Rhodium(II)-Catalysed Intramolecular Annulation of 1-Sulfonyl-1,2,3-Triazoles with Pyrrole and Indole Rings: Facile Synthesis of N-Bridgehead Azepine Skeletons

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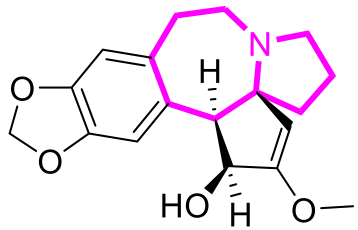
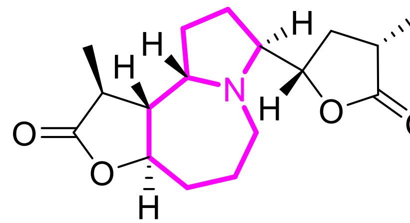
Azepine Skeleton

N-Bridgehead Azepine skeletons are widely distributed in nature:

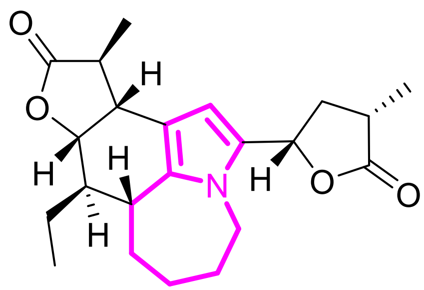
- ***Cephalotaxus alkaloids*** → antileukemic activity
- ***Stemona alkaloids*** → Chinese and Japanese Folk medicine, extracts and teas were used as remedies of respiratory disease, including tuberculosis and anthelmintics
- ***Venom/frog alkaloids***
- ***Anthramycin***



