Synthesis of Substituted Imidazoles via Organocatalysis

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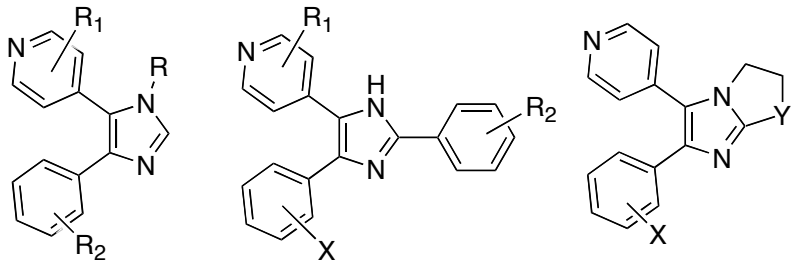
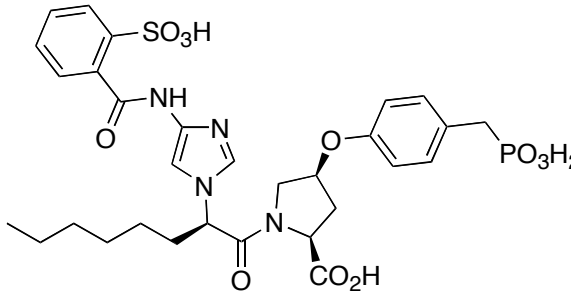
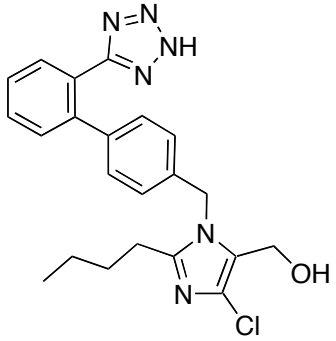
Imidazoles as Targets in Medicinal Chemistry



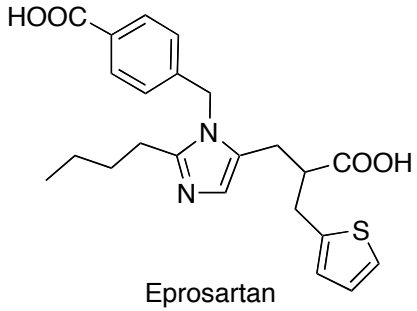
Imidazole CSAID Ligands -- SKB



Orally available Angiotensin II inhibitor -- Lilly



Losartan

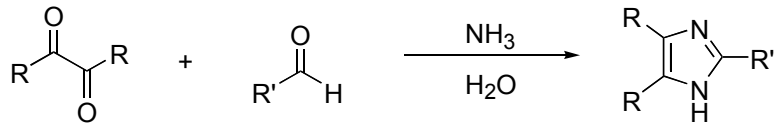


Eprosartan

p38 MAP kinase inhibitors

Debus Reaction

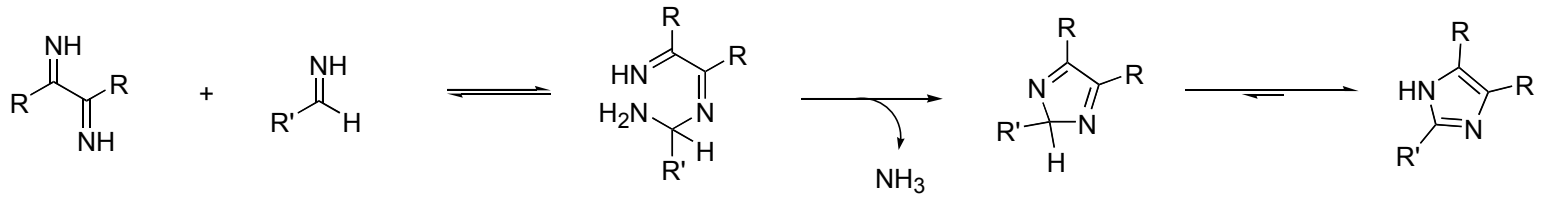
Debus imidazole synthesis



reaction provides 2- monosbstituted, and 2,(3,4 *homo*)trisubstituted imidazoles

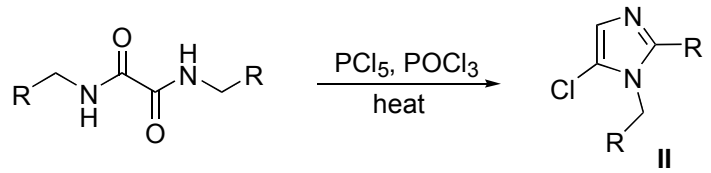
Debus, H. *Liebigs Ann. Chem.* **1858**, *107*, 199.

