Career-in-Review:
Neil K. Garg

Zhen Liu

01/07/2016

Prof. Neil K. Garg

1996–2000 New York University (Sc. B.)

2000–2005 Caltech (Ph. D.)
Supervisor: Brian M. Stoltz

2005–2007 UC Irvine (Postdoc)
Supervisor: Larry E. Overman

2007–2012 Assistant Professor (UCLA)

2012–2013 Associate Professor (UCLA)

2013–present Full Professor (UCLA)

Selected Awards
2010 Thieme Chemistry Journal Award
2010 NSF CAREER Award
2015 Arthur C. Cope Scholar Award
2016 Tetrahedron Young Investigator Award
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Contents

– *Aryne Chemistry*

– *Interrupted Fischer Indolization*

– *Metal-Catalyzed Cross-Coupling Reactions*

– *Summary and Outlook*

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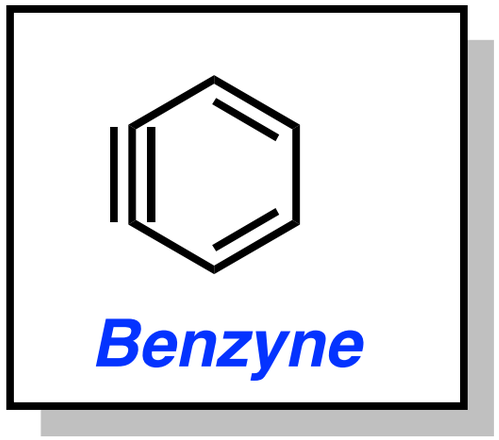
– Aryne Chemistry

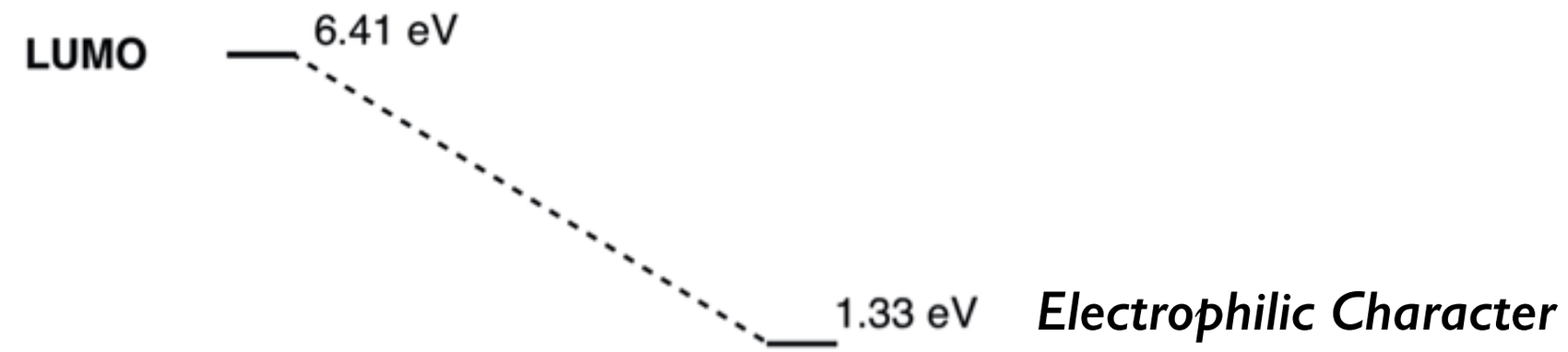
– Interrupted Fischer Indolization

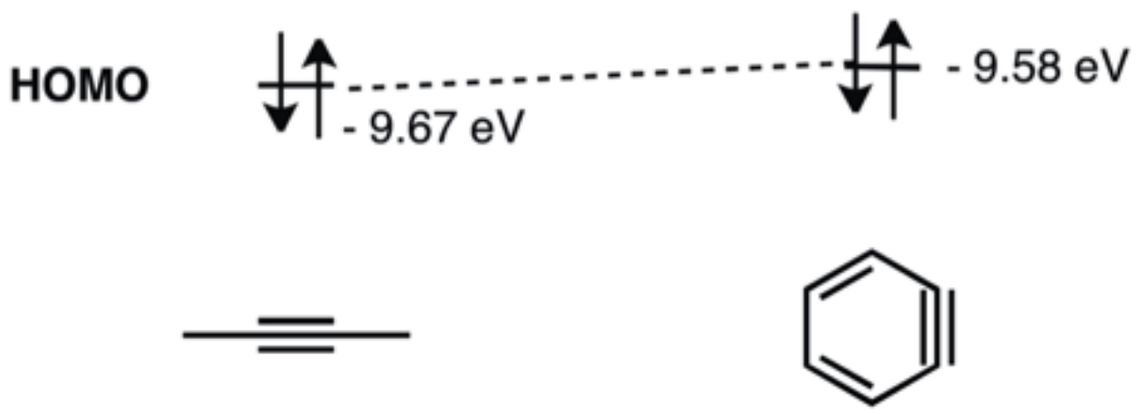
– Metal-Catalyzed Cross-Coupling Reactions

– Summary and Outlook

Aryne Chemistry



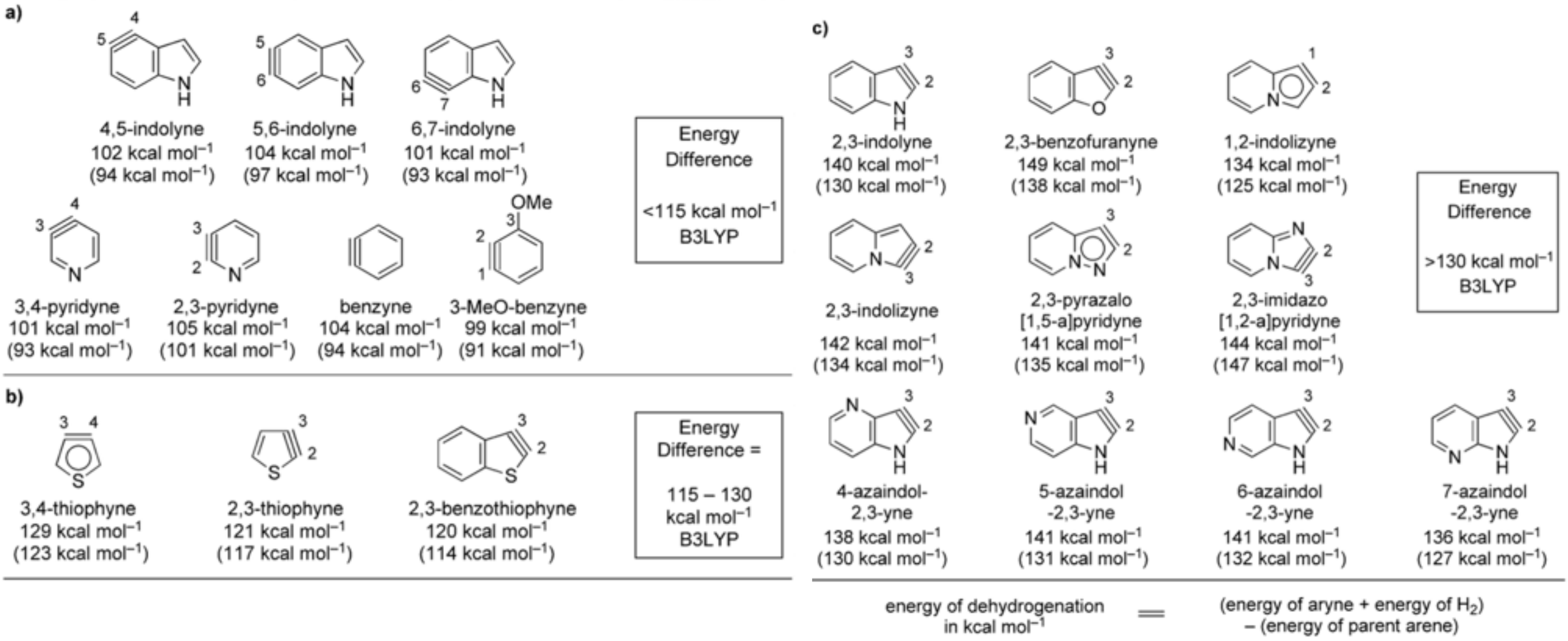




Hoffmann, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499.

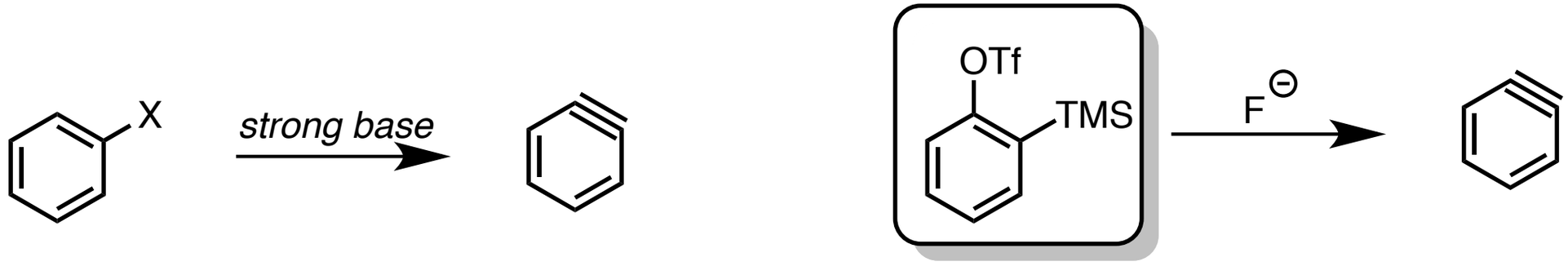
Aryne Chemistry

Three Categories

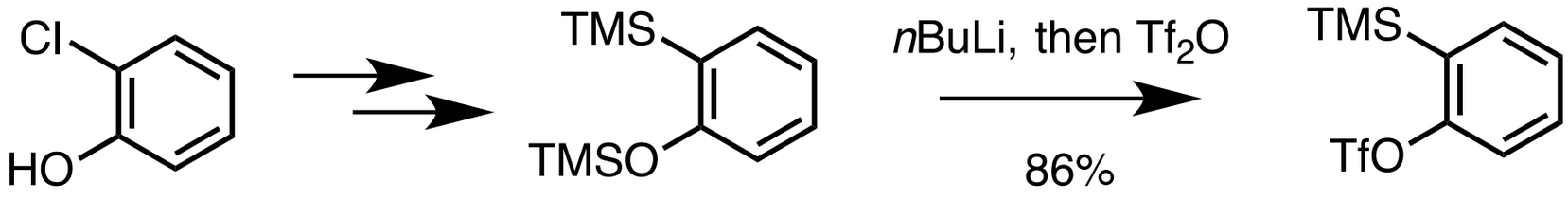


Goetz, A. E.; Bronner, S. M.; Cisneros, J. D.; Melamed, J. M.; Paton, R. S.; Houk, K. N.; Garg, N. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 2758.

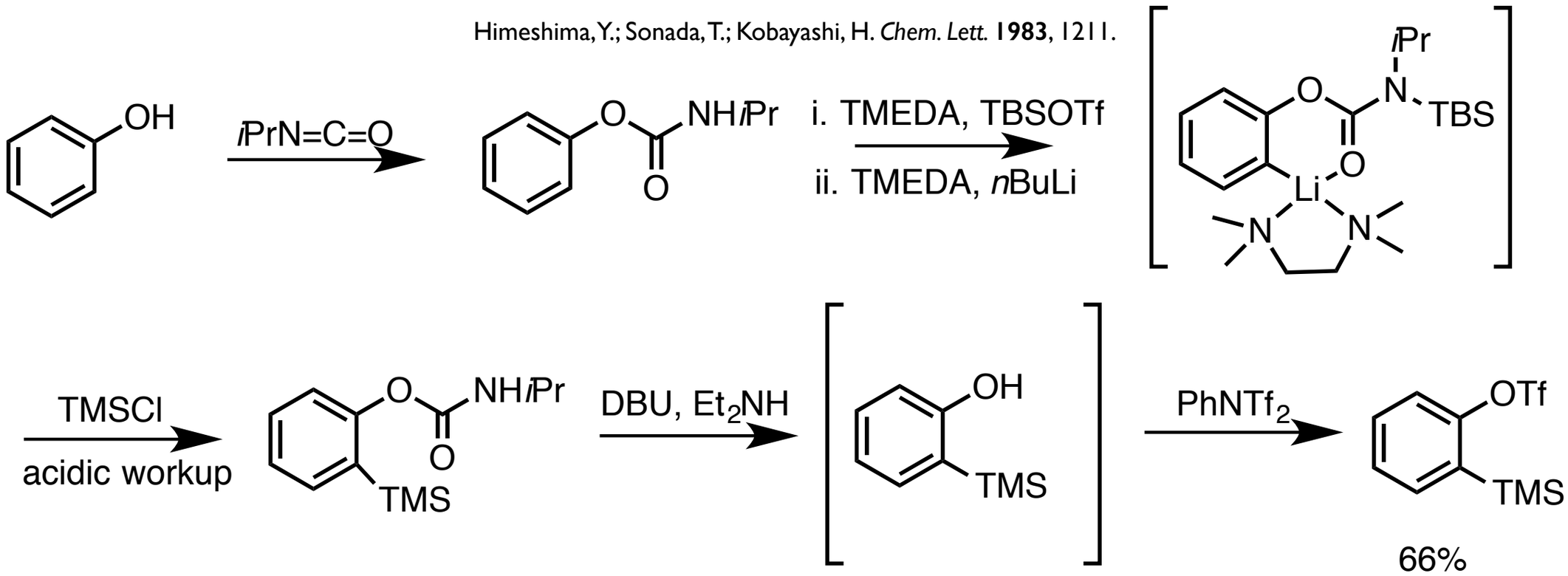
Aryne Chemistry



***Kobayashi*, 1983**

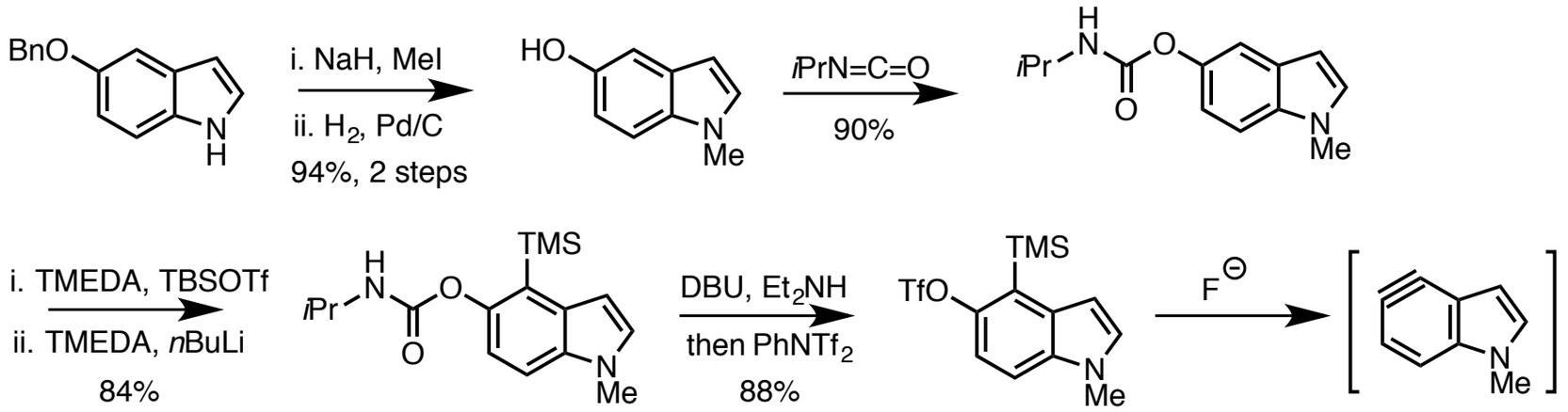


Himeshima, Y.; Sonada, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.