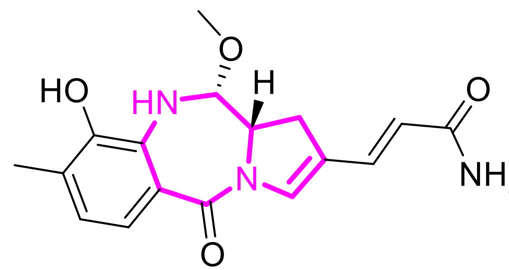
Cephalotaxin



Stemonine

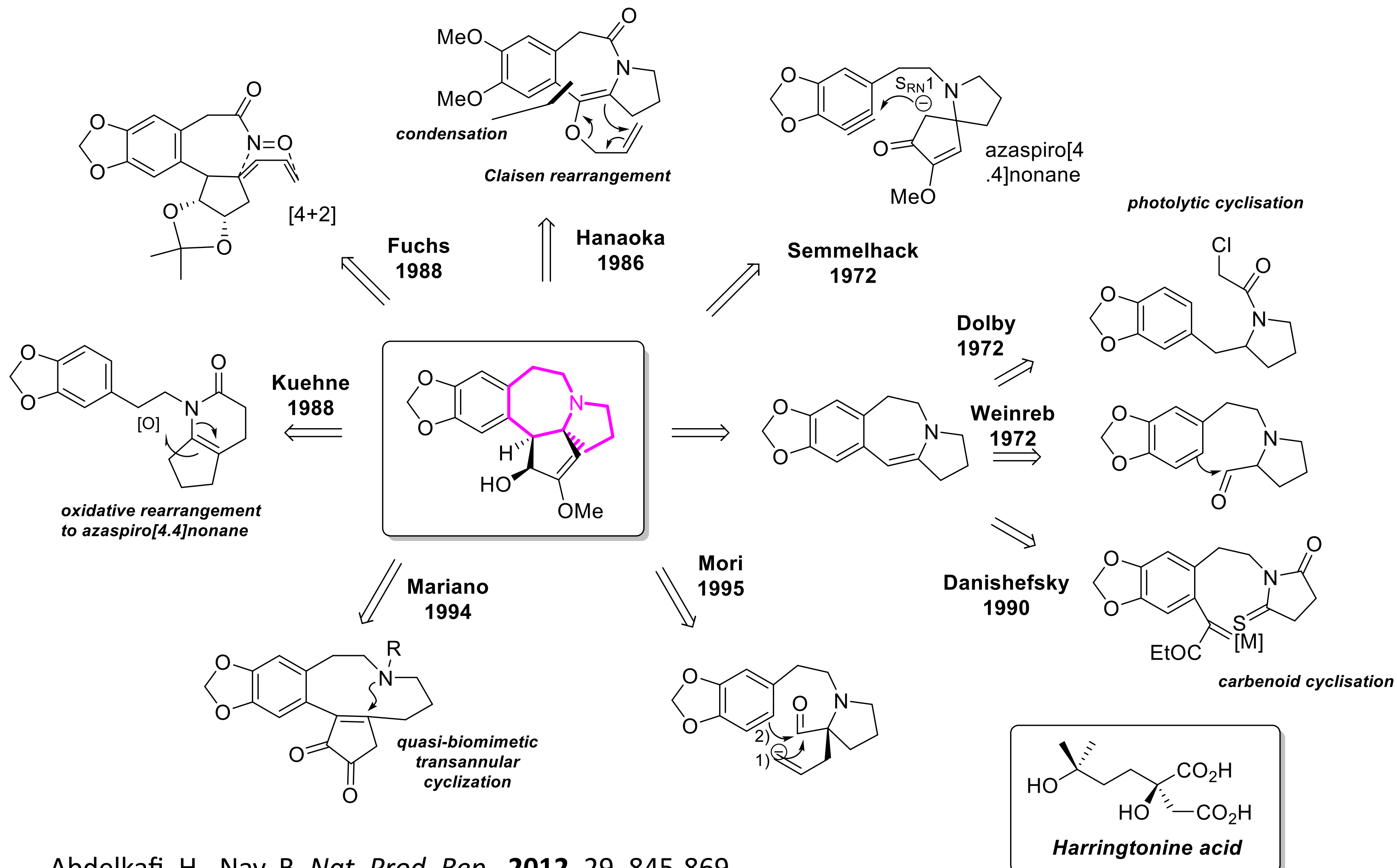


bisdehydrotuberostemonine



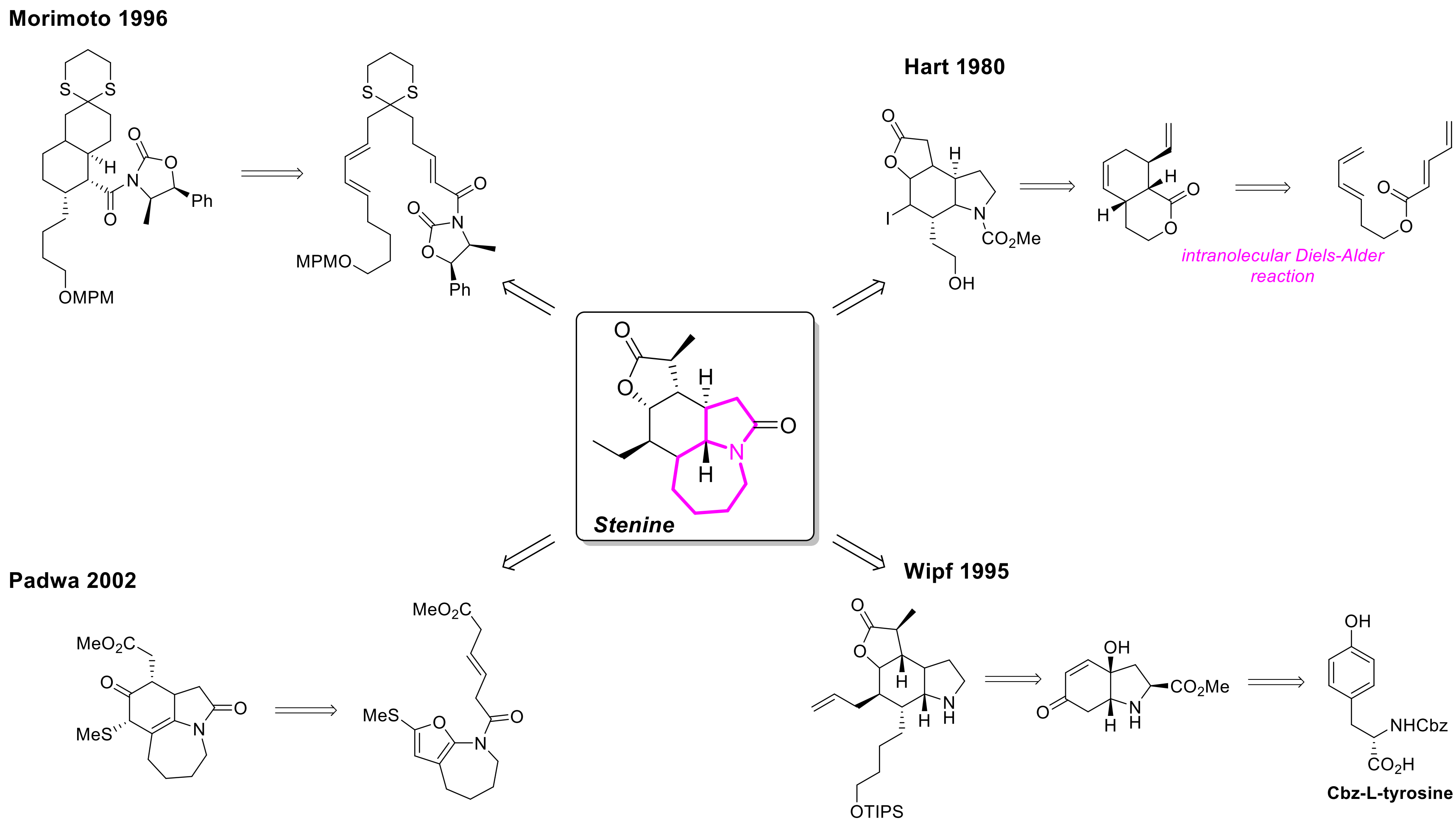