Proposed Mechanism of the Debus Reaction



Wallach Reaction

Wallach chloroimidazole synthesis

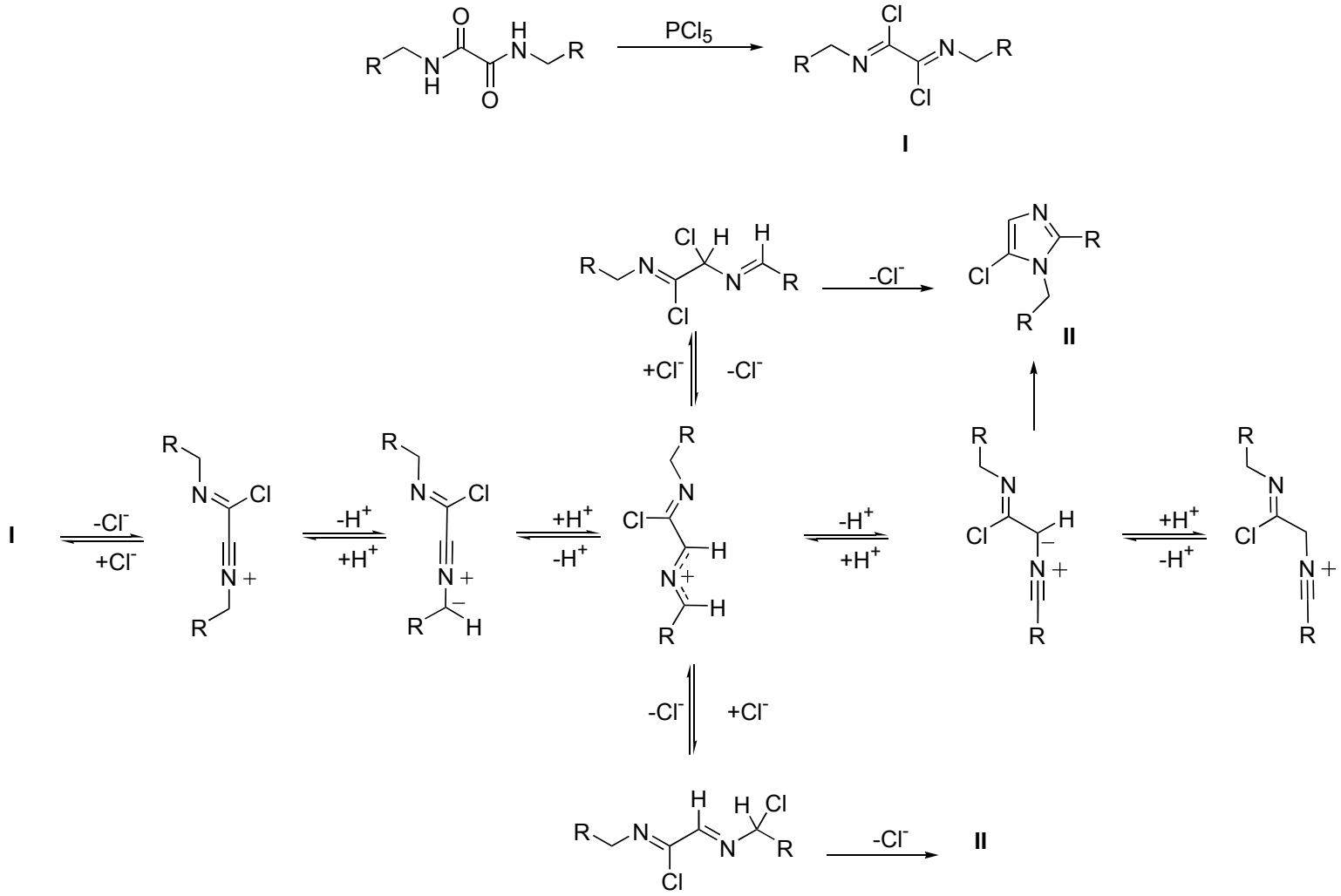


II

Provides 1,2 disubstituted chloroimidazoles

Wallach, O. *Ber. Dtsch. Chim. Ges.* **1881**, *14*, 420.

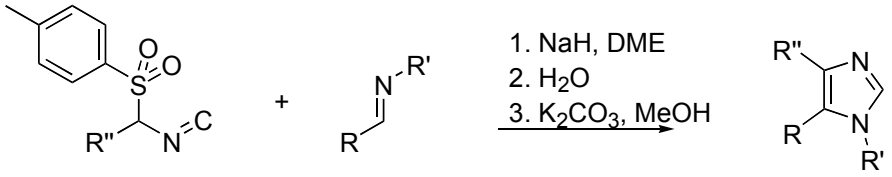
Proposed Mechanism of the Wallach Reaction



Benincori, T.; Brenna, E.; Sannicolo, F. *J. Chem Soc. Perk. Trans. I* **1993**, 675-679.

TosMIC Based Imidazole Synthesis

Synthesis from TosMIC

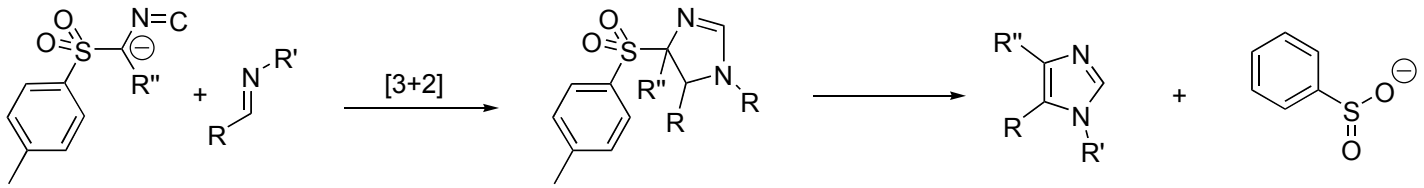


Process regioselectively provides 1,5-di and a limited number of 1,4,5-trisubstituted imidazoles

TosMIC = tosylmethyl isocyanide

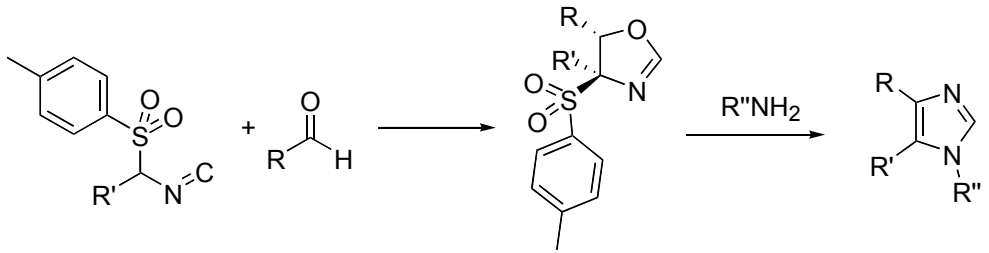
van Leusen, A. M.; Wildeman, J.; Oldenziel, O. H. *J. Org. Chem.* **1977**, *42*, 1153-9