Bronner, S. M.; Garg, N. K. *J. Org. Chem.* **2009**, *74*, 8842.

Aryne Chemistry



Selected Examples

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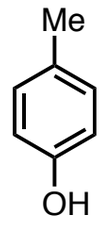
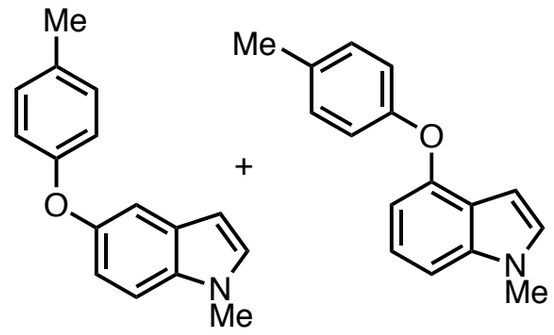
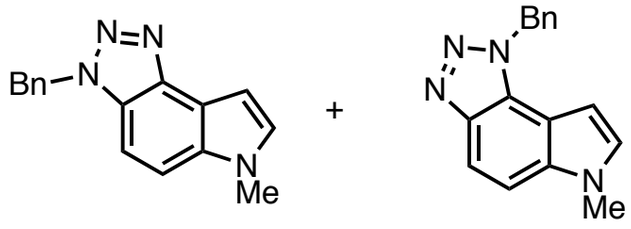
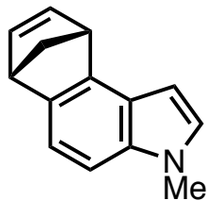
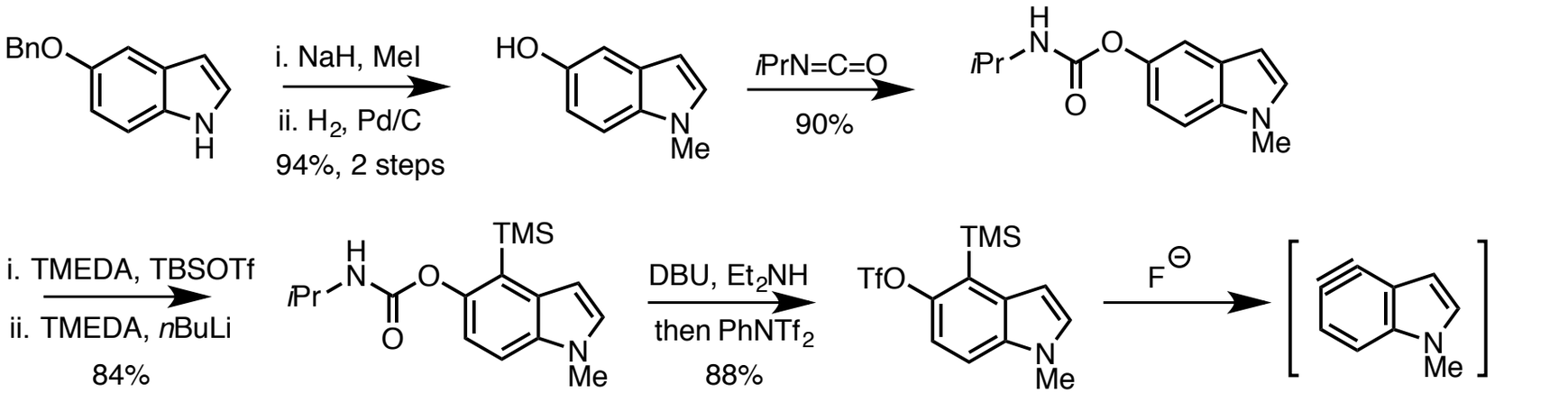
1			80% (3:1)
2	N_3–Bn		86% (2.4:1)
3			65%

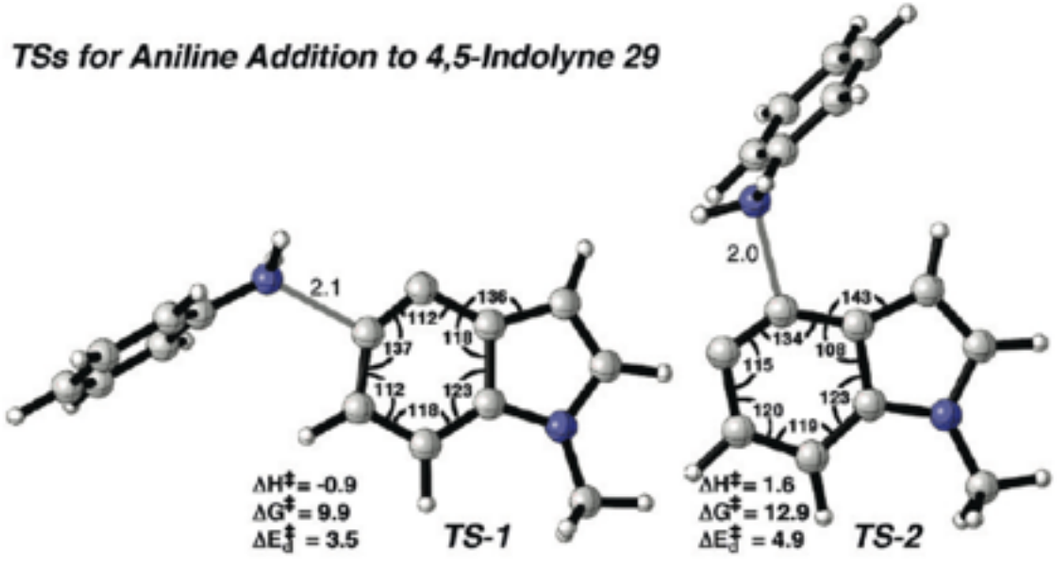
Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007.

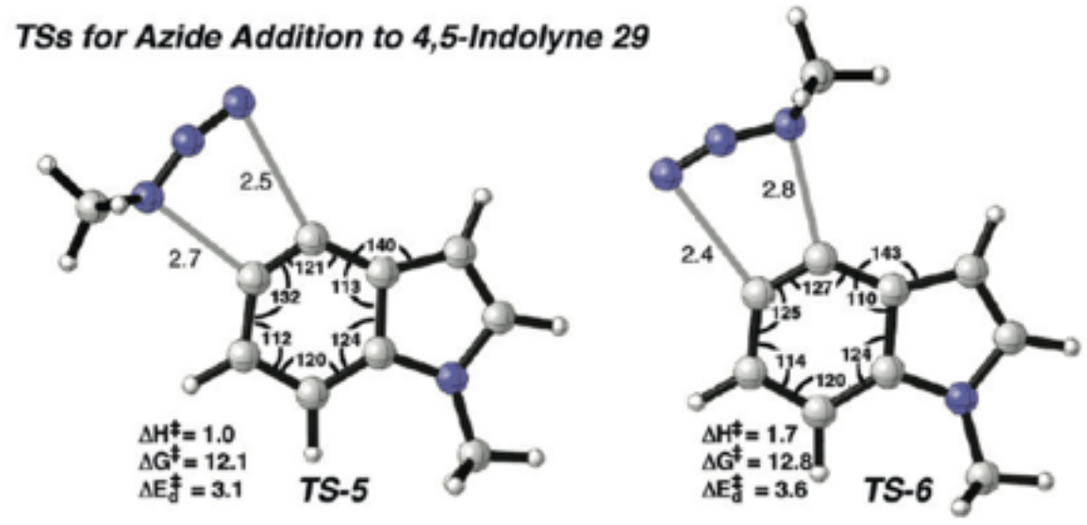
Aryne Chemistry

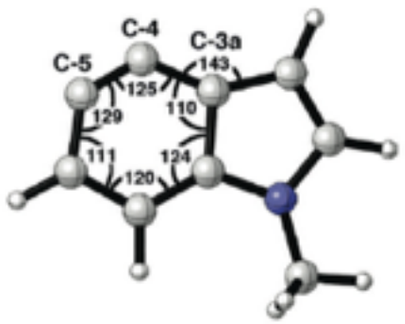


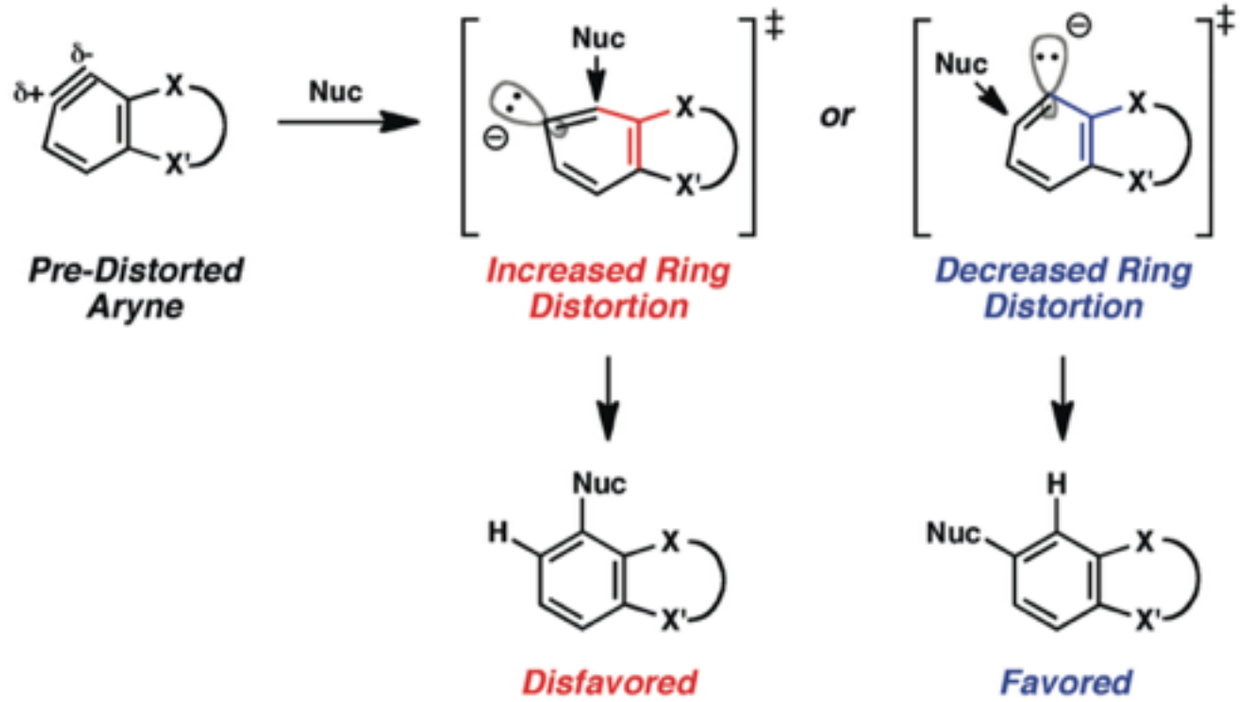
Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007.