Anthramycin

Synthetic Strategies to Cephalotaxine Alkaloids

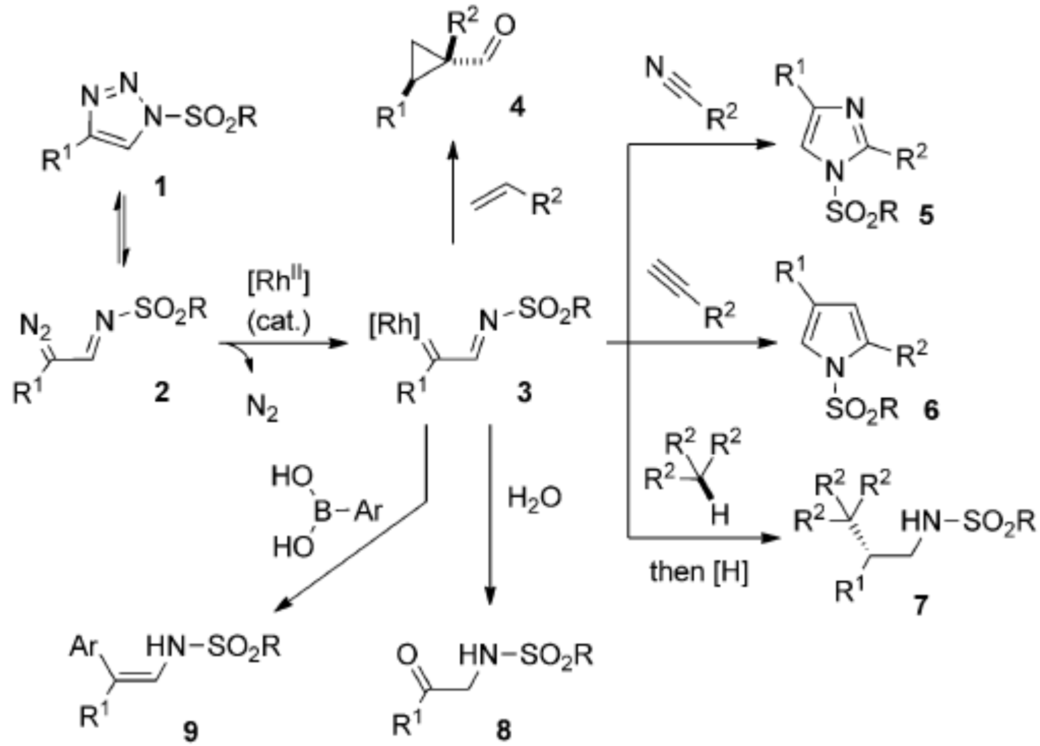


Abdelkafi, H., Nay, B. *Nat. Prod. Rep.*, **2012**, 29, 845-869