Mechanism of TosMIC based Imidazole Synthesis



Extension of the TosMIC Chemistry

An Extension of the TosMIC chemistry



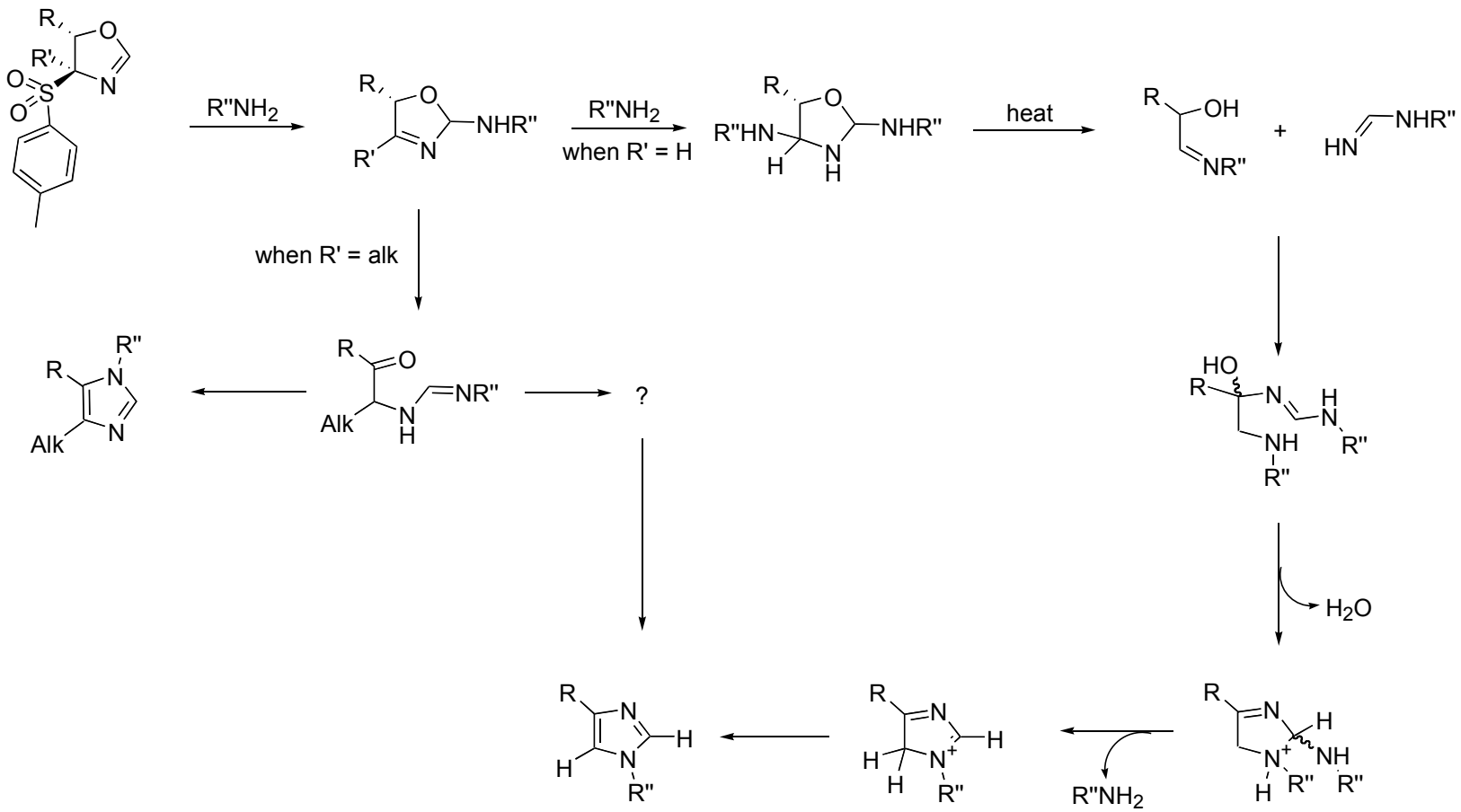
Horne, D. A.; Yakushijin, K.; Buchi, G. *Heterocycles*, **1994**, 139

R' = H or Alk
R" = H or Alk
R and R' cannot both = Alk

Process regioselectively provides 4, 1,4, and 4,5 mono- and disubstituted imidazoles

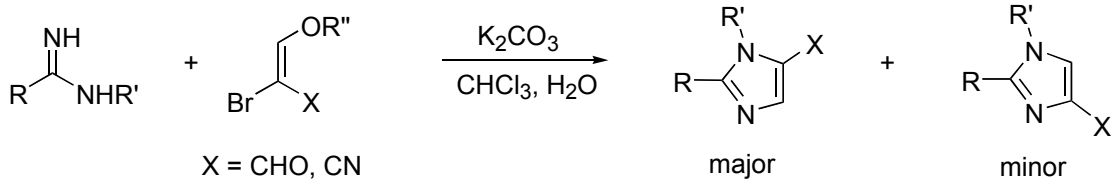
1,4,5 trisubstituted imidazoles are not easily made with this methodology as a regioisomeric mixture of products results.

