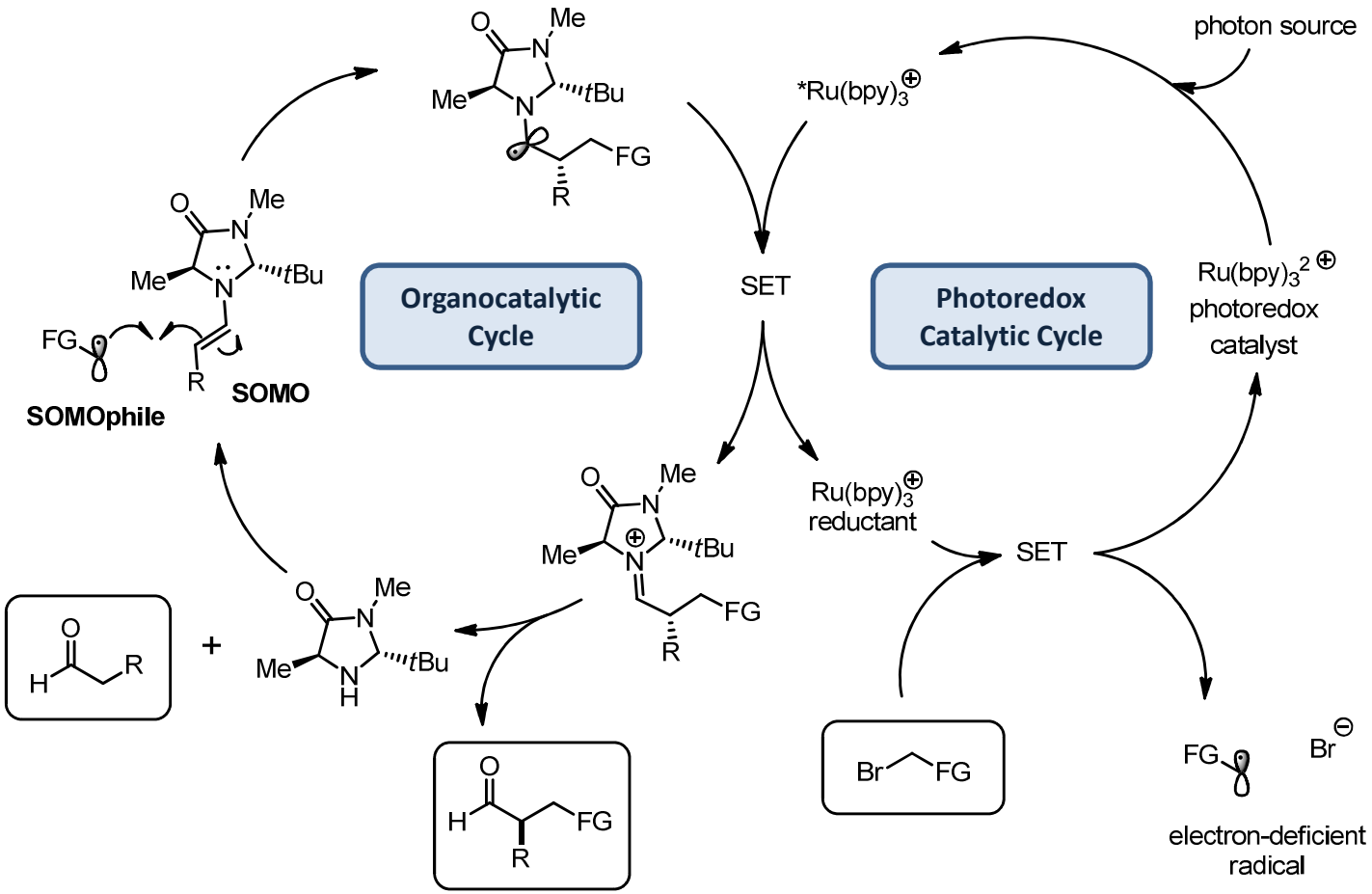


Nicewicz, D. A.; MacMillan, D. W. C. *Science*, **2008**, *322*, 77; Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875; Shih, H-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600