Synthetic Strategies to Stemona Alkaloids

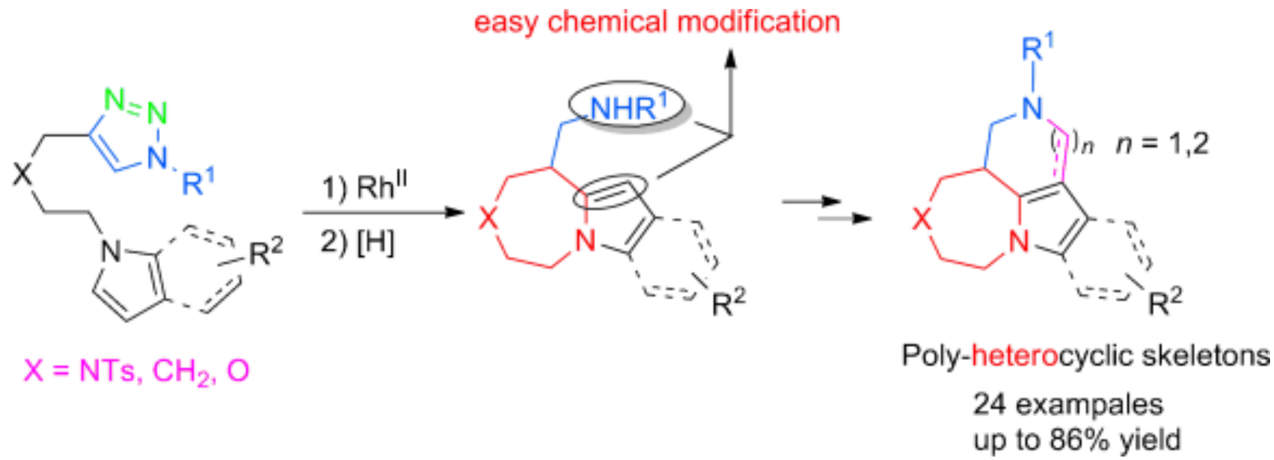


1-Sulfonyl-1,2,3-Triazoles and their Application in Organic Synthesis