Modified TosMIC Imidazole Mechanism



Synthesis of Imidazoles from Amidines

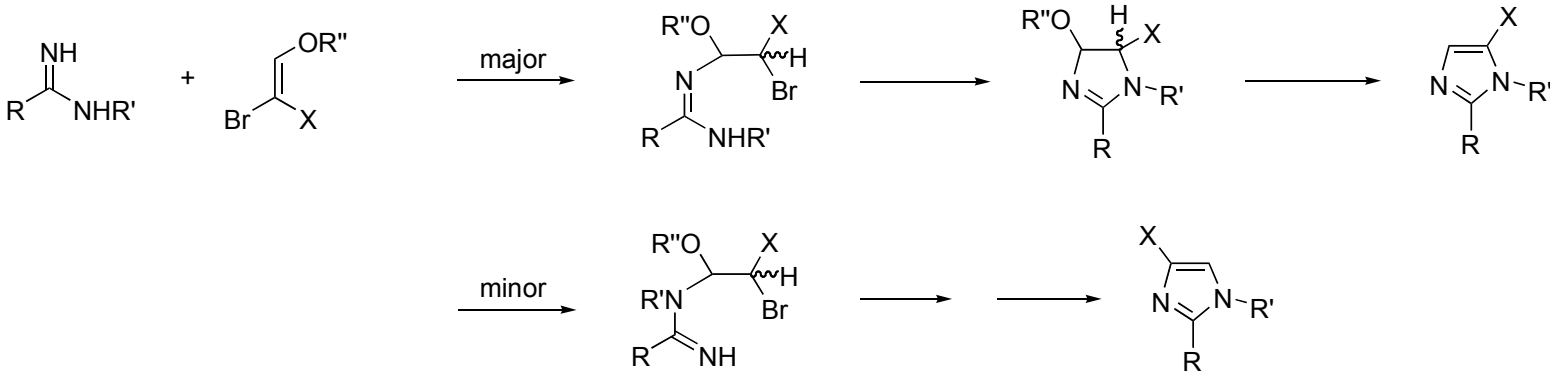
Selective synthesis of 1,2,5 substituted imidazoles



modest yields, good selectivity ammenable to the synthesis of multikilogram quantities of pharmaceutical intermediates

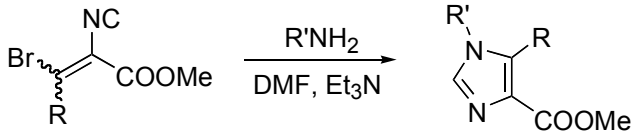
Shilcrat, S. C.; Mokhallalati, M. K.; Fortunak, J. M. D.; Pridgen, L. N. *J. Org. Chem.* **1997**, *62*, 8449.

Imidazoles from Amidines -- Mechanism



Imidazole carboxylates from BICAs

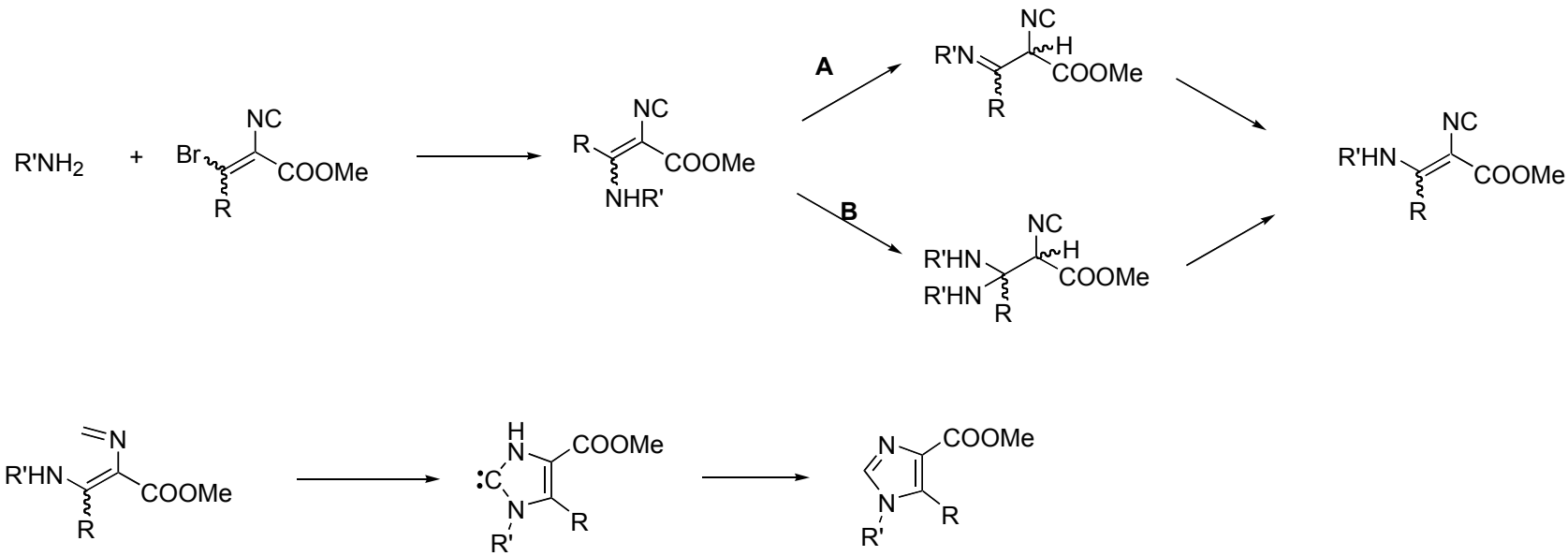
1,5 imidazole carboxylates from amines and 3-bromo-2-isocyanoacrylates (**BICAs**)



Nunami, K.-I.; Yamada, M.; Fukui, T.; Matsumoto, K. *J. Org. Chem.* **1994**, *59*, 7635.