Literature Review

Combined Amino/Metal Catalysis

Enamines and SOMO Photoredox Catalysis

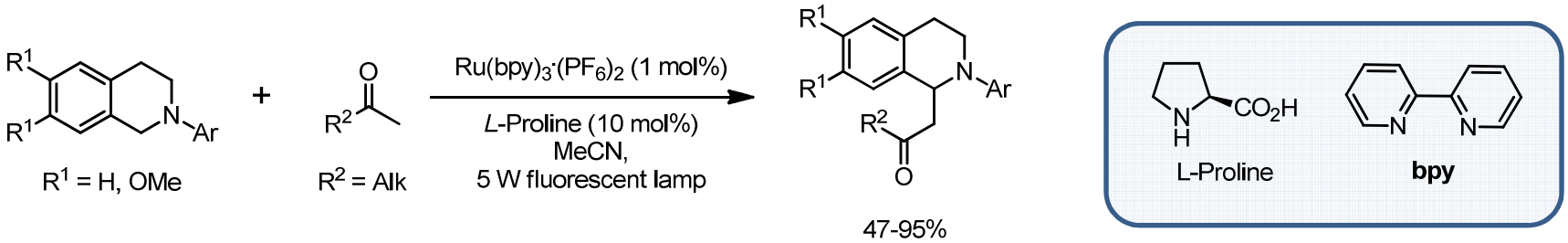


Literature Review

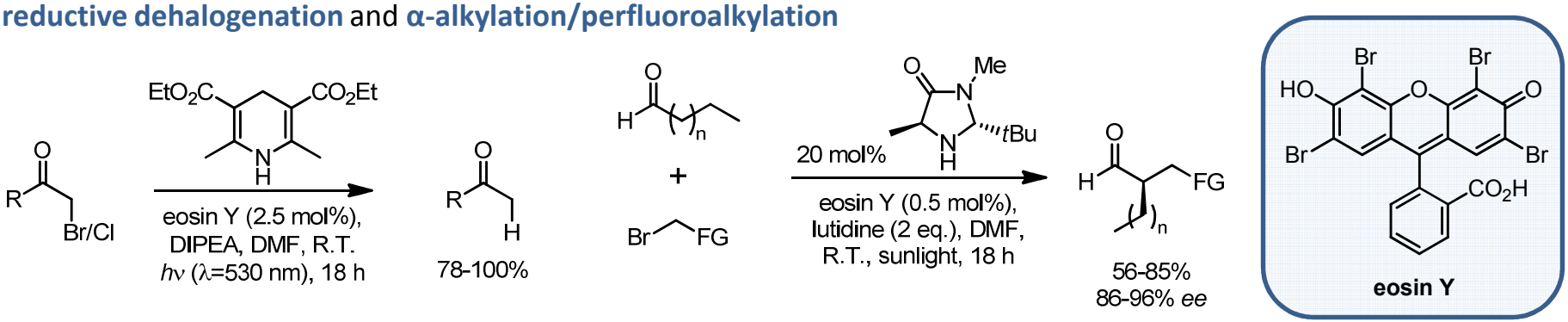
Combined Amino/Metal Catalysis

Enamines and SOMO Photoredox Catalysis

o In 2010 the Fabry group also reported a **combined enamine catalysis with photoredox catalysis** for a **direct Mannich reaction**



o Recently this methodology has been expanded to incorporate **metal-free organophotoredox catalysis** for both **reductive dehalogenation** and **α-alkylation/perfluoroalkylation**



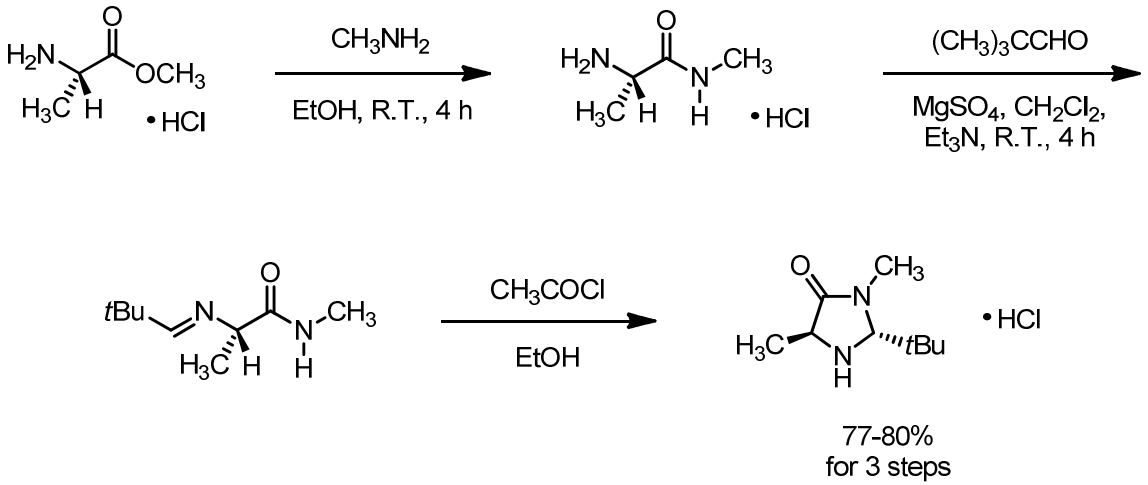
Rueping, M.; Vilas, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360; Neumann, M.; Füldner, S.; König, B.; Zeitler, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 951