Aryne Chemistry—Aryne Distortion Model



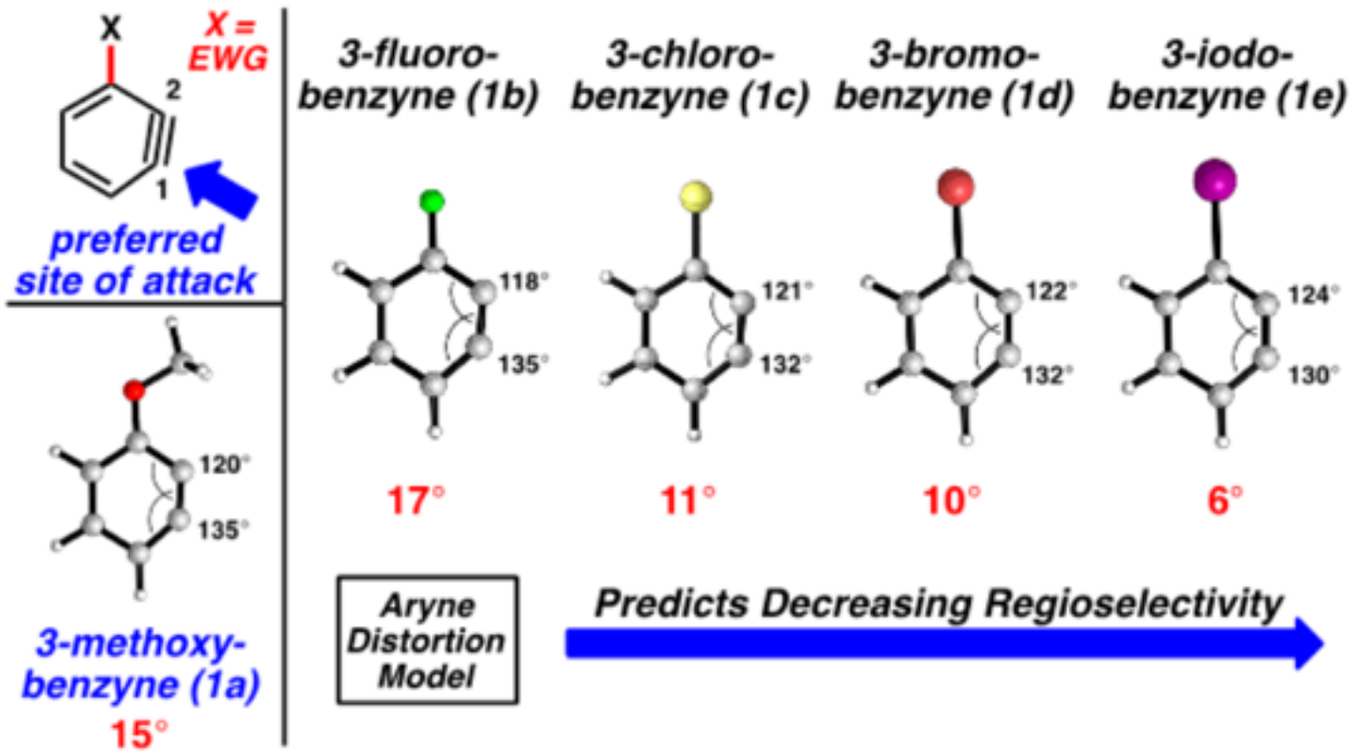




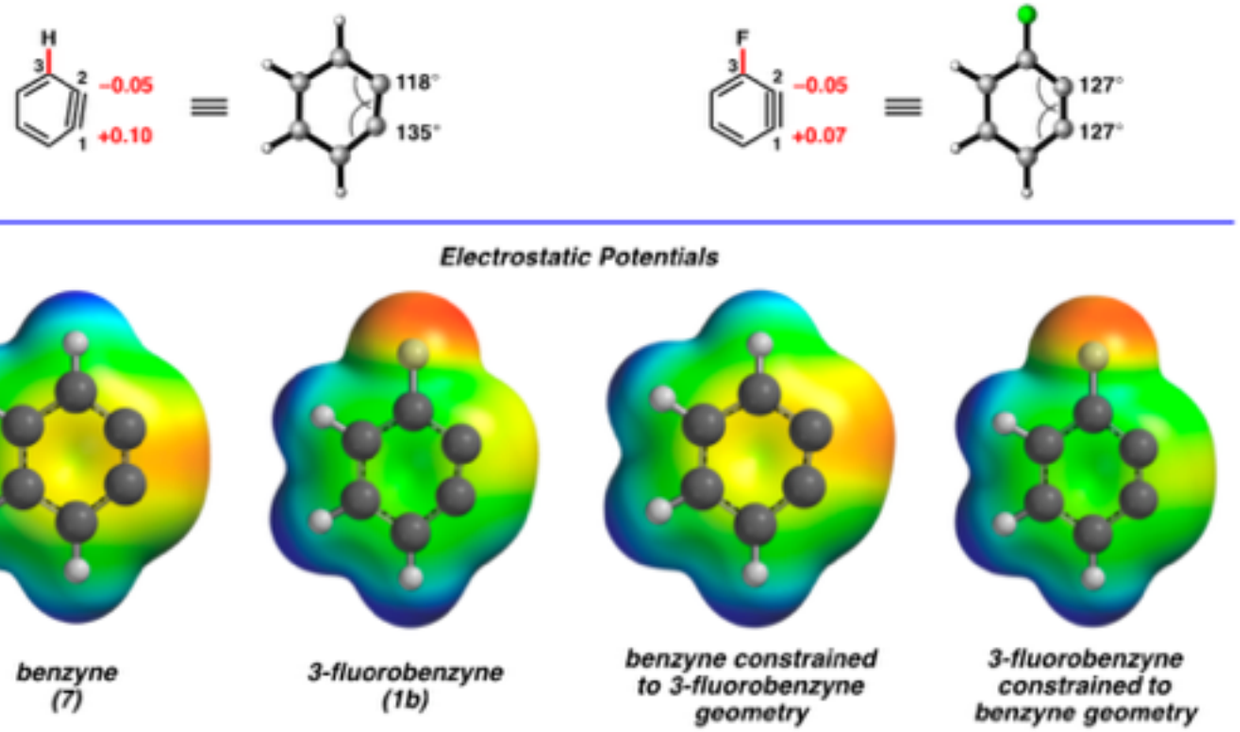


Im, G-Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933.

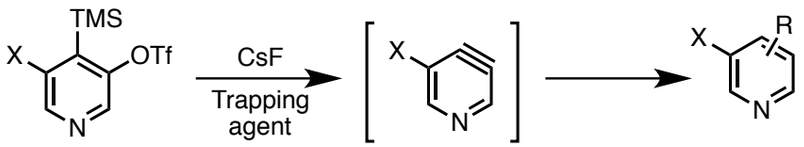
Aryne Chemistry—Aryne Distortion Model

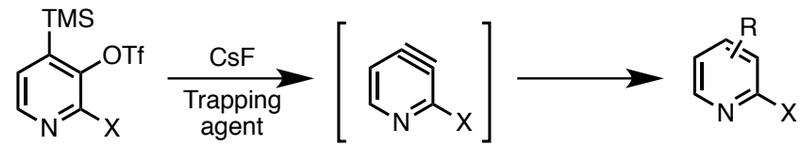


Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 15798.



Aryne Chemistry





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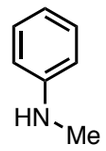
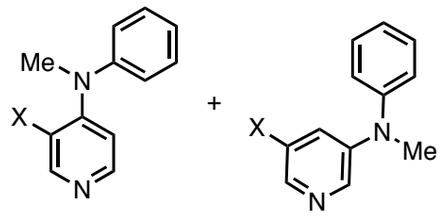
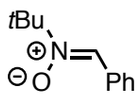
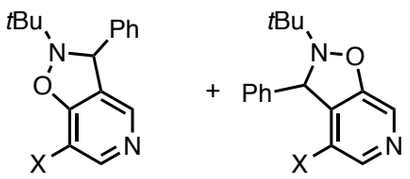
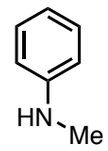
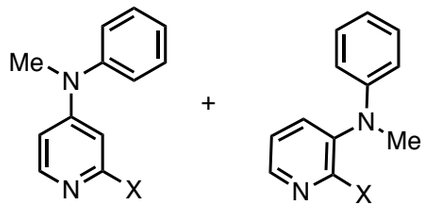
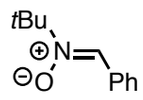
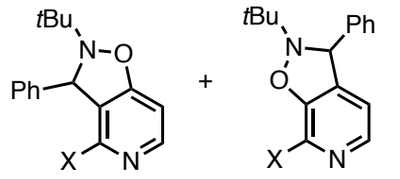
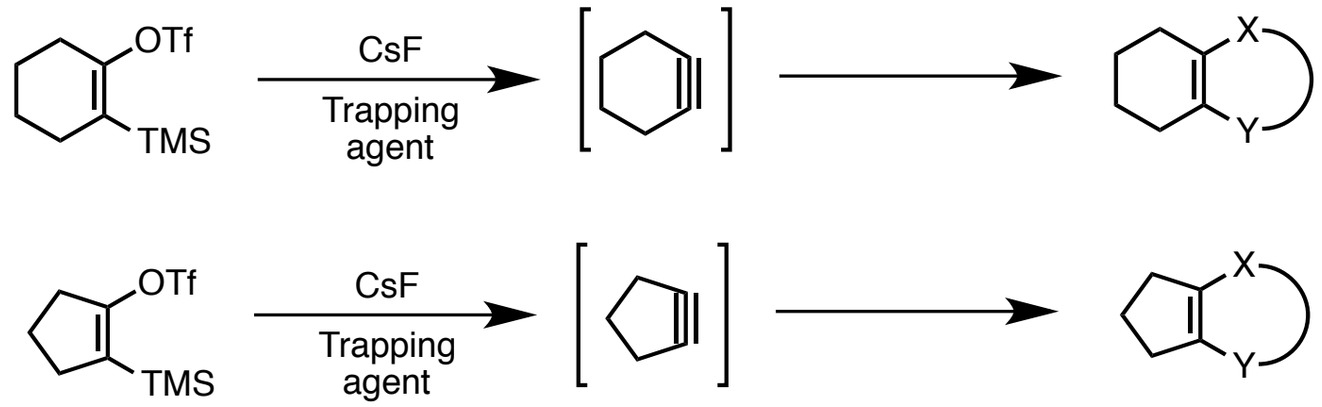
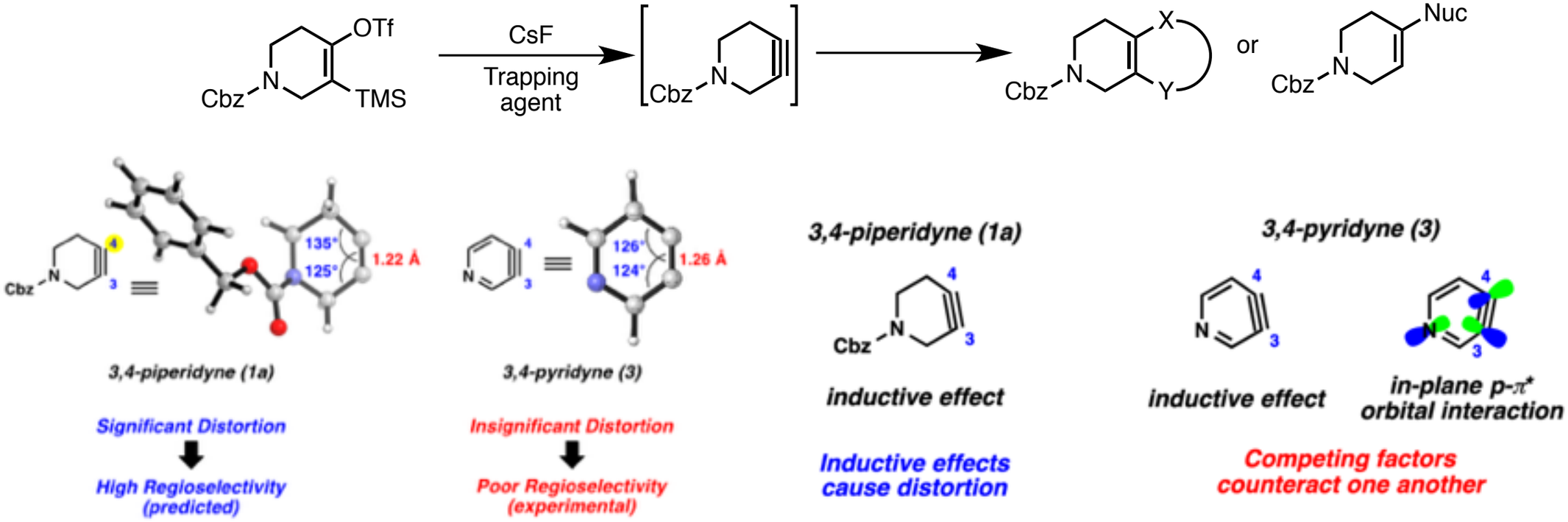
entry	trapping agent	products	yield (ratio)
1			X = H 1.9:1 (77%) X = Br 1:5.8 (64%)
2			X = H 1.9:1 (76%) X = Br 1:3.3 (60%)
3			X = H 1.9:1 (77%) X = OSO_2NMe_2 >15:1 (64%)
4			X = H 1.9:1 (76%) X = OSO_2NMe_2 10.7:1 (61%)

Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013**, *5*, 54.

Cycloalkyne Chemistry

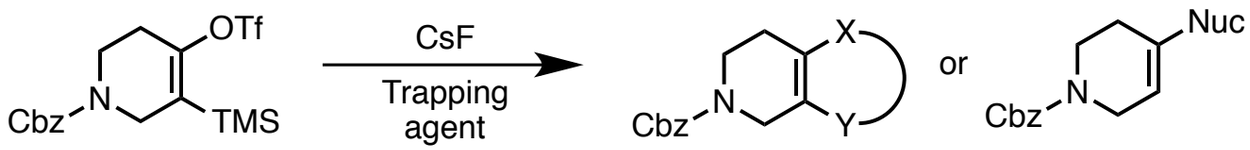


Medina, J. M.; McMahon, T. C.; Jiménez-Osés, G.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 14706.

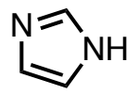
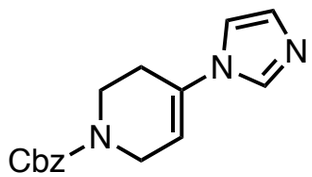
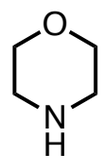
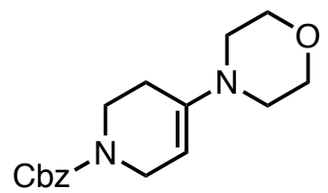
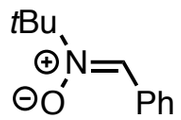
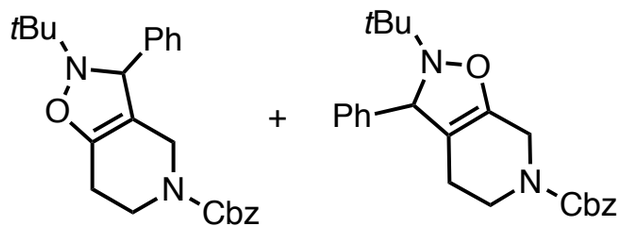


McMahon, T. C.; Medina, J. M.; Yang, Y.-F.; Simmons, B. J.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2015**, *137*, 4082.