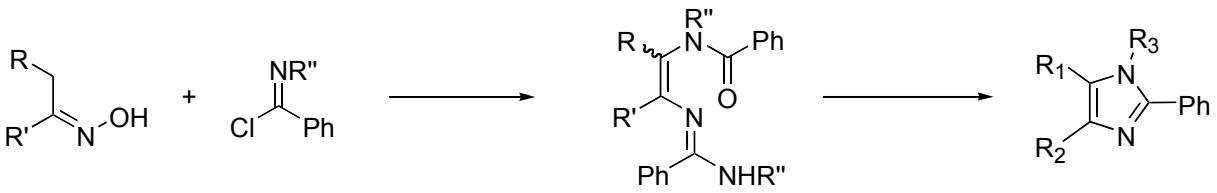
Complementary to the amidine methodology

BICA Mechanism



Hetero Cope Rearrangement -- A Strategy to Highly Substituted Imidazoles

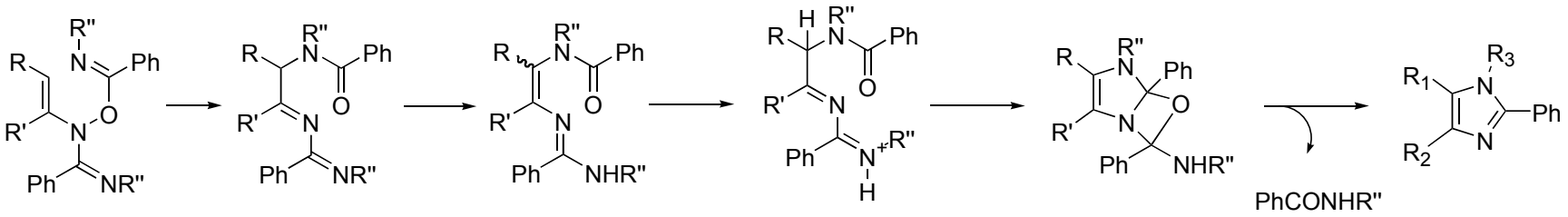
Hetero-Cope Rearrangements to regioselectively provide highly Substituted imidazoles



highly regioselective synthsis of tetrasubstituted imidazoles. Limited by R-group requirements.

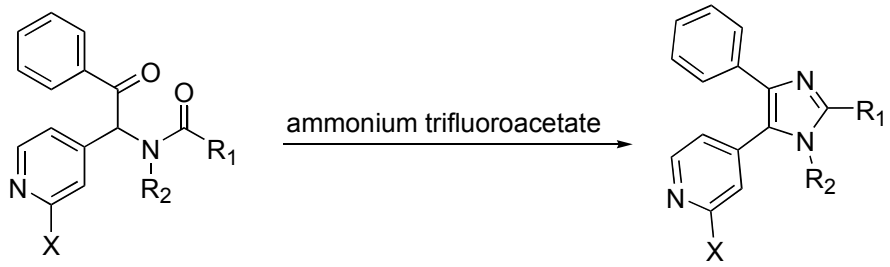
Lantos, I.; Zhang, W.-Y.; Shui, X,; Eggleston, D. S. *J. Org Chem.* , **1993**, *58*, 7092.

Mechanism of the Hetero Cope Rearrangement Approach



Highly Substituted Imidazoles From □□Ketoamides

Regioselective synthesis of tetrasubstuted imidazoles from □□ketoamides under neutral reaction conditions



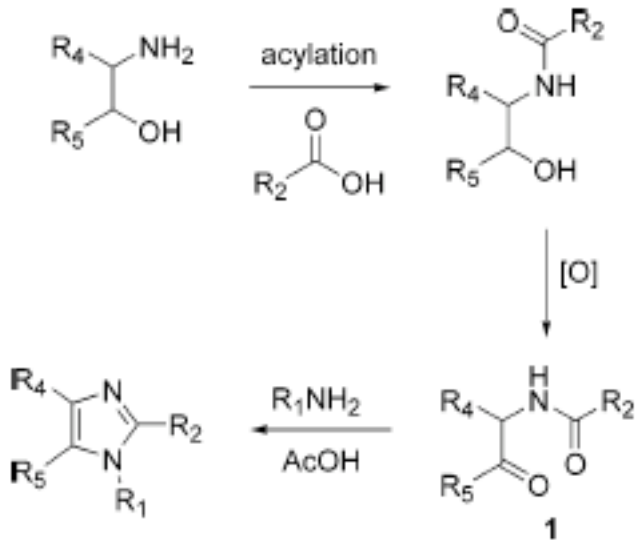
Methodology tolerates variance at positions 1,2 and 5 quite well.

Position 4 usually, but not always, aromatic.

Claiborne, C. F.; Liverton, N. J.; Nguyen, K. *Tetrahedron Lett.* **1998**, *39*, 8939.

Synthesis of □-Ketoamides… Nontrivial??