Literature Review

Combined Amino/Metal Catalysis

MacMillan's Catalyst

- The organocatalyst is easily synthesised on a large scale from readily available starting materials



Graham, T. H.; Horning, B. D.; MacMillan, D. W. C. *Org. Synth.* **2011**, *88*, 42

Literature Review

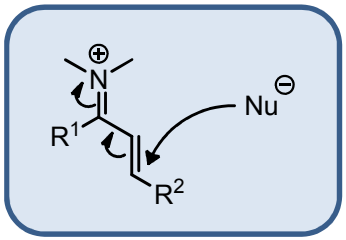
Combined Amino/Metal Catalysis

1. Introduction
2. Aminocatalysis and metal catalysis
   i. Enamine Addition to Transition Metal-Activated Electrophiles
   ii. Enamines and Rhodium-Catalysed Hydroformylation
   iii. Enamines and SOMO Catalysis
   iv. Transition Metal-Activated Nucleophiles with Iminium Catalysis
3. Natural Product Applications
4. Summary

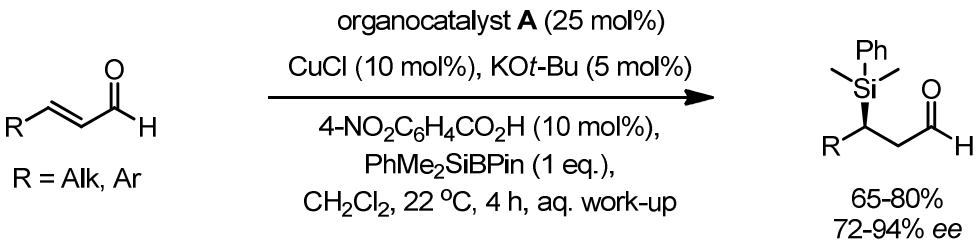
Literature Review

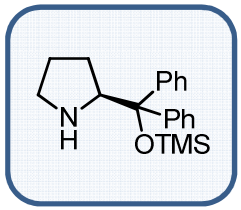
Combined Amino/Metal Catalysis

Transition Metal-Activated Nucleophiles with Iminium Catalysis

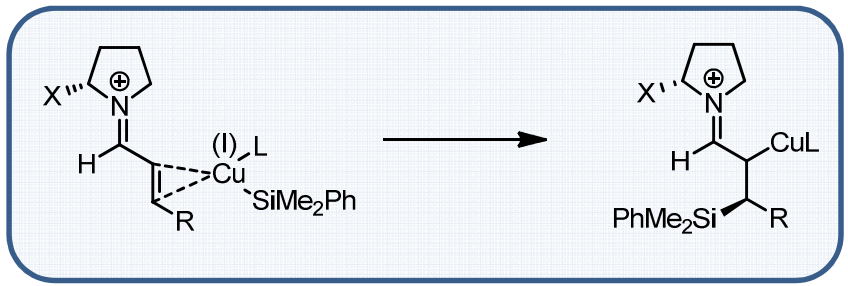


o The first example of the combination of a transition **metal's activation of a nucleophile** and a **chiral amine's iminium activation of an enal** was reported by Córdova's group in 2011





o Control reactions were carried out to confirm that both catalysts were needed to effect the transformation and investigations into the mechanism were conducted



o DFT calculations confirmed nucleophilic attack of the silyl moiety from a $PhMe_2SiCuL$ species on the iminium intermediate

o The enantioselectivity was found to be due to the steric repulsion between the nucleophile and the bulky organocatalyst

Ibrahem, I.; Santoro, S.; Himo, F.; Córdova, A. *Adv. Synth. Catal.* **2011**, *353*, 245