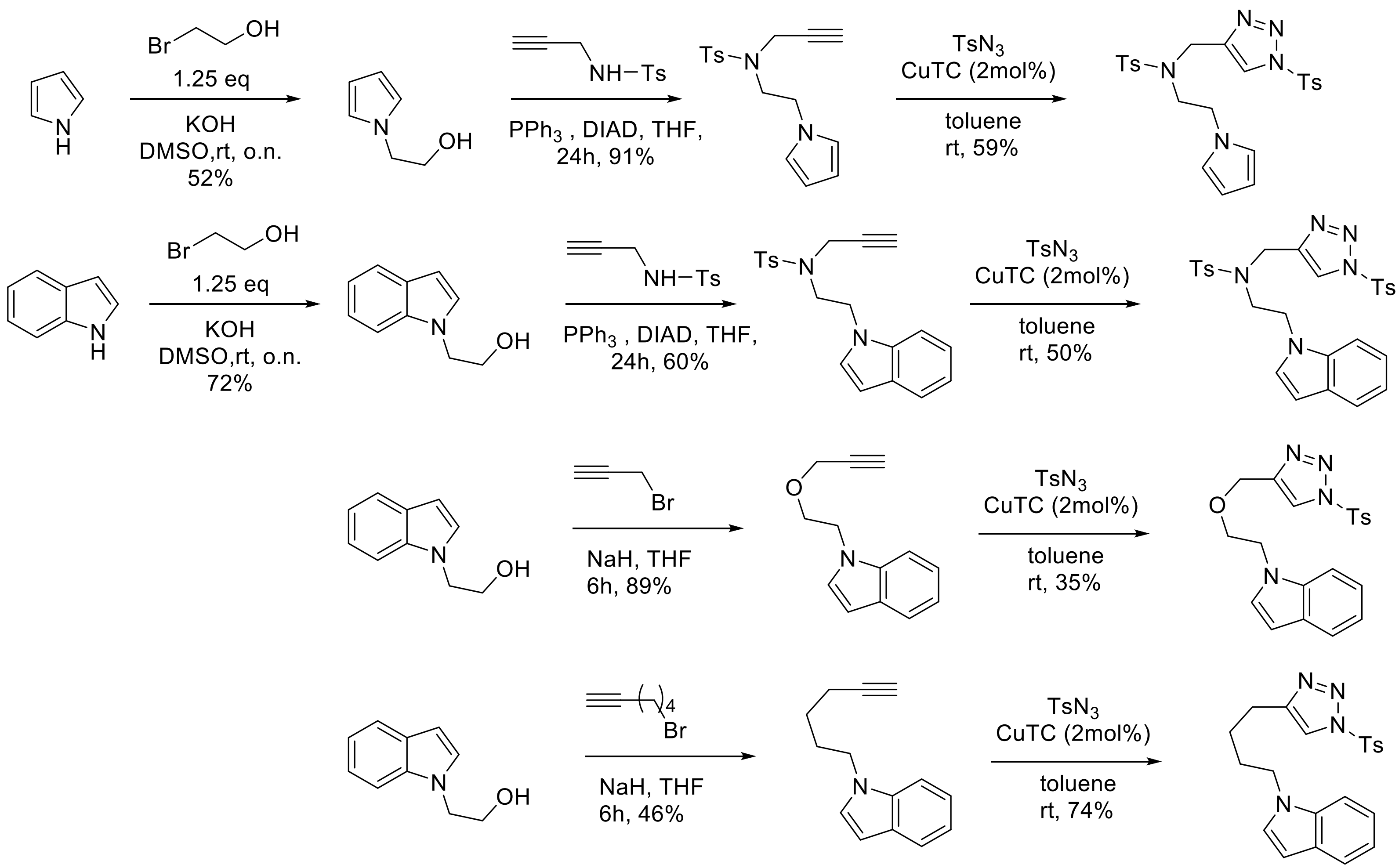


Gevorgyan et al. *Angew. Chem. Int. Ed.* **2013**, 52, 1371-1373

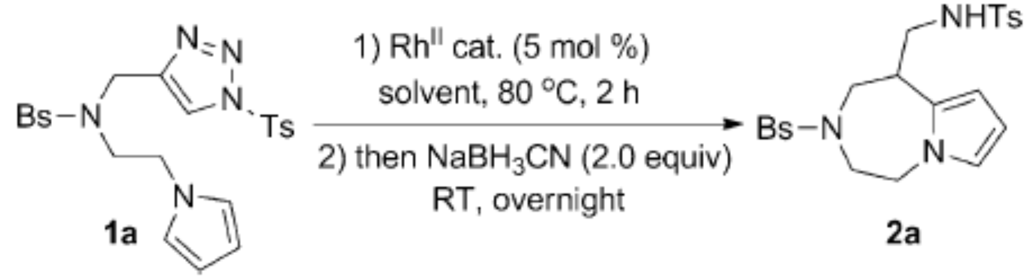