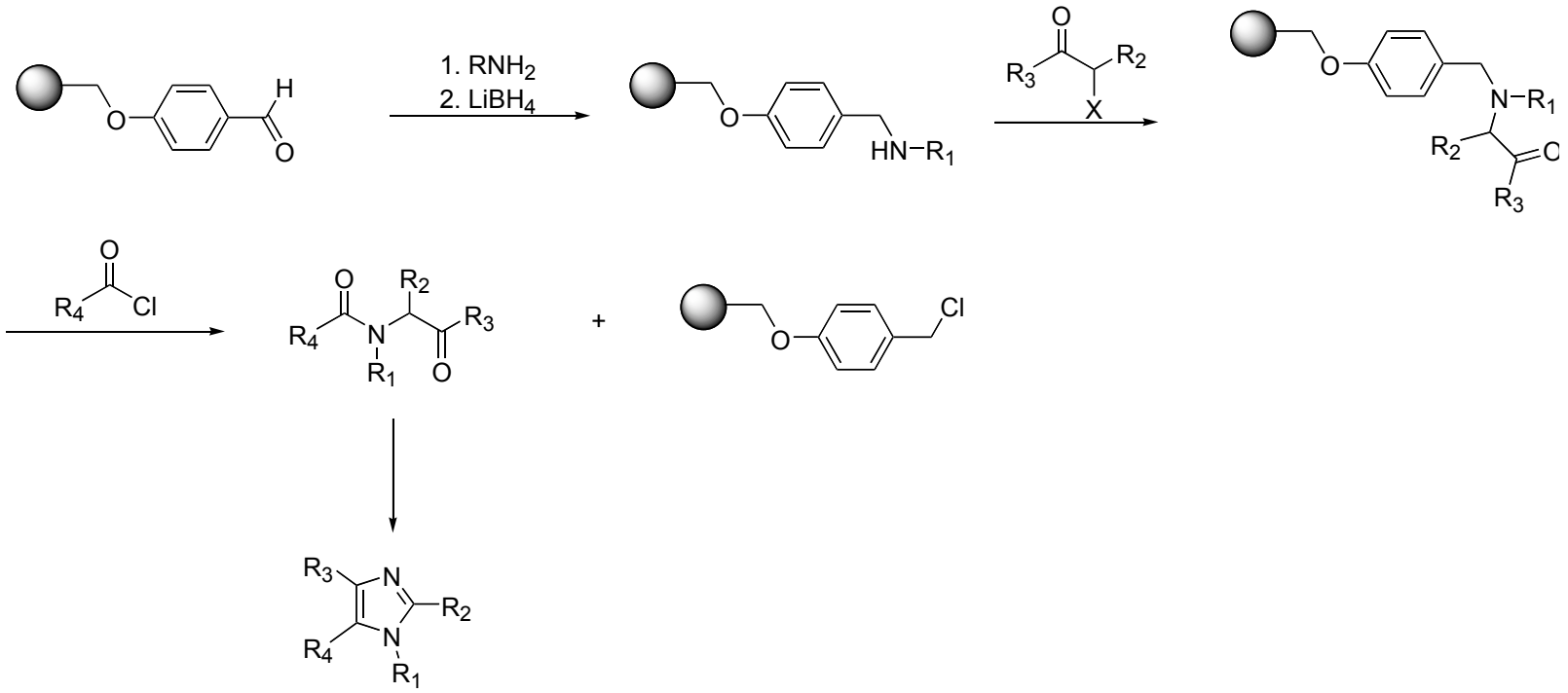
Scheme 1



1

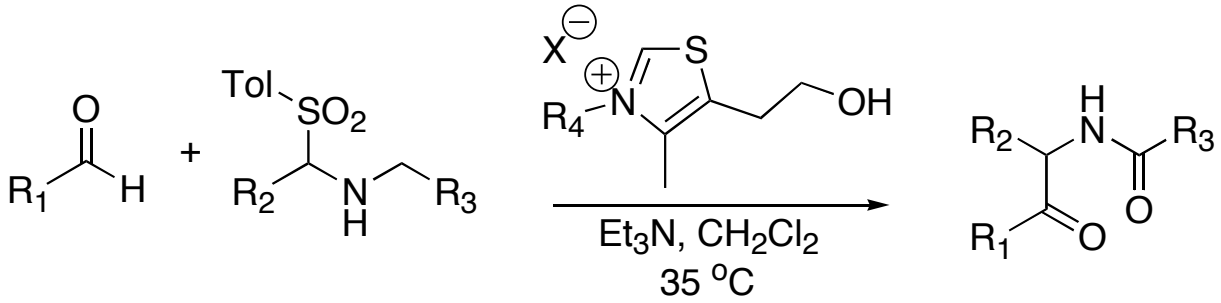
A Traceless Synthesis of □-Ketoamides

A traceless entry into □-ketoamides -- and tetrasubstituted imidazoles



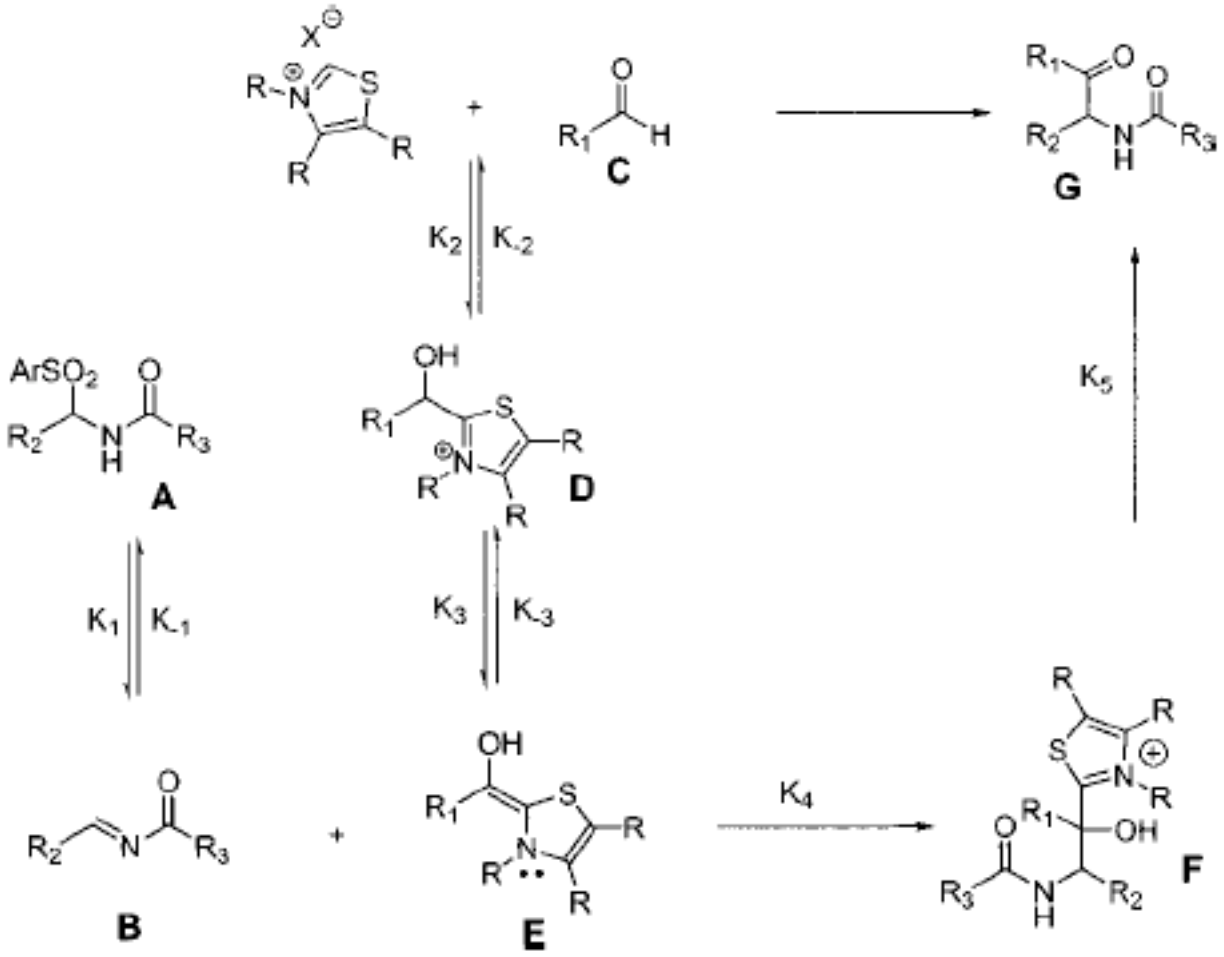
Lee, H. B.; Balasubramanian, S. *Org. Lett.* **2000**, *2*, 323.