Literature Review

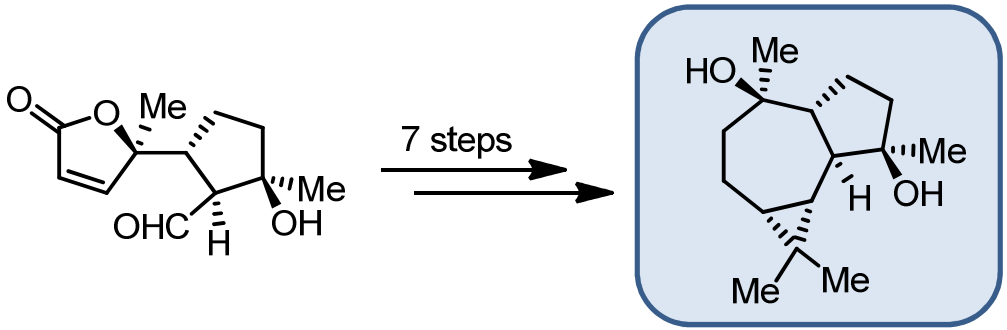
Combined Amino/Metal Catalysis

1. Introduction
2. Aminocatalysis and metal catalysis
   i. Enamine Addition to Transition Metal-Activated Electrophiles
   ii. Enamines and Rhodium-Catalysed Hydroformylation
   iii. Enamines and SOMO Catalysis
   iv. Transition Metal-Activated Nucleophiles with Iminium Catalysis
3. Natural Product Applications
4. Summary

Literature Review

Combined Amino/Metal Catalysis

Natural Product Applications



(-)-Aromadendranediol

- A sesquiterpene natural product, isolated from the marine coral *Sinularia mayi* and from the leaves of the Amazonian tree *Xylopia brasiliensis*

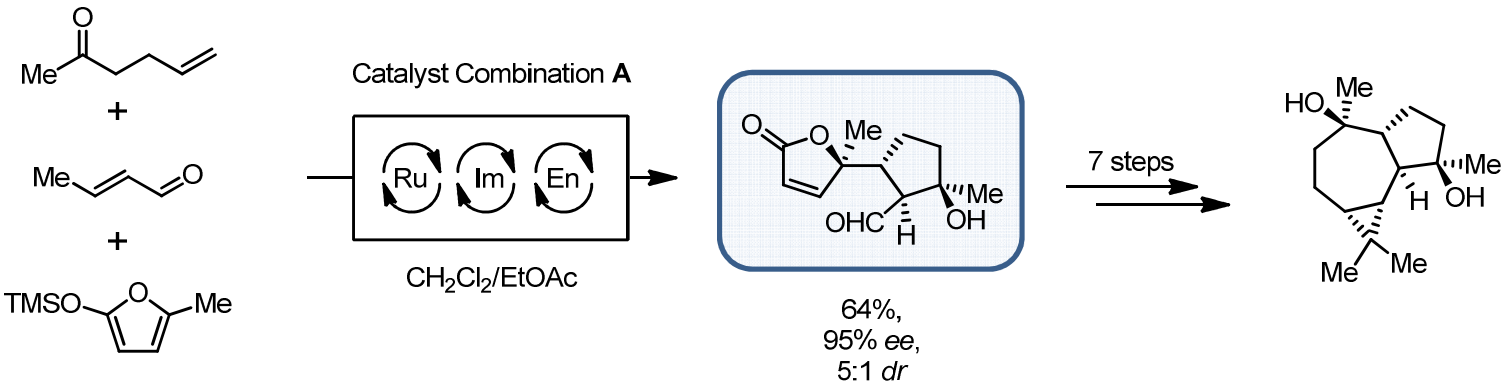
- Known to be a constituent of extracts used in Chinese and Brazilian folk medicines as sedatives, analgesics or to treat lung inflammation

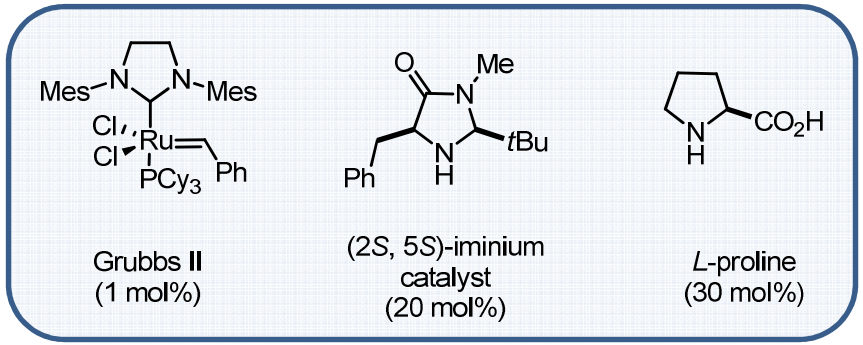
Grondal, C.; Jeanty, M.; Enders, D. *Nature*, **2010**, *2*, 167