This work: Facile Synthesis of the Azepine Core



Synthesis of Triazole Precursor



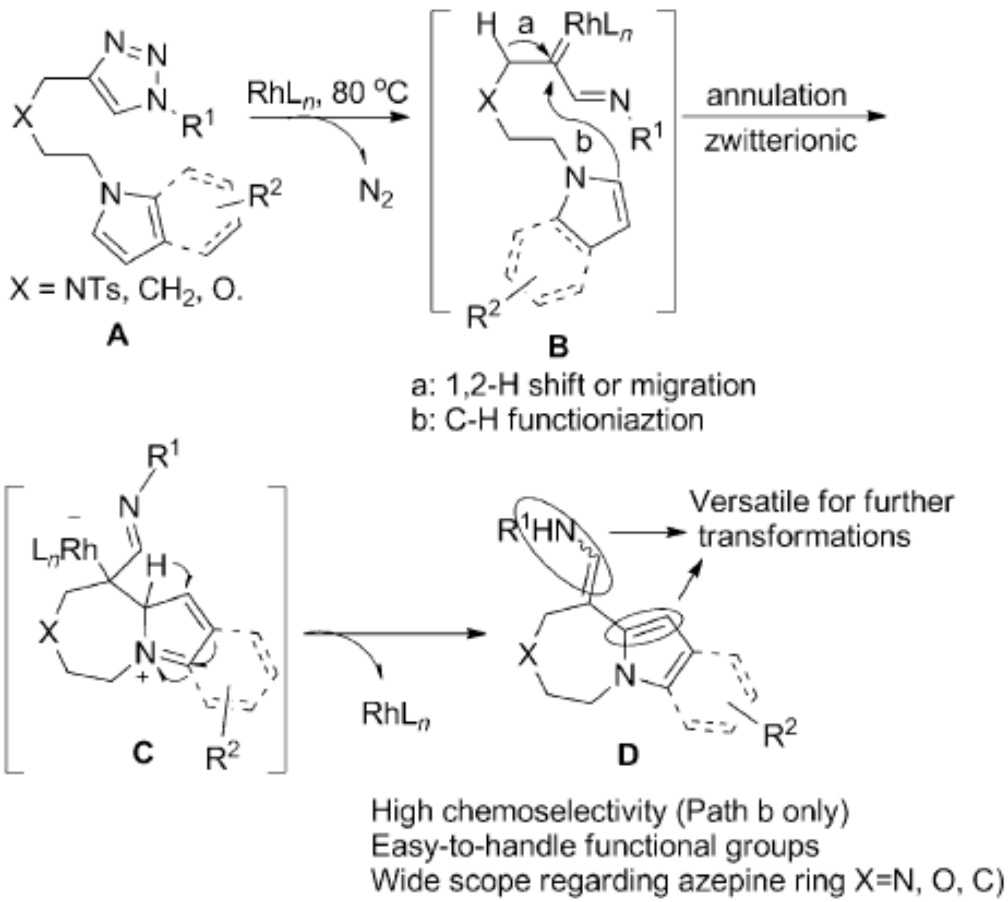
Initial studies: Optimization of Reaction Conditions