Thiazolium Catalyzed Synthesis of □-Ketoamides



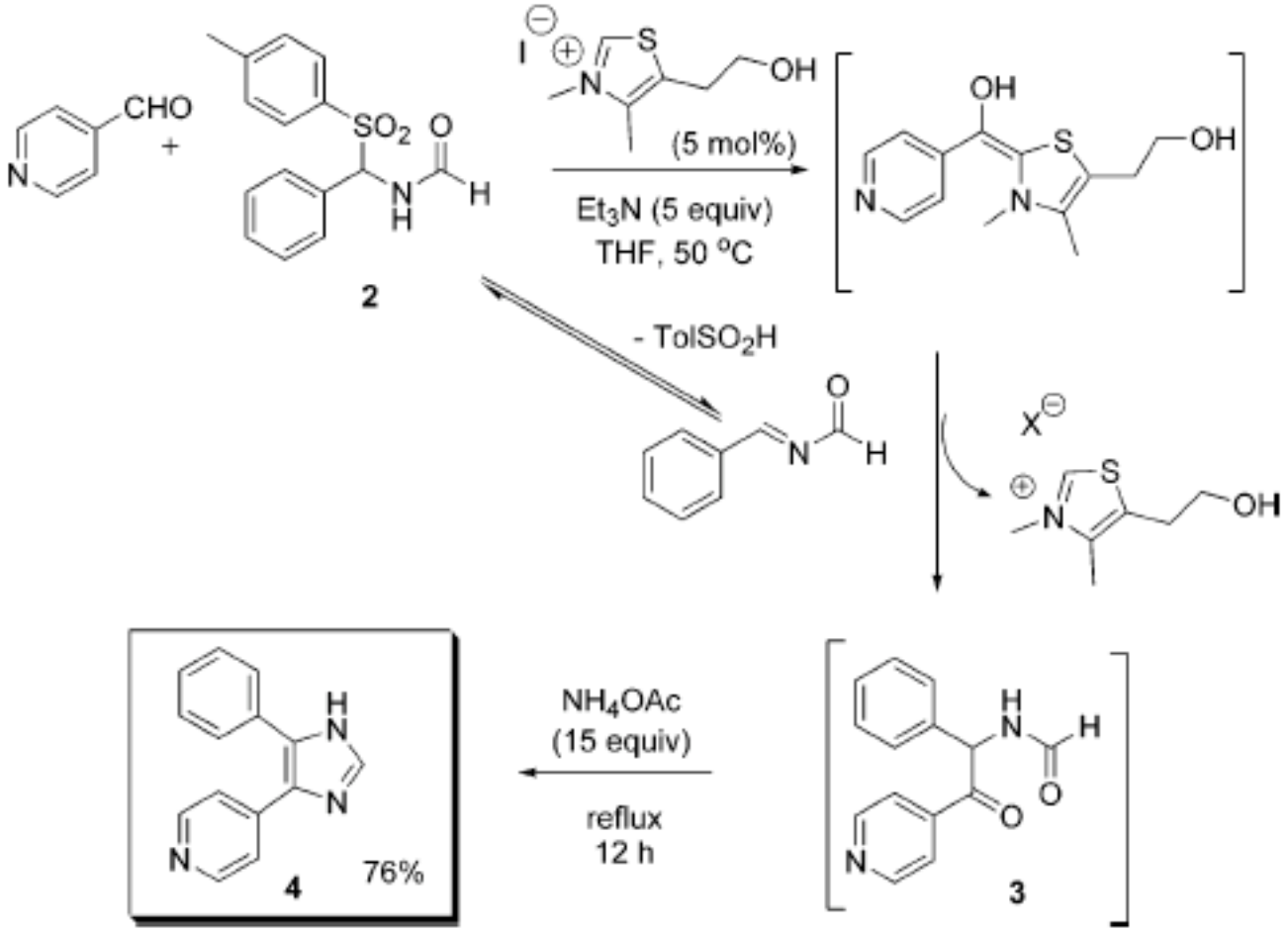
Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. *J. Am. Chem. Soc.* **2001**, 9696.