Literature Review

Combined Amino/Metal Catalysis

(-)-Aromadendranediol



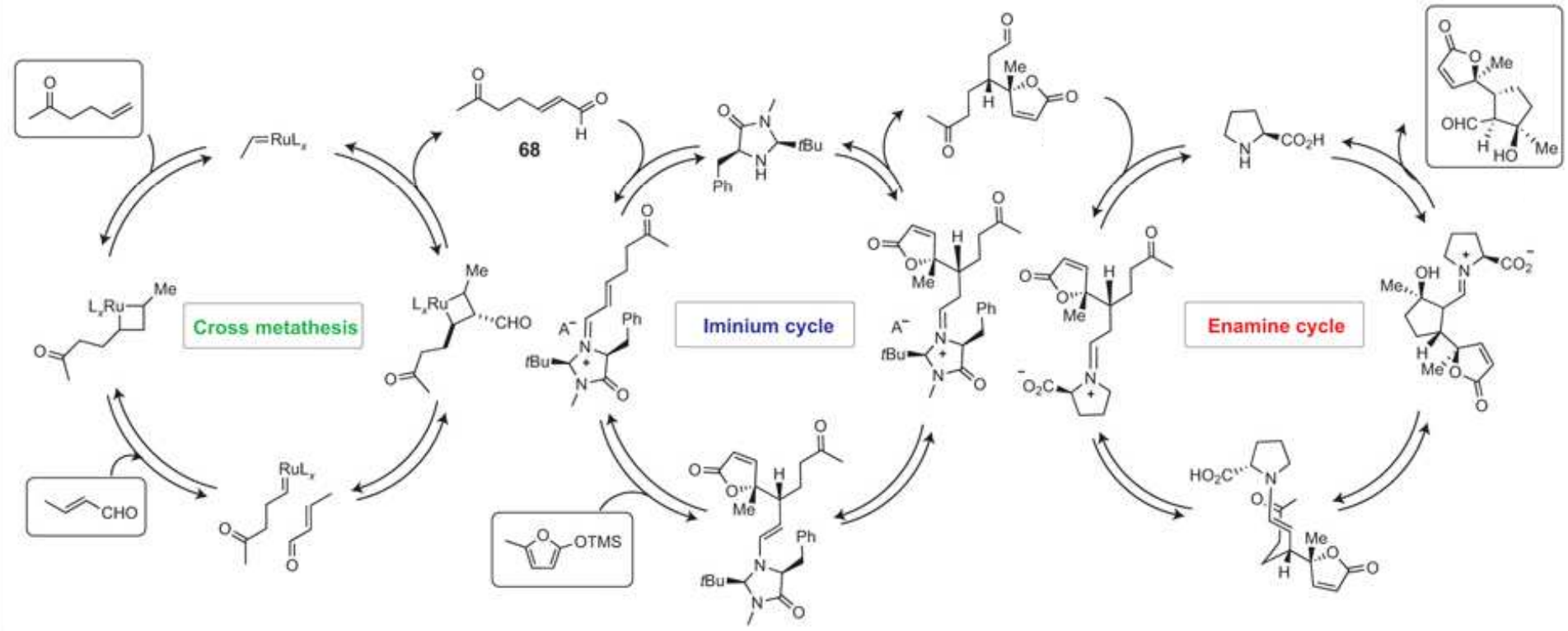


Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew,. Chem. Int. Ed.* **2009**, *48*, 4349

Literature Review

Combined Amino/Metal Catalysis

(-)-Aromadendranediol

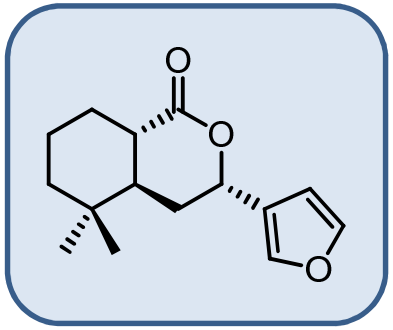


Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew,. Chem. Int. Ed.* **2009**, *48*, 4349