Entry[a]	[Rh]	Solvent	Yield [%][b]
1	$[Rh_2(Oct)_4]$	DCE	86
2	$[Rh_2(Piv)_4]$	DCE	80
3	$[Rh_2(esp)_4]$	DCE	77
4	$[Rh_2(OAc)_4]$	DCE	78
5	$[Rh_2(Adc)_4]$	DCE	80
6	$[Rh_2(tfa)_4]$	DCE	0
7	$[Rh_2(S\text{-}NTTL)_4]$	DCE	70
8	$[Rh_2(Oct)_4]$	toluene	78
9	$[Rh_2(Oct)_4]$	cyclohexane	–[c]
10	$[Rh_2(Oct)_4]$	$CHCl_3$	–[c]

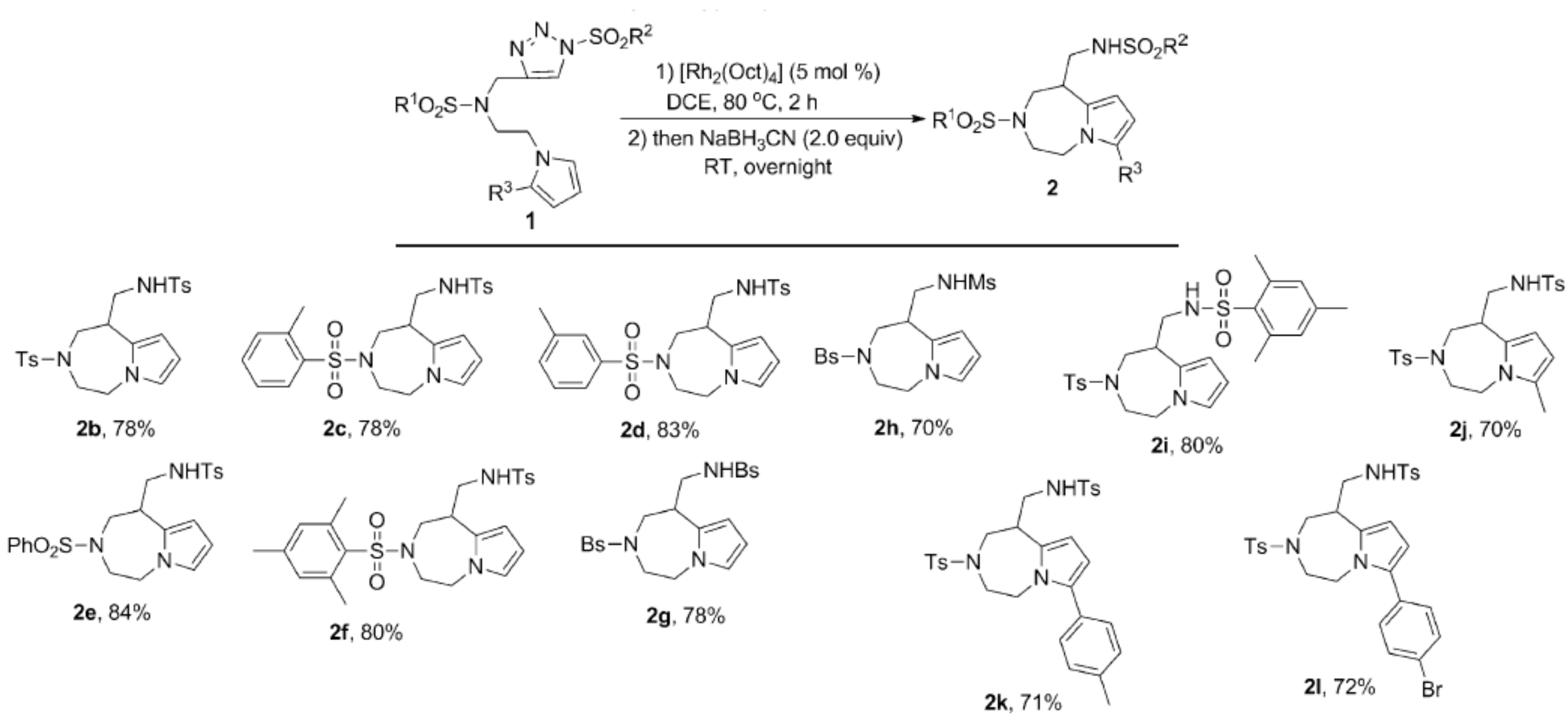
[a] Reaction conditions: **1a** (0.1 mmol), cat. (5 mol%), dry solvent (1.0 mL). [b] Yield of isolated product. [c] Not determined. DCE = 1,2-dichloroethane.