Mechanism of β-Ketoamide Synthesis by Organocatalysis

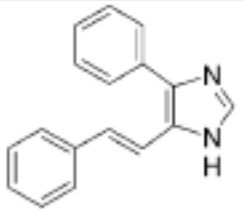
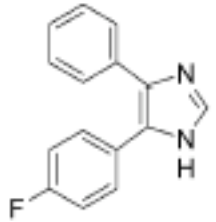
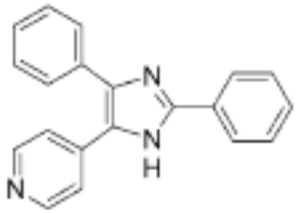
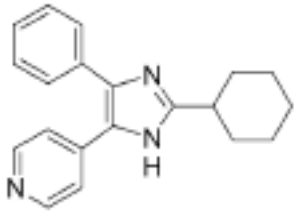
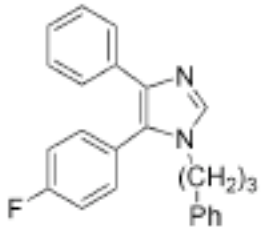
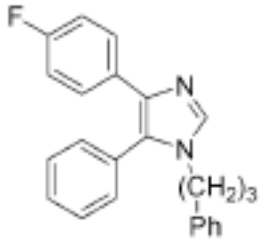
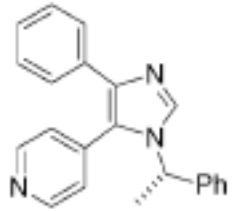
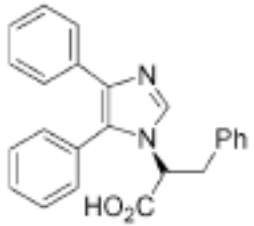


Murry, J. A.; Frantz, D. E.; Soheili, A.; Tillyer, R.; Grabowski, E. J. J.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 9696.

Regioselective, "One Pot" Synthesis of Substituted Imidazole

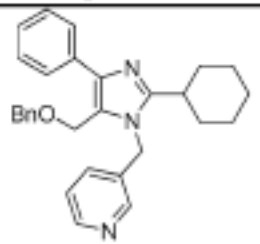
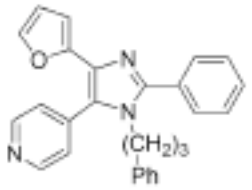
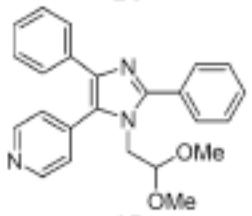
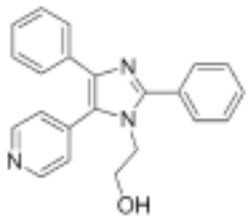


One-Pot Synthesis of Di- and Trisubstituted Imidazoles

entry	product	isolated yield[a]
1	 **5**	47%[b] 68%[c]
2	 **6**	82%[c]
3	 **7**	78%[c]
4	 **8**	55%[b] 82%[c]
5	 **9**	35%[b] 58%[c]
6	 **10**	42%[b] 61%[c]
7	 **11**	83%[c] >98% ee
8	 **12**	48%[b] 73%[c] >98% ee

[a] Reaction yields and isolations were not optimized and represent the result of a single experiment. [b] Product isolated by crystallization from the crude product mixture. [c] Product isolated by SiO_2 chromatography.

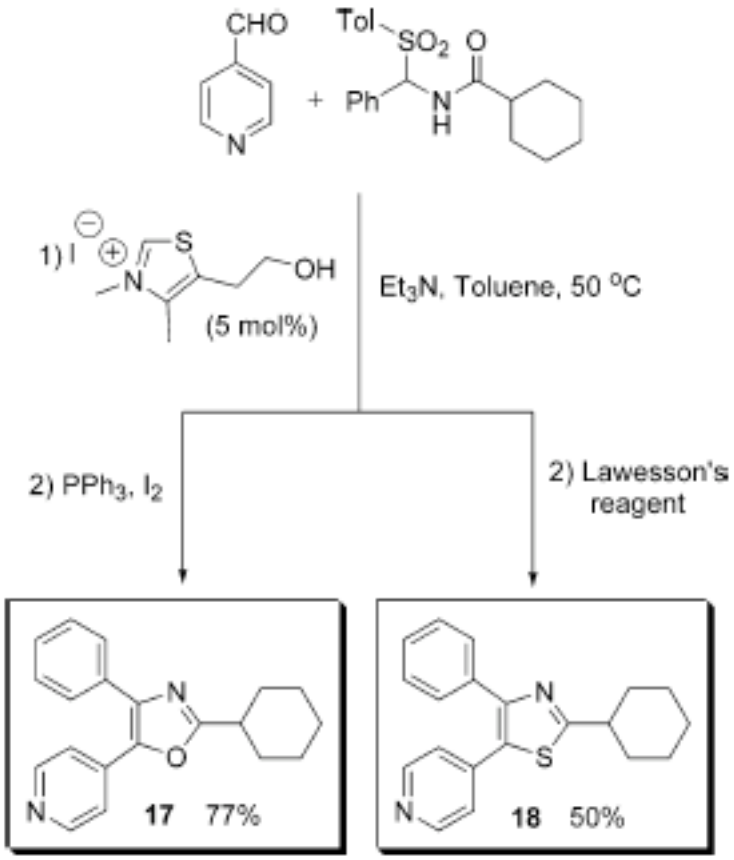
Synthesis of Tetrasubstituted Imidazoles

entry	product	isolated yield[a]
1	 **13**	22%
2	 **14**	76%
3	 **15**	80%
4	 **16**	75%

[a] Reaction yields were not optimized and represent the result of a single experiment. Products isolated by SiO_2 chromatography.

Application to the Synthesis of Substituted Oxazoles and Thiazoles

Scheme 3



Conclusions

- A rapid, one-pot, regioselective, organocatalyzed synthesis of highly functionalized imidazoles from □-ketoamides has been described

- The methodology has been extended to the synthesis of substituted oxazoles and thiazoles