Literature Review

Combined Amino/Metal Catalysis

Natural Product Applications



(+)-Ricciocarpin A

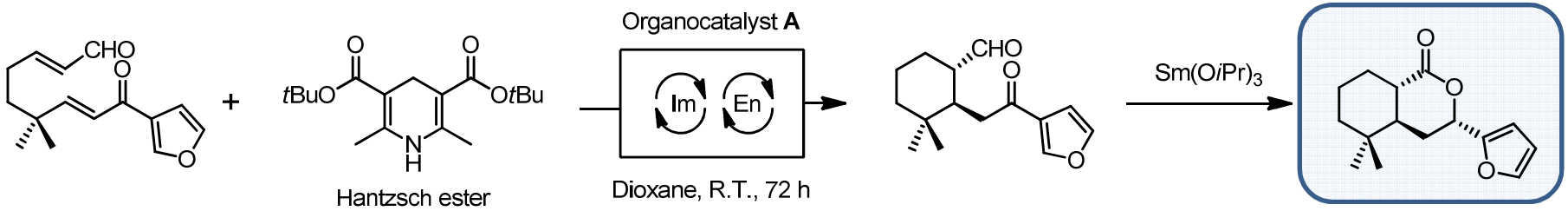
- A furanosesquiterpene lactone isolated from the liverwort *Ricciocarpos natans*
- Possesses potent molluscicidal activity against the water snail *Biomphalaria glabrata*, which contributes to the parasitic disease schistosomiasis

Grondal, C.; Jeanty, M.; Enders, D. *Nature*, **2010**, *2*, 167

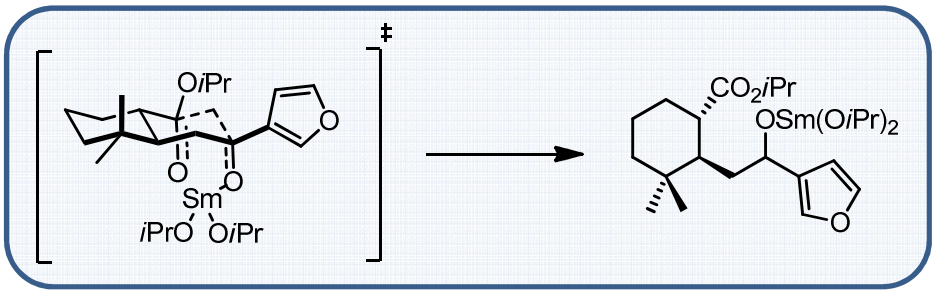
Literature Review

Combined Amino/Metal Catalysis

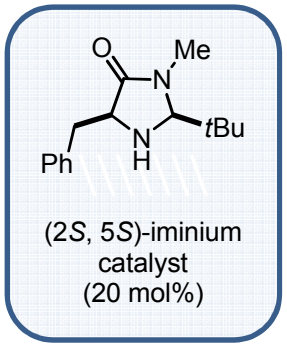
(+)-Ricciocarpin A



- Initially mainly the undesired *cis*-isomer was obtained but by using a one-pot method the isomerisation to the desired *trans*-isomer was strongly accelerated by the $Sm(OiPr)_3$
- The $Sm(OiPr)_3$ also allowed a highly diastereoselective Tishchenko reaction to occur to yield the desired natural product as a single *trans*-diastereomer with excellent enantioselectivity in only 3 steps



- Methodology also used to synthesise different derivatives by altering the furan functional group



Michrowska, A.; List, B. *Nature Chem.* **2009**, *1*, 225

Literature Review

Combined Amino/Metal Catalysis

1. Introduction
2. Aminocatalysis and metal catalysis
   i. Enamine Addition to Transition Metal-Activated Electrophiles
   ii. Enamines and Rhodium-Catalysed Hydroformylation
   iii. Enamines and SOMO Catalysis
   iv. Transition Metal-Activated Nucleophiles with Iminium Catalysis
3. Natural Product Applications
4. Summary

Literature Review

Combined Amino/Metal Catalysis

Summary

- Enables unprecedented transformations not currently possible by the use of each catalytic system alone
- One pot approach – reducing waste and time
- Allows access to highly functionalised aldehydes and ketones in good stereo- and regio- control
- Still a relatively new area of research