Cycloalkyne Chemistry

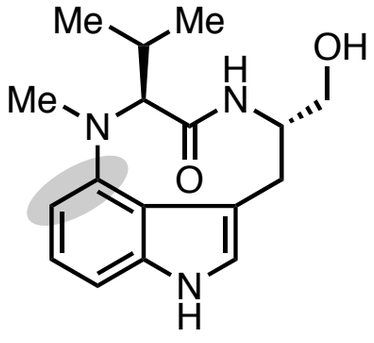


Selected Examples

entry	trapping agent	products	yield (ratio)
1			78% (>20:1)
2			99% (>20:1)
3			84% (12.7:1)

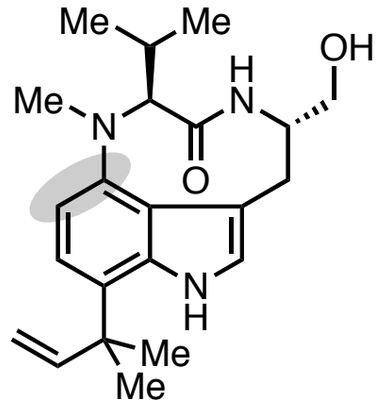
McMahon, T. C.; Medina, J. M.; Yang, Y.-F.; Simmons, B. J.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2015**, *137*, 4082.

Applications of Aryne Chemistry



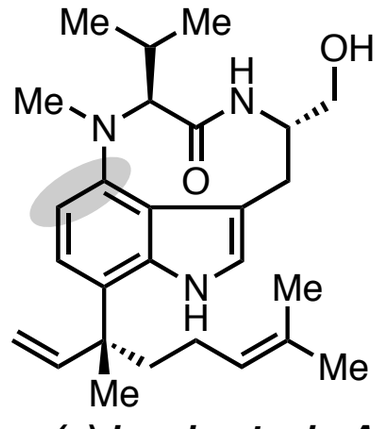
(–)-indolactam V

J. Am. Chem. Soc. **2011**, *133*, 3832.



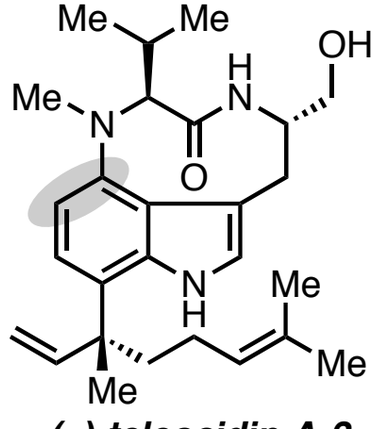
(–)-pendolmycin

Chem. Sci. **2014**, *5*, 2184.



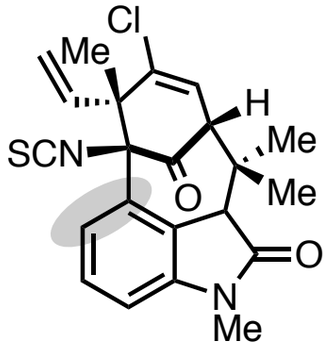
(–)-lyngbyatoxin A

Chem. Sci. **2014**, *5*, 2184.



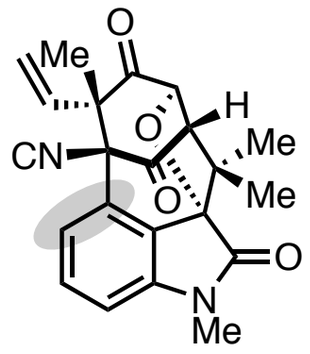
(–)-teleocidin A-2

Chem. Sci. **2014**, *5*, 2184.



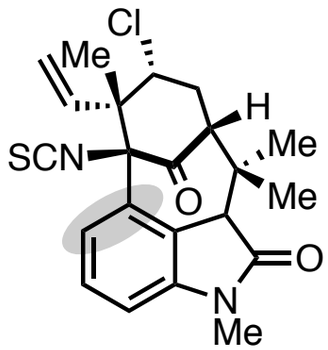
(–)-N-methylwelwitindolinone C isothiocyanate

J. Am. Chem. Soc. **2011**, *133*, 15797.



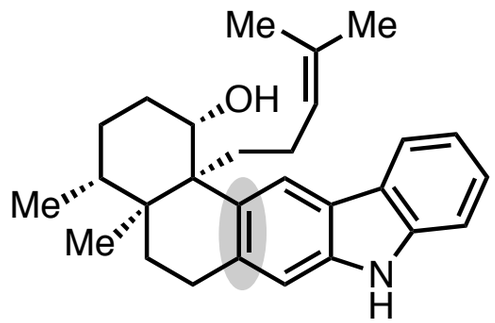
N-methylwelwitindolinone D isonitrile

Angew. Chem. Int. Ed. **2013**, *52*,12422.



(–)-N-methylwelwitindolinone B isothiocyanate

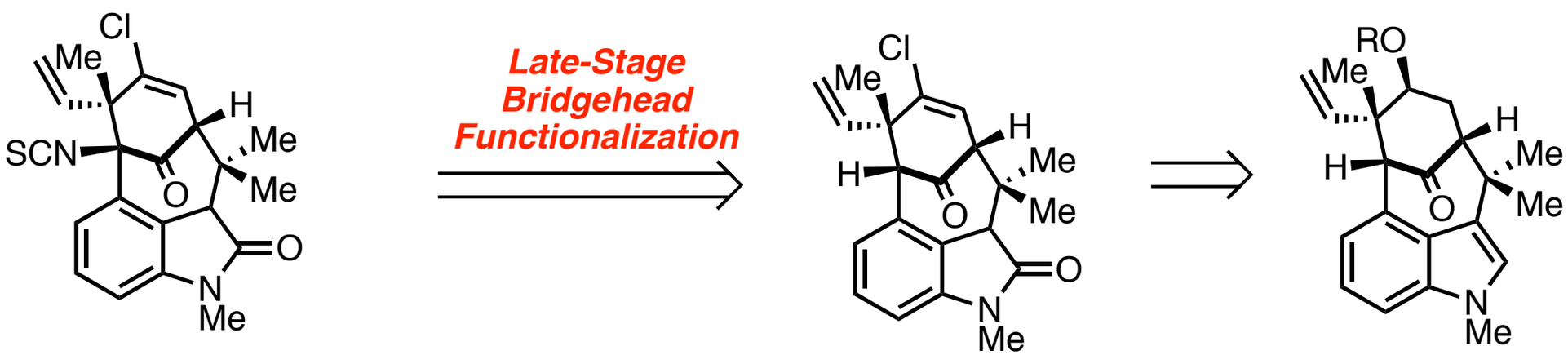
J. Am. Chem. Soc. **2014**, *136*, 14710.



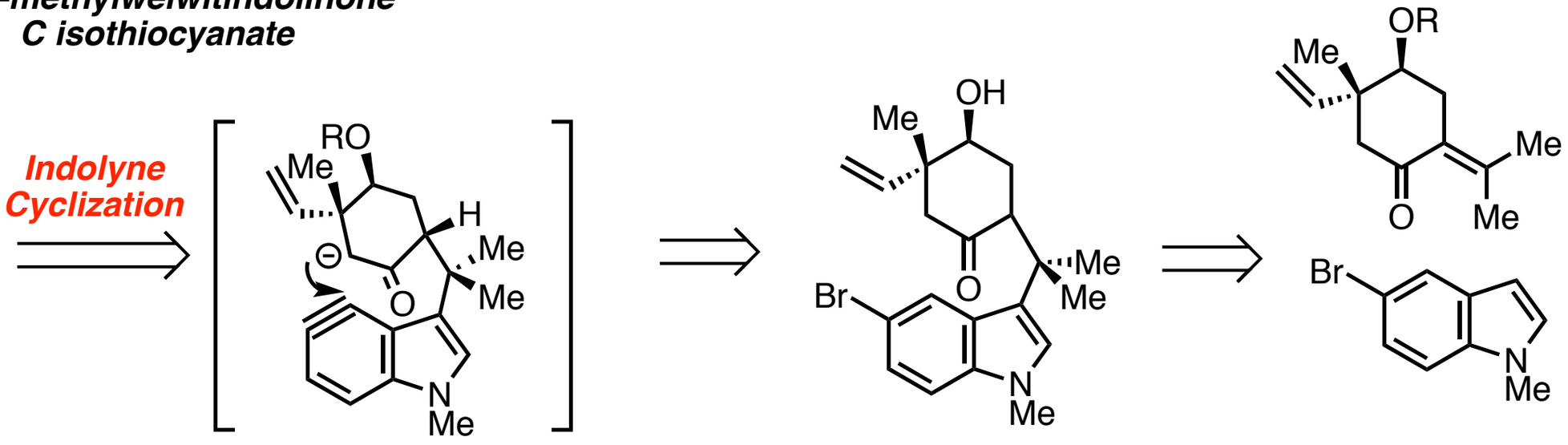
tubingensin A

J. Am. Chem. Soc. **2014**, *136*, 3036.

(–)-N-Methylwelwitindolinone C Isothiocyanate—Retrosynthetic Analysis

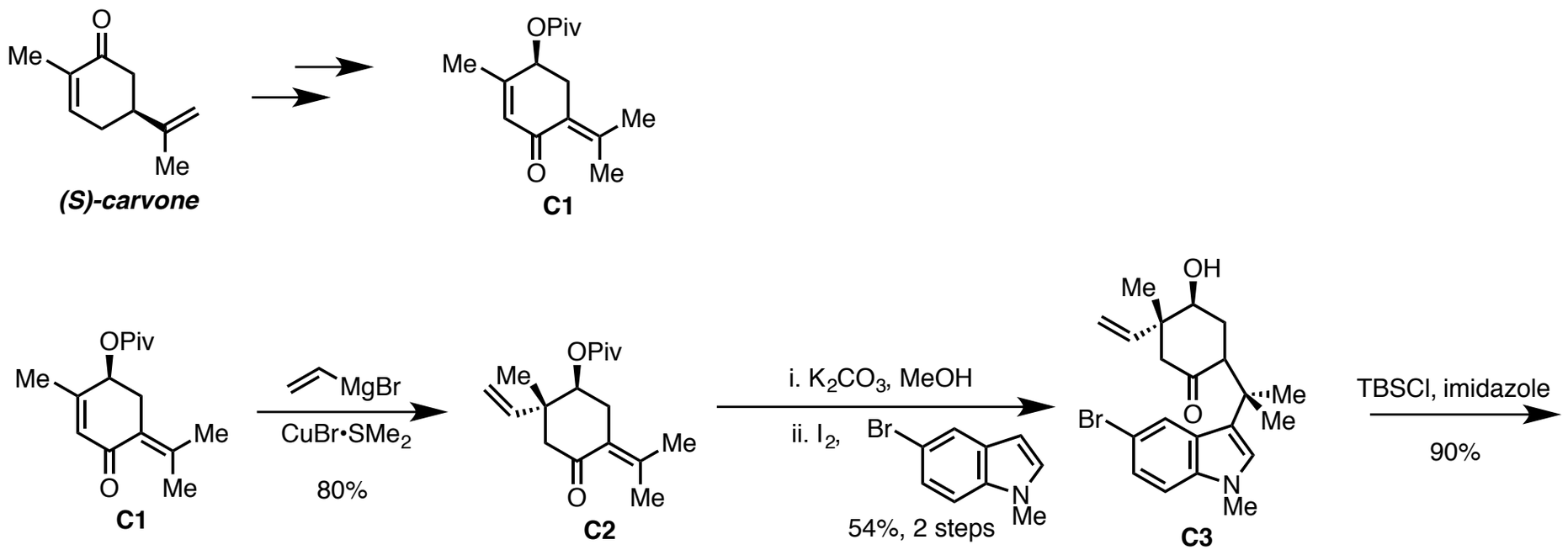


(–)-N-methylwelwitindolinone C isothiocyanate



Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797.