Mechanistic Explanation

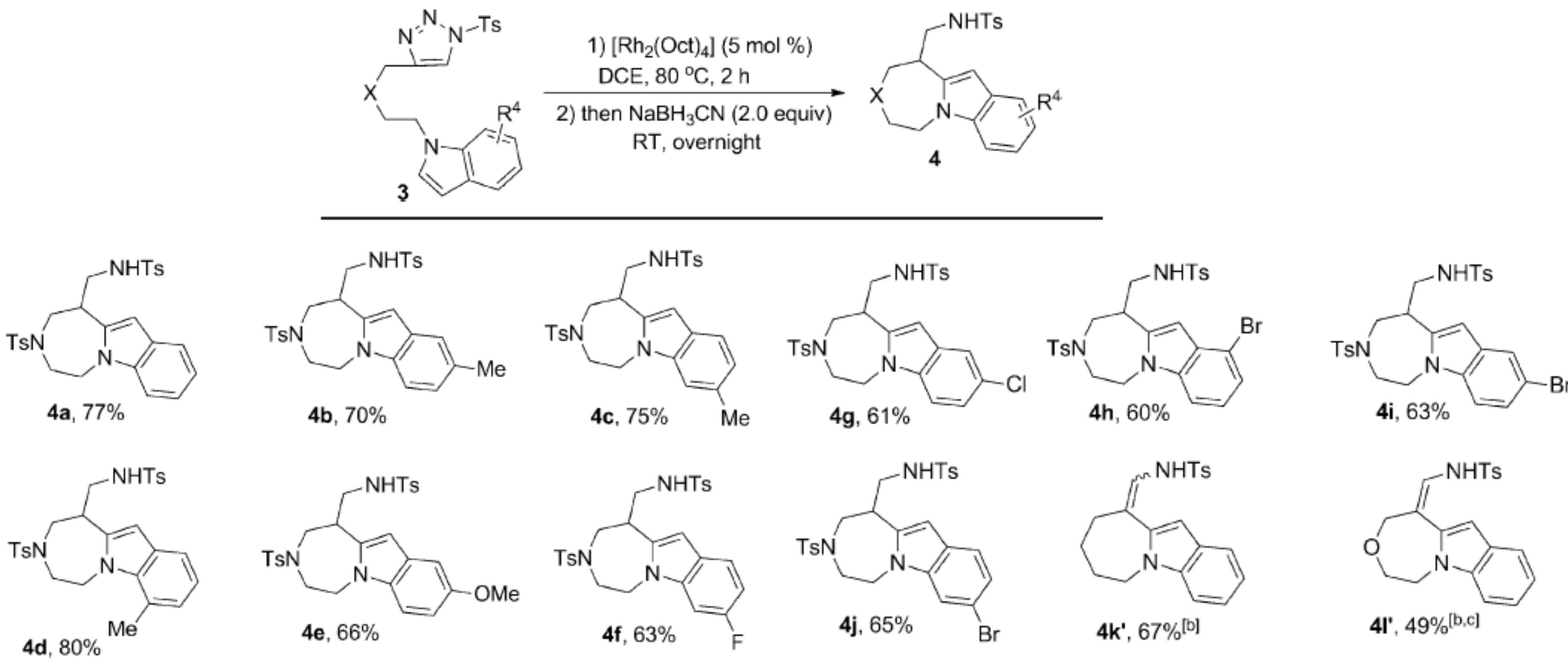


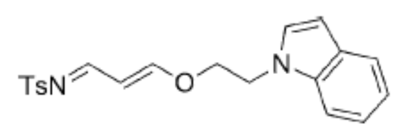
Supression of 1,2 H Migration (path a) due to the highly electrophilic character of pyrrole and indole

Scope and Limitations



Scope and Limitations

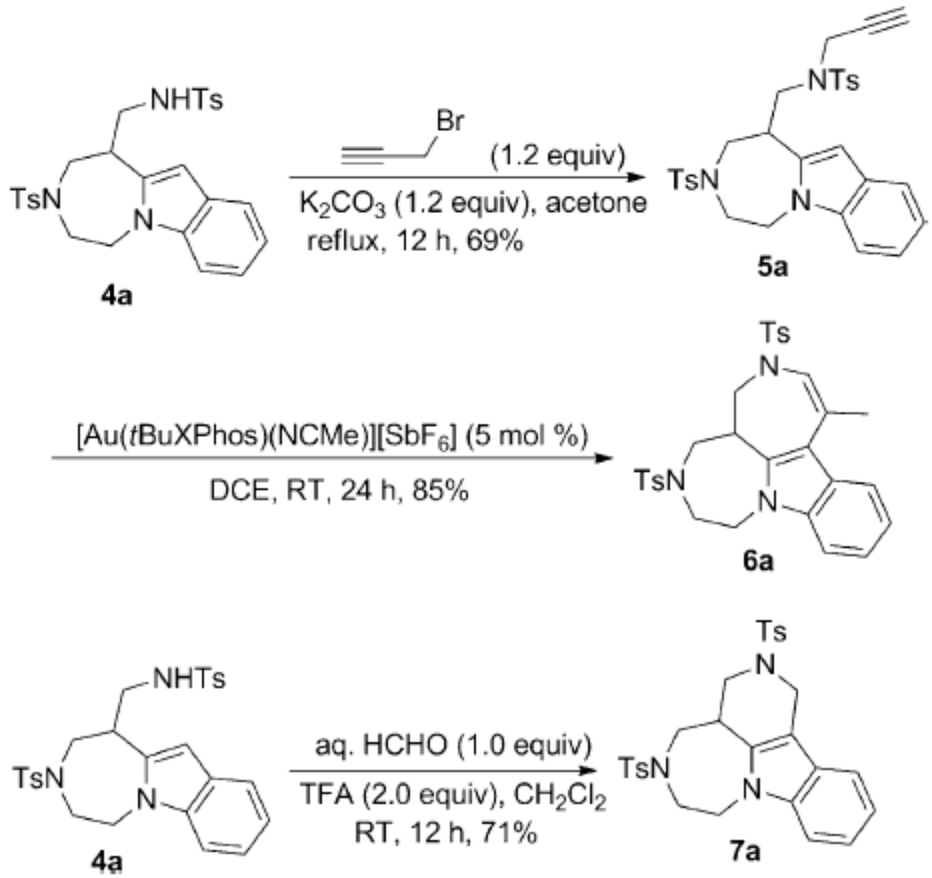




4l''

- Consistently moderate to good yield (60-80%)
- High group tolerance, **but:**
- Oxygen tether in the substrate affords the β-hydride elimination product 4l"

Construction of polycyclic azepine skeletons



Scheme 2. Transformations of **4a** into **5a**, **6a**, and **7a**. TFA = trifluoroacetic acid.

Conclusion

- Nice addition to the Rh(II) cat triazole chemistry
- Easy handling of reagents
- Mild reaction conditions
- High chemoselectivity with a wide scope with respect to the azepine ring (N, C, O)