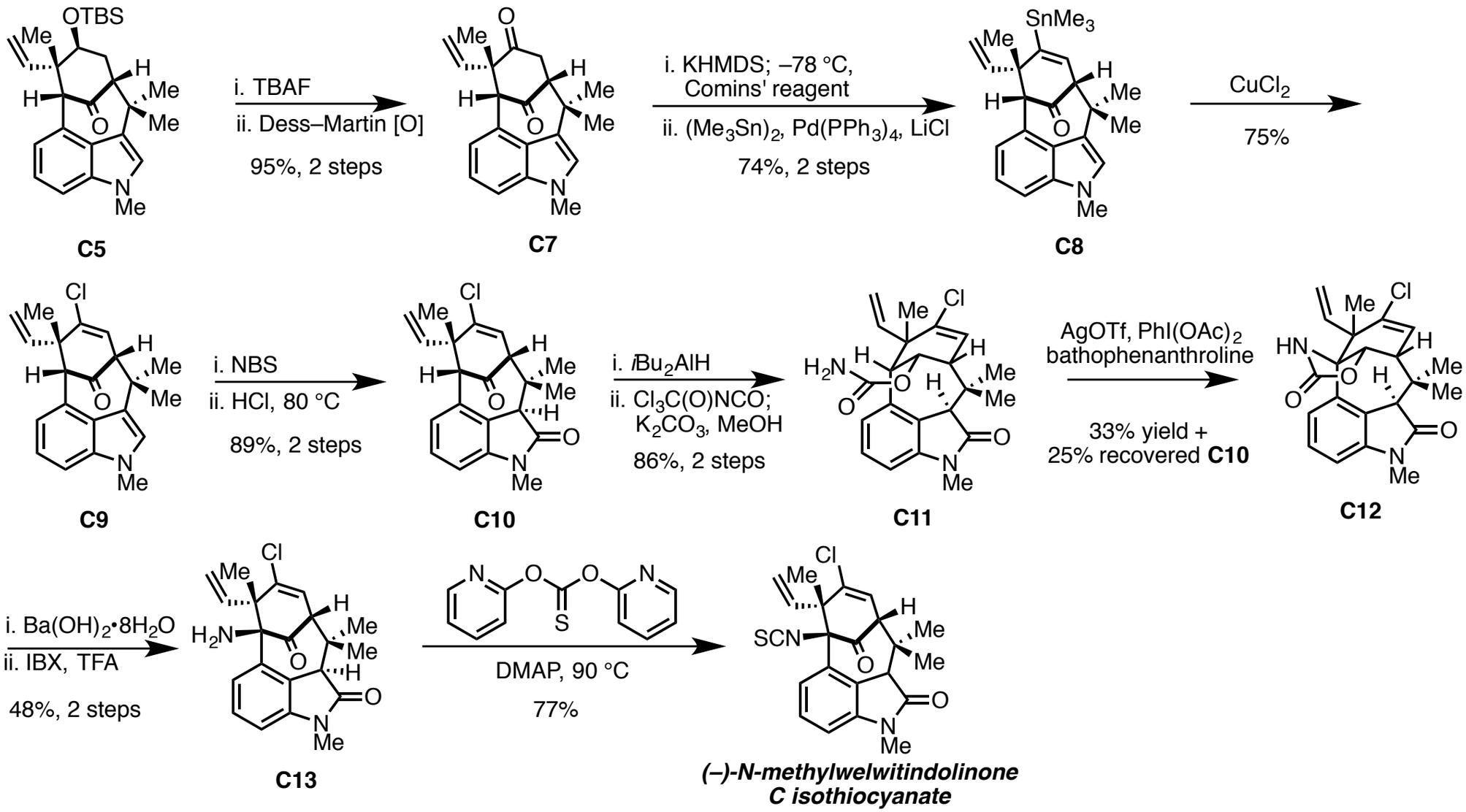
(–)-N-Methylwelwitindolinone C Isothiocyanate—Total Synthesis



2.5 : 1

Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797.

(–)-N-Methylwelwitindolinone C Isothiocyanate—Total Synthesis



Huters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 15797.

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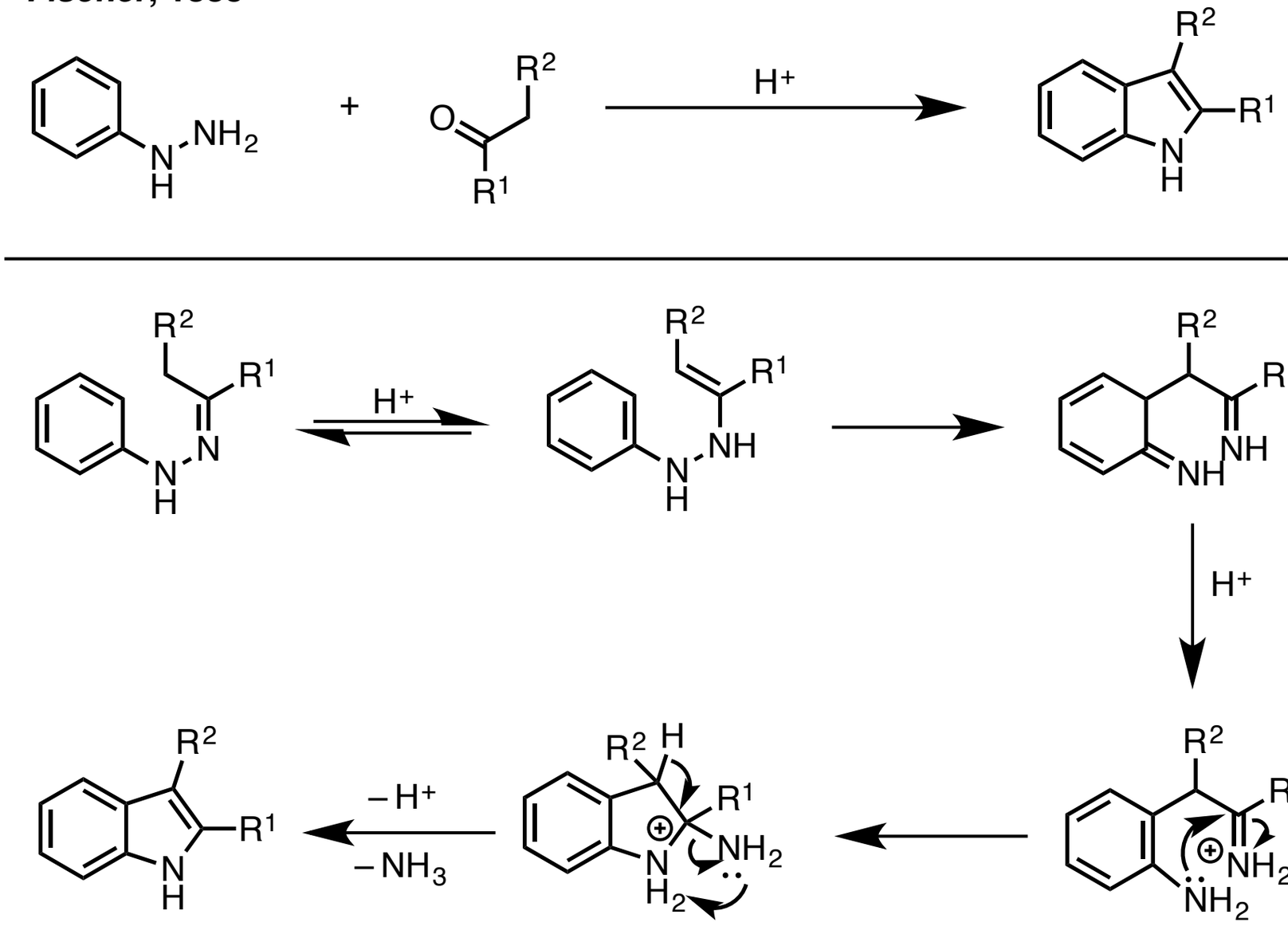
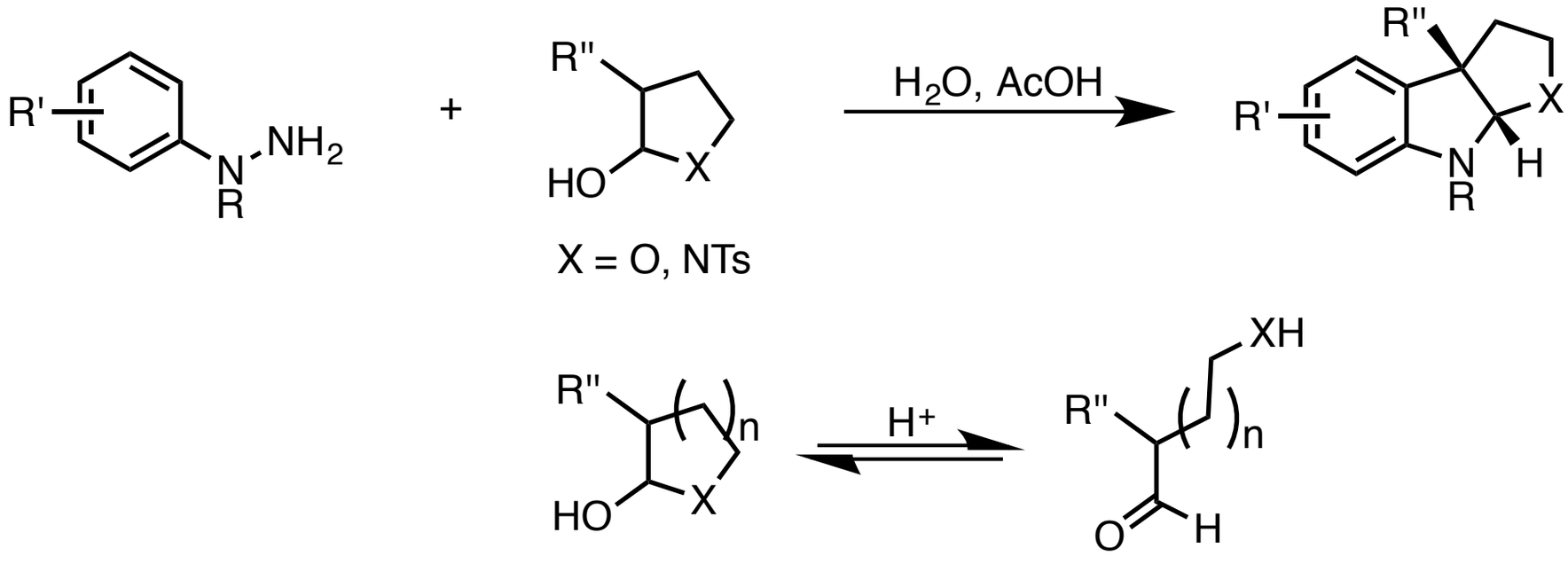
Fischer Indole Synthesis

***Fischer*, 1883**



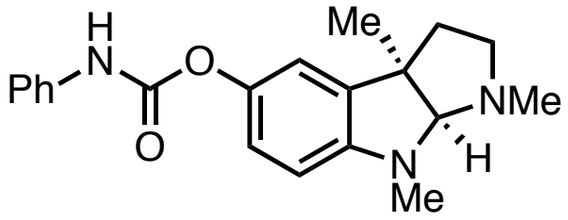
Fischer, E.; Jourdan, F. *Chem. Ber.* **1883**, *16*, 2241.

Interrupted Fischer Indolization



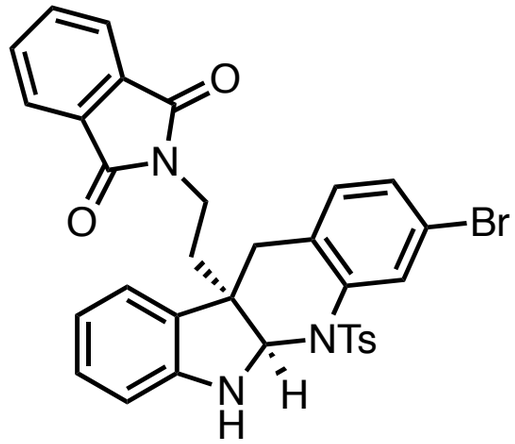
Boal, B.W.; Schammel, A.W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458.

Applications of Interrupted Fischer Indolization



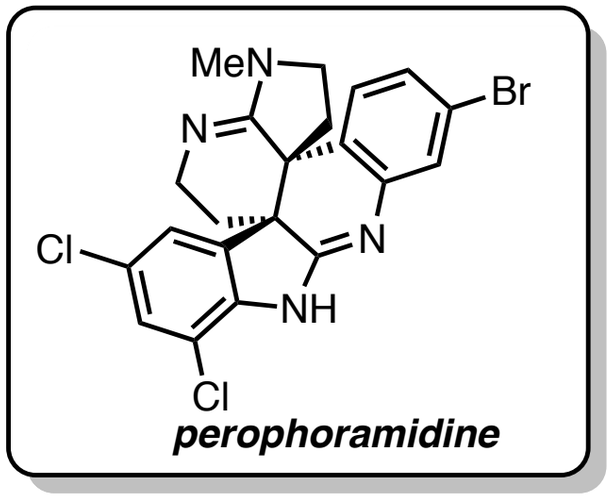
(+)-phenserine
Alzheimer's therapeutic

J. Org. Chem. **2012**, *77*, 725.

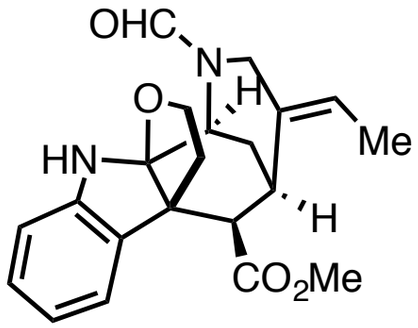


tetracyclic indoline core of perophoramidine

Org. Lett. **2012**, *14*, 4556.

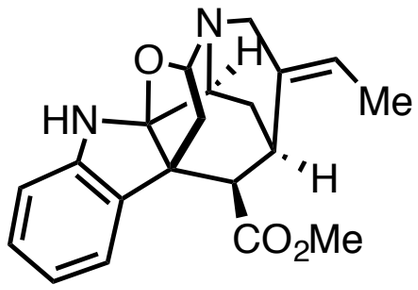


perophoramidine



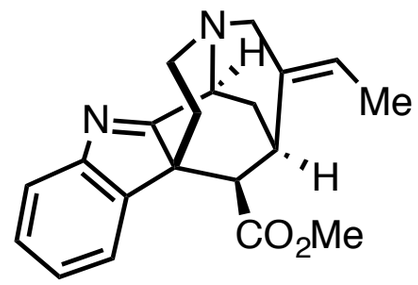
(±)-Aspidophylline A

J. Am. Chem. Soc. **2011**, *133*, 8877.



Picrinine

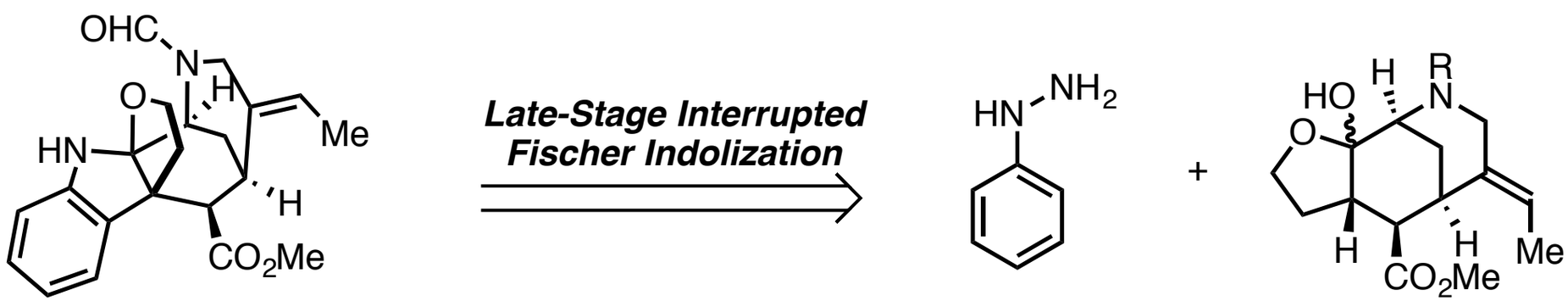
J. Am. Chem. Soc. **2014**, *136*, 4504.

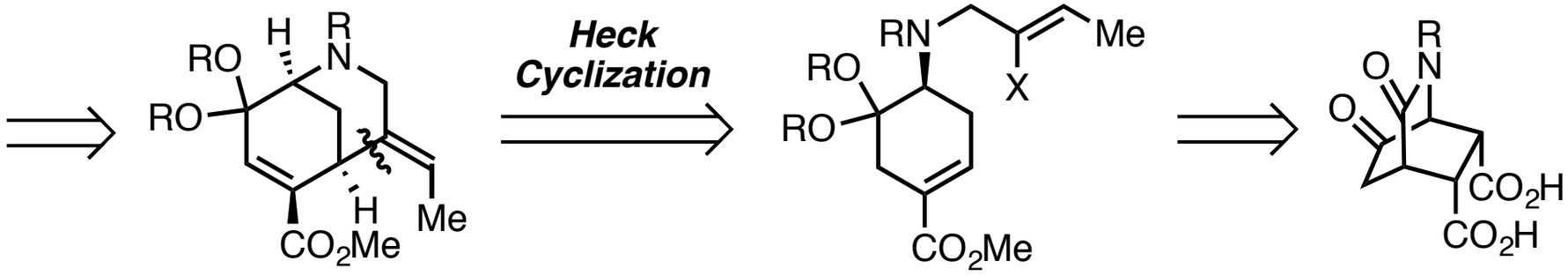


Strictamine

J. Am. Chem. Soc. **2014**, *136*, 4504.

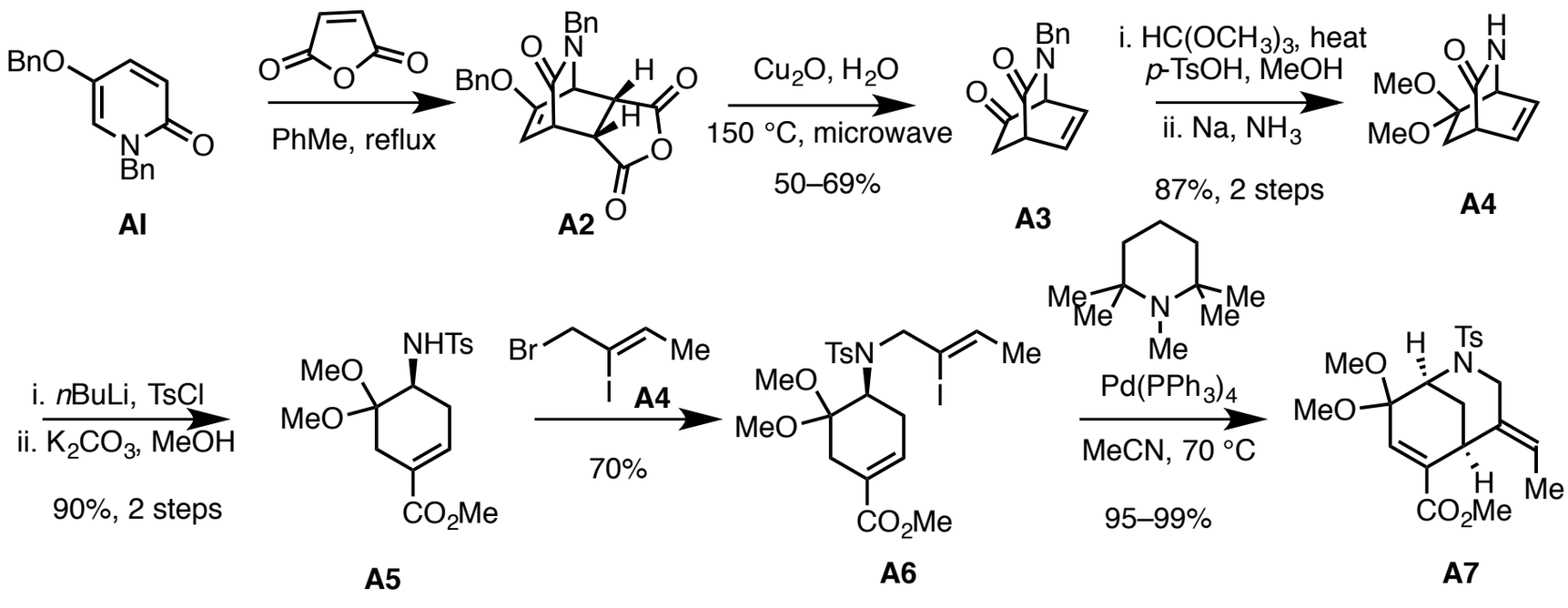
(±)-Aspidophylline A—Retrosynthetic Analysis

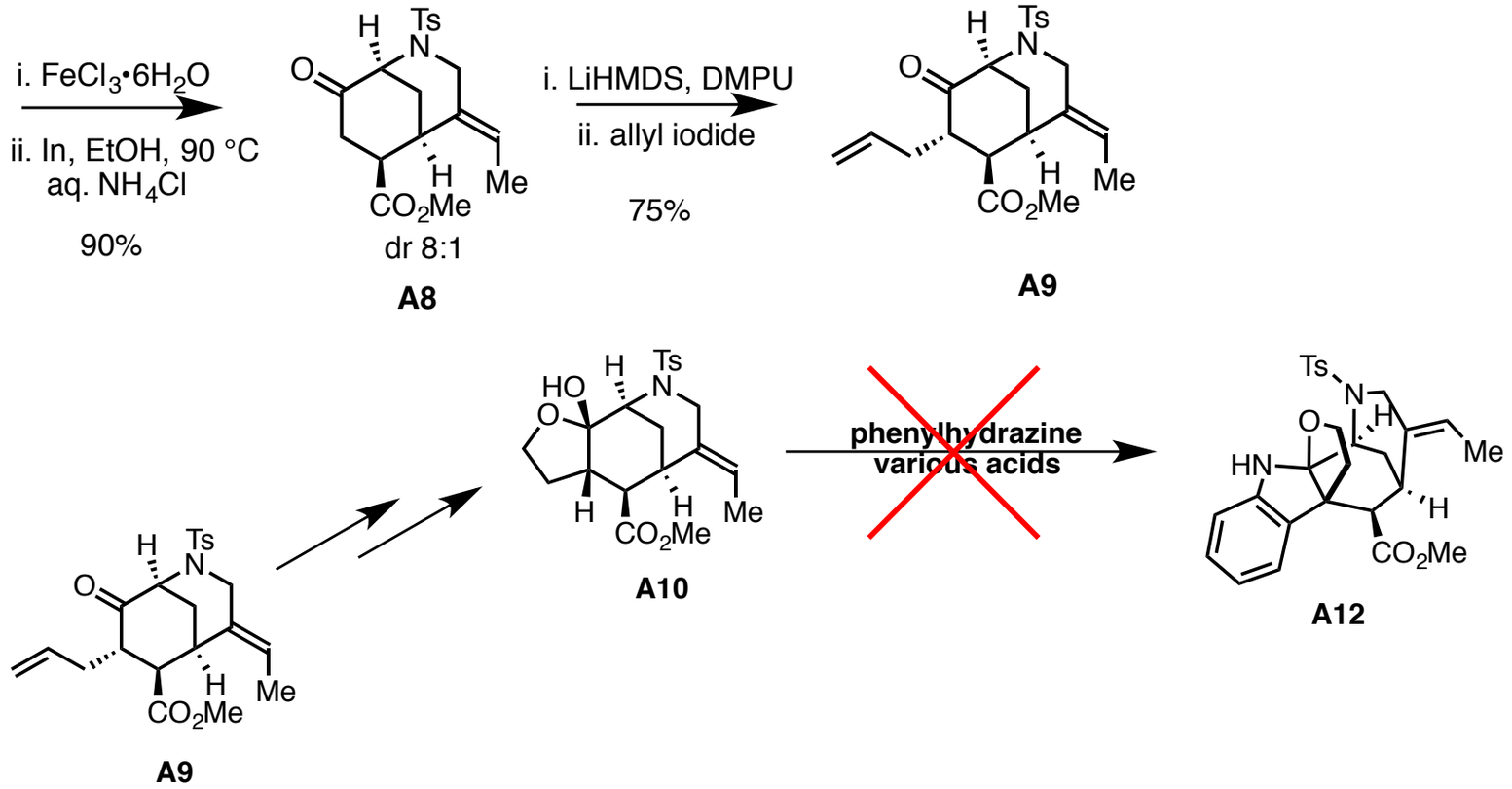




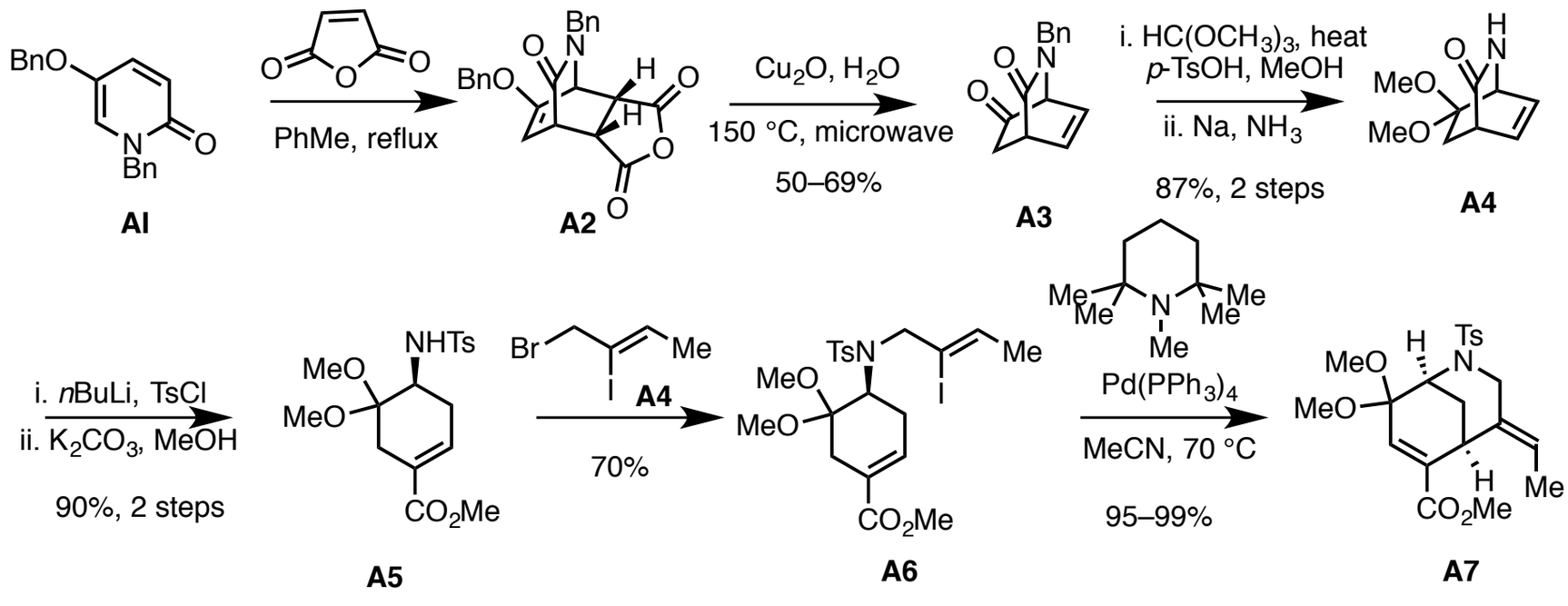
Zu, L.; Ben, W. B.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 8877.

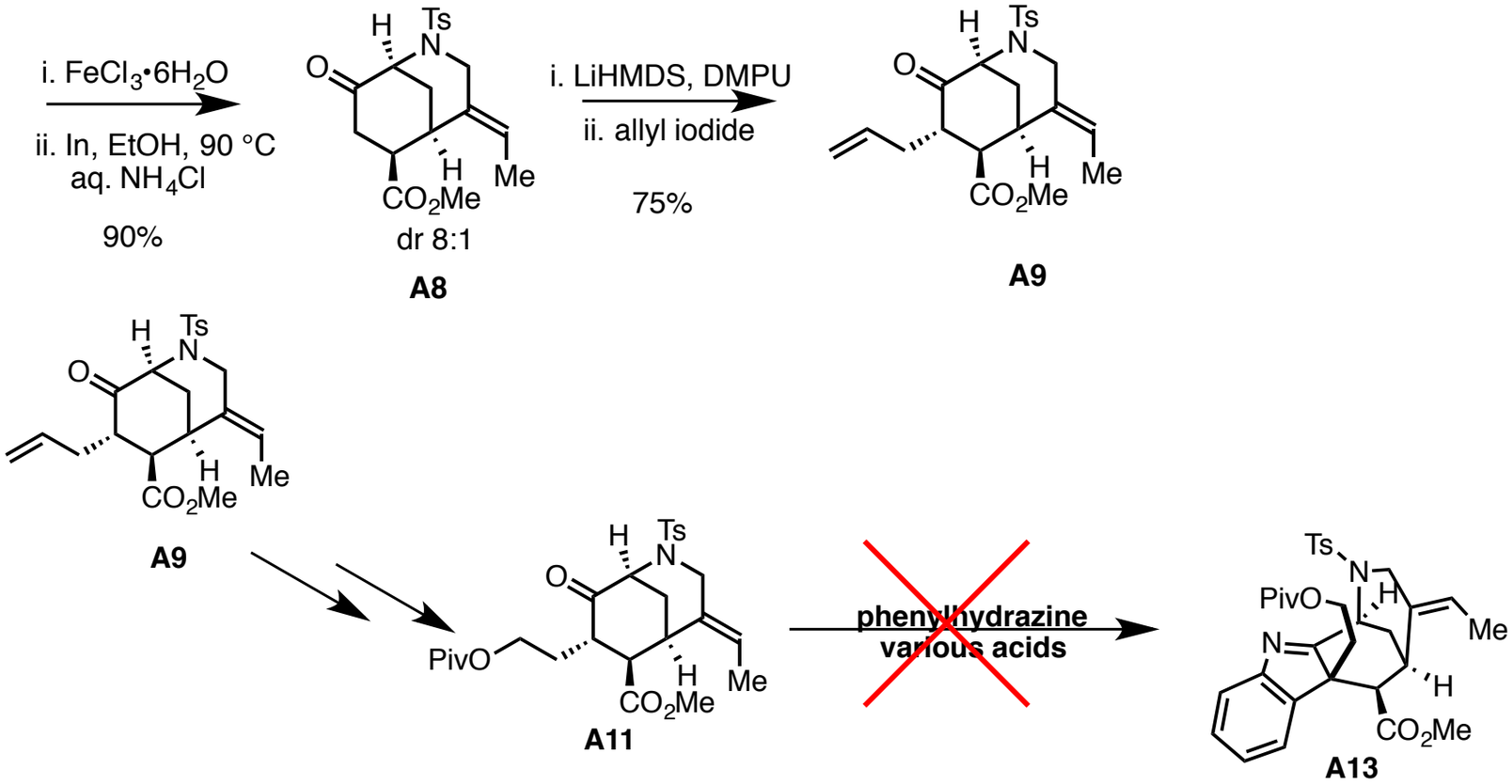
(±)-Aspidophylline A—Total Synthesis



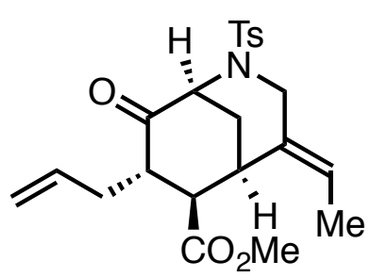


(±)-Aspidophylline A—Total Synthesis





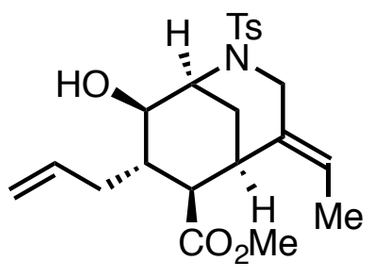
(±)-Aspidophylline A—Total Synthesis



A9

$NaBH_4$

98%

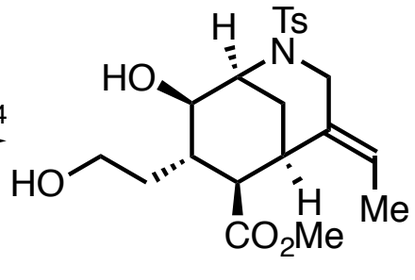


A14

i. OsO_4, $NaIO_4$

ii. $NaBH_4$

83%, 2 steps

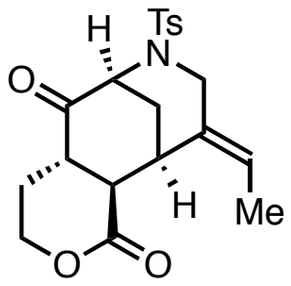


A15

i. H_2SO_4

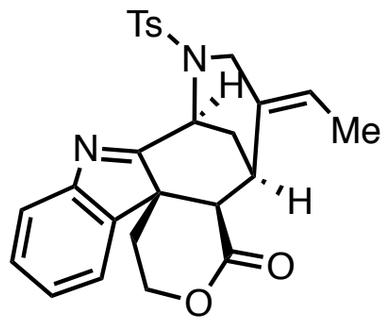
ii. Dess–Martin [O]

76%, 2 steps



A16

TFA

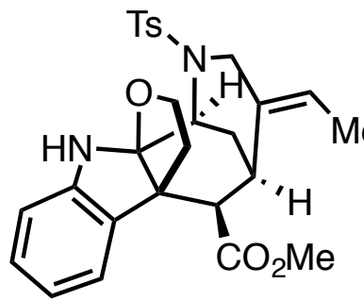


A17 *(not isolated)*

70%

(one pot, from **A16***)*

K_2CO_3

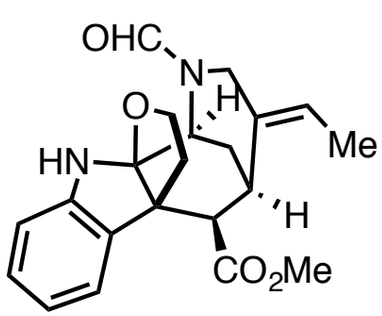


A12

i. Mg, NH_4Cl

ii. formic acid, DIC, DMAP

68%, 2 steps



(±)-Aspidophylline A

Contents

– Aryne Chemistry

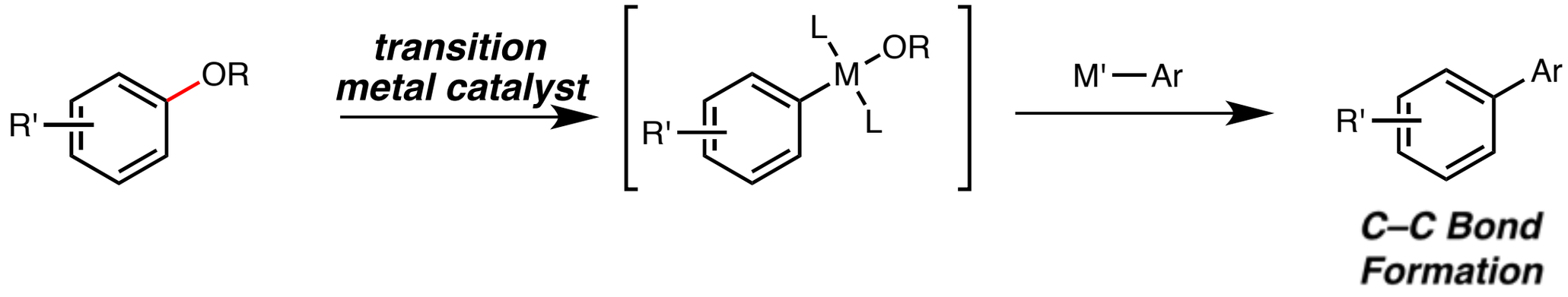
– Interrupted Fischer Indolization

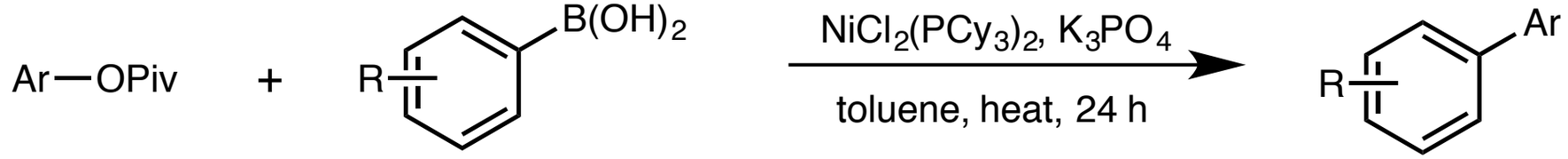
– Metal-Catalyzed Cross-Coupling Reactions

– Summary and Outlook

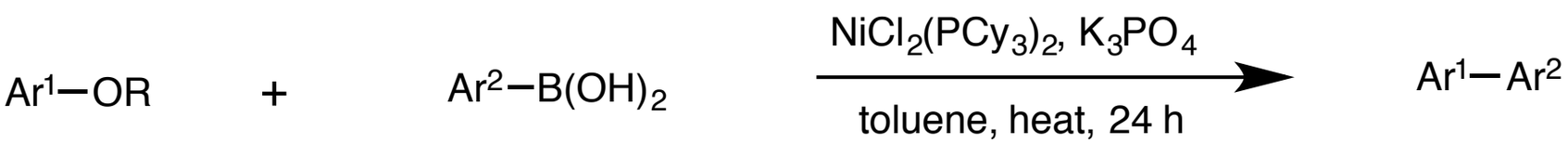
C–O Bond Activation

Traditionally difficult when anything other than OTf





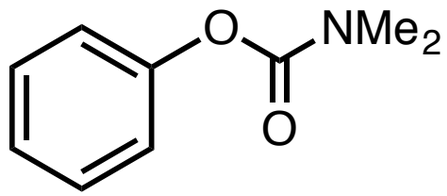
Quasdorf, K.W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422.

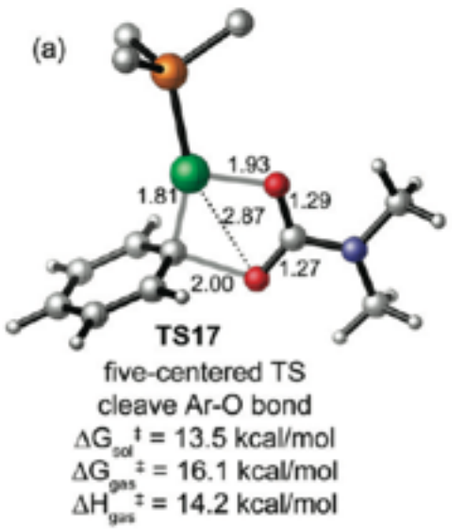


R = $C(O)NEt_2$, CO_2tBu, SO_2NMe_2

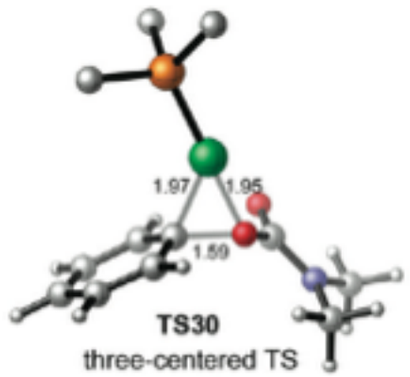
Quasdorf, K.W.; Riener, M.; Petrova, K.V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748.

C–O Bond Activation

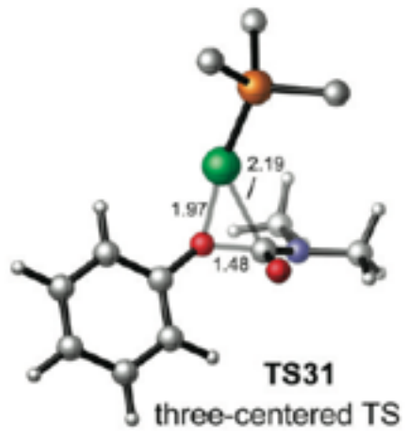




TS17
five-centered TS
cleave Ar-O bond
$\Delta G_{sol}^{\ddagger}$ = 13.5 kcal/mol
$\Delta G_{gas}^{\ddagger}$ = 16.1 kcal/mol
$\Delta H_{gas}^{\ddagger}$ = 14.2 kcal/mol



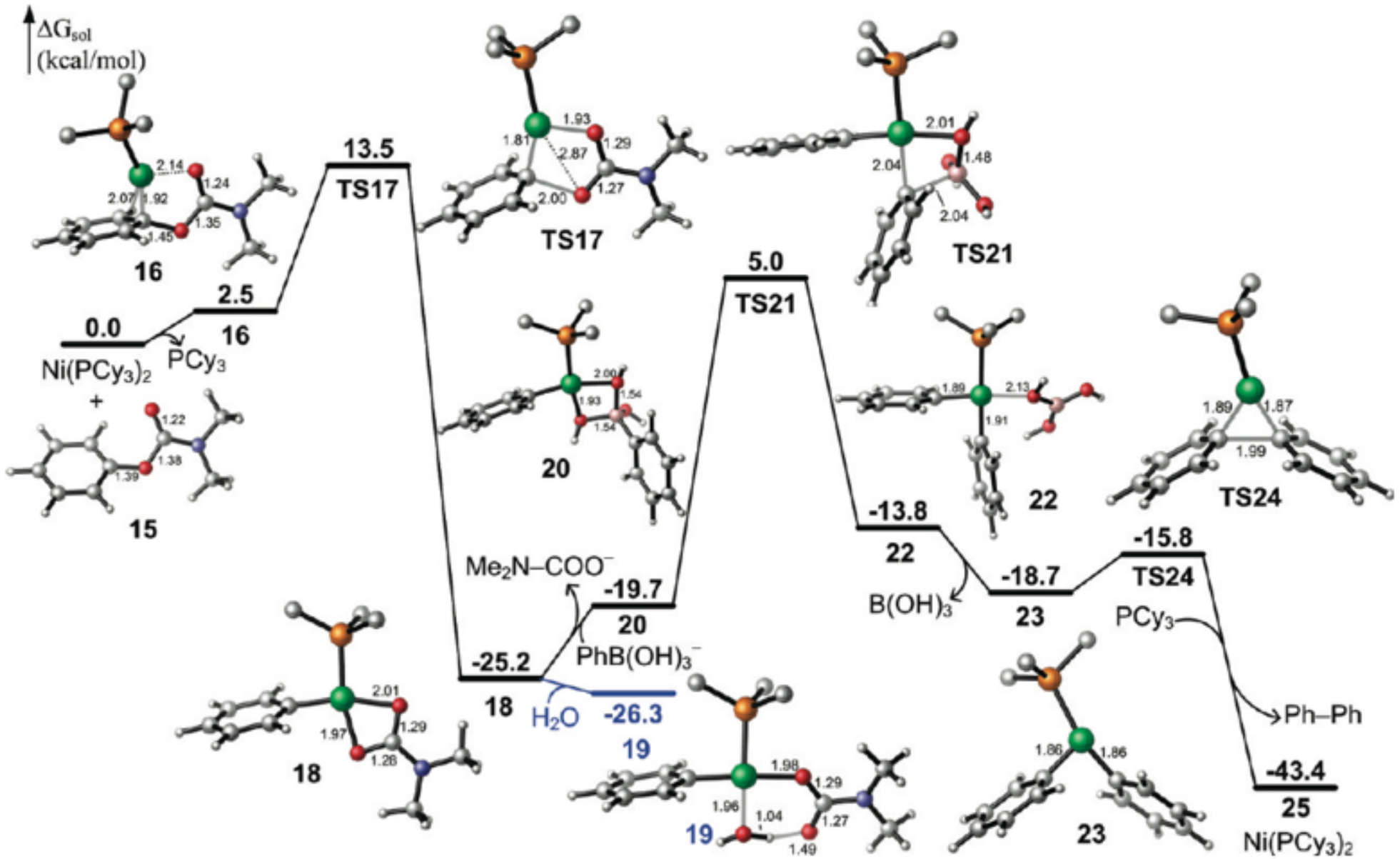
TS30
three-centered TS
cleave Ar-O bond
$\Delta G_{sol}^{\ddagger}$ = 20.9 kcal/mol
$\Delta G_{gas}^{\ddagger}$ = 25.8 kcal/mol
$\Delta H_{gas}^{\ddagger}$ = 24.2 kcal/mol



TS31
three-centered TS
cleave O-carbonyl bond
$\Delta G_{sol}^{\ddagger}$ = 17.4 kcal/mol
$\Delta G_{gas}^{\ddagger}$ = 22.9 kcal/mol
$\Delta H_{gas}^{\ddagger}$ = 20.7 kcal/mol

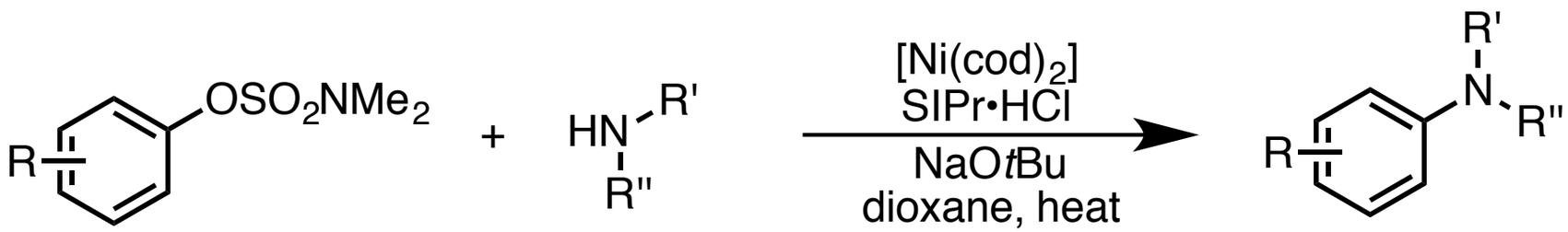
Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352.

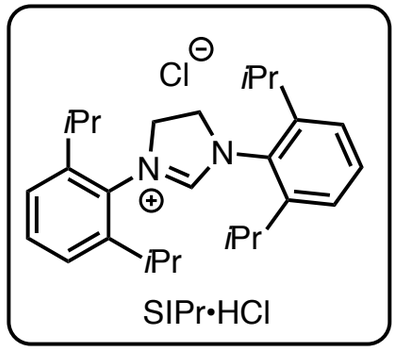
C–O Bond Activation



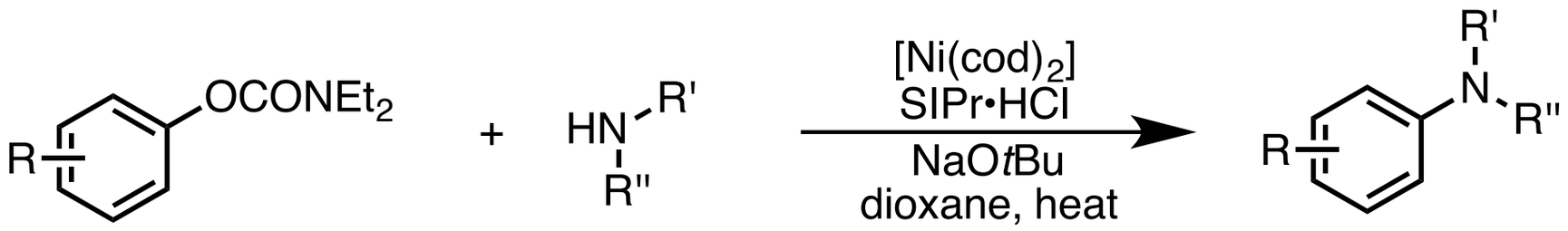
Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352.

C–O Bond Activation

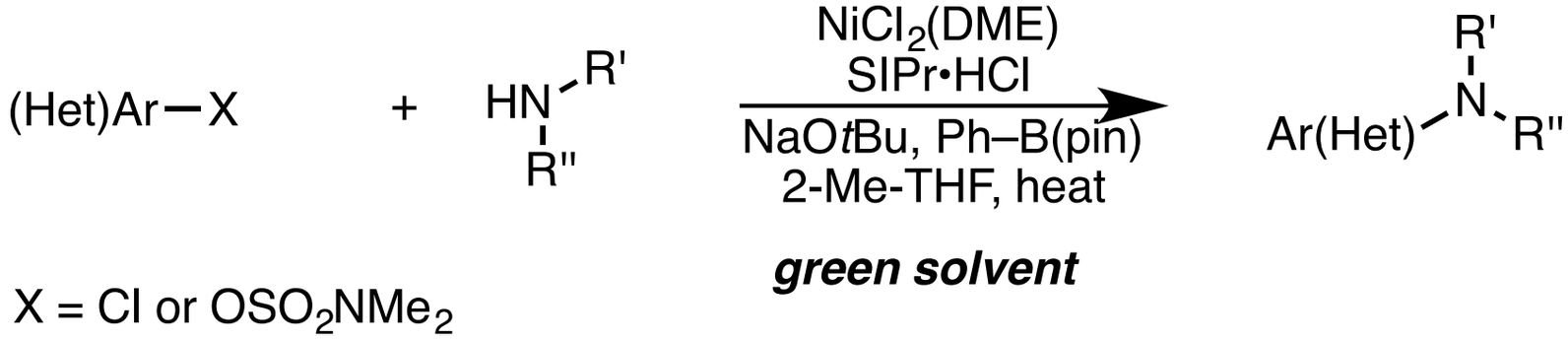




Ramgren, S. D.; Silberstein, A. L.; Yang, Y.; Garg, N. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 2171.

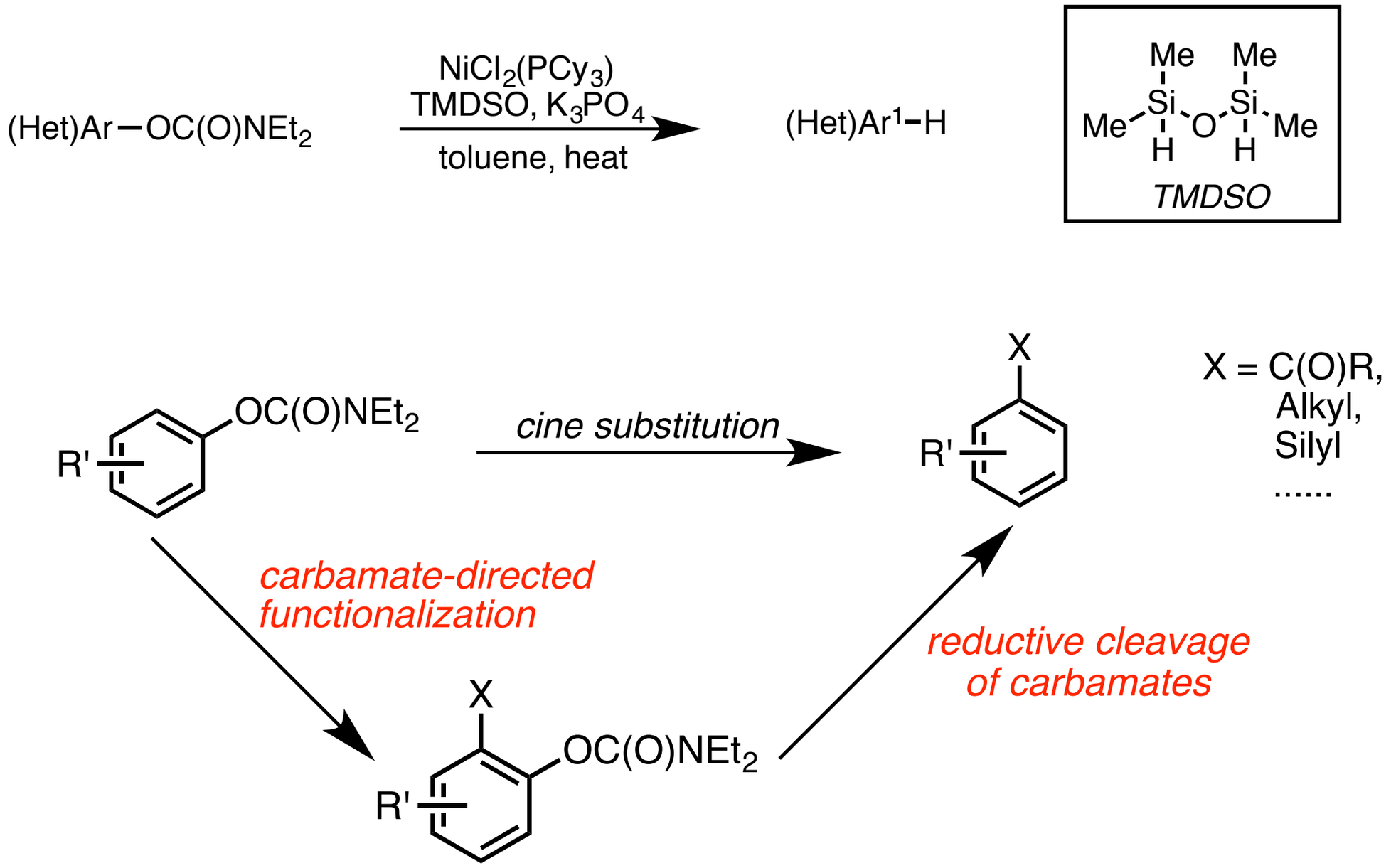


Mesganaw, T.; Silberstein, A. L.; Ramgren, S. D.; Fine Nathel, N. F.; Hong, Xin; Liu, P.; Garg, N. K. *Chem. Sci.* **2011**, *2*, 1766.



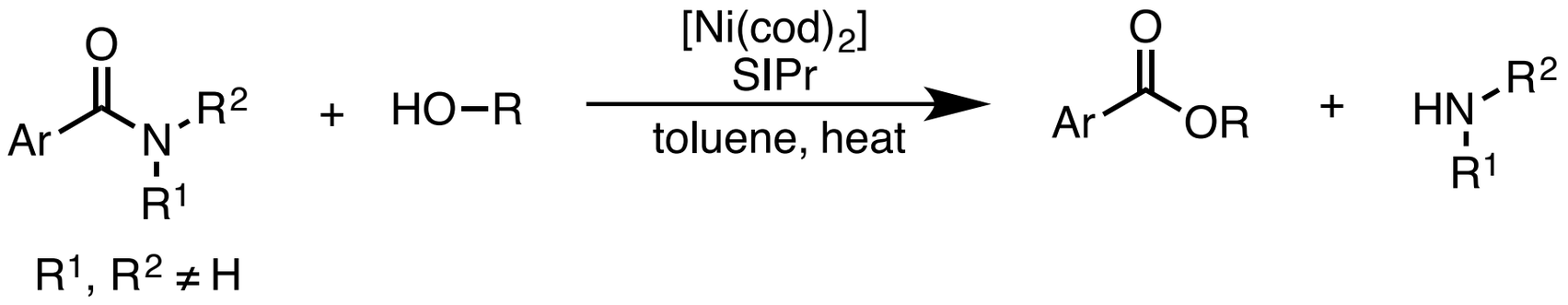
Hie, L.; Ramgren, S. D.; Mesganaw, T.; Garg, N. K. *Org. Lett.* **2012**, *14*, 4182.
Fine Nathel, N. F.; Kim, J.; Hie, L.; Jiang, X. Y.; Garg, N. K. *ACS Catal.* **2014**, *4*, 3289.

C–O Bond Activation



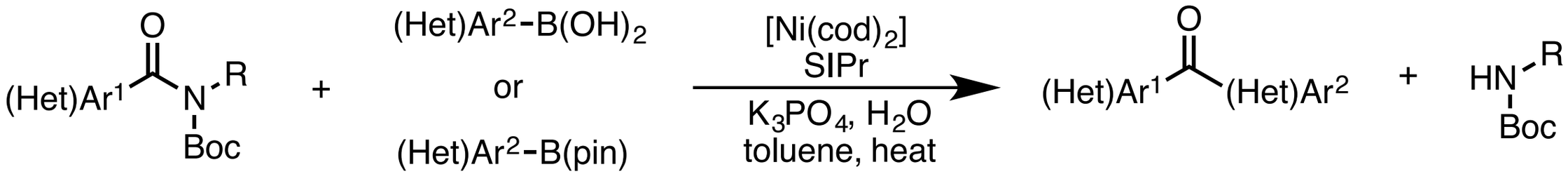
Mesganaw, T.; Fine Nathel, N. F.; Garg, N. K. *Org. Lett.* **2012**, *14*, 2918.

C–N Bond Activation



R^1, $R^2 \neq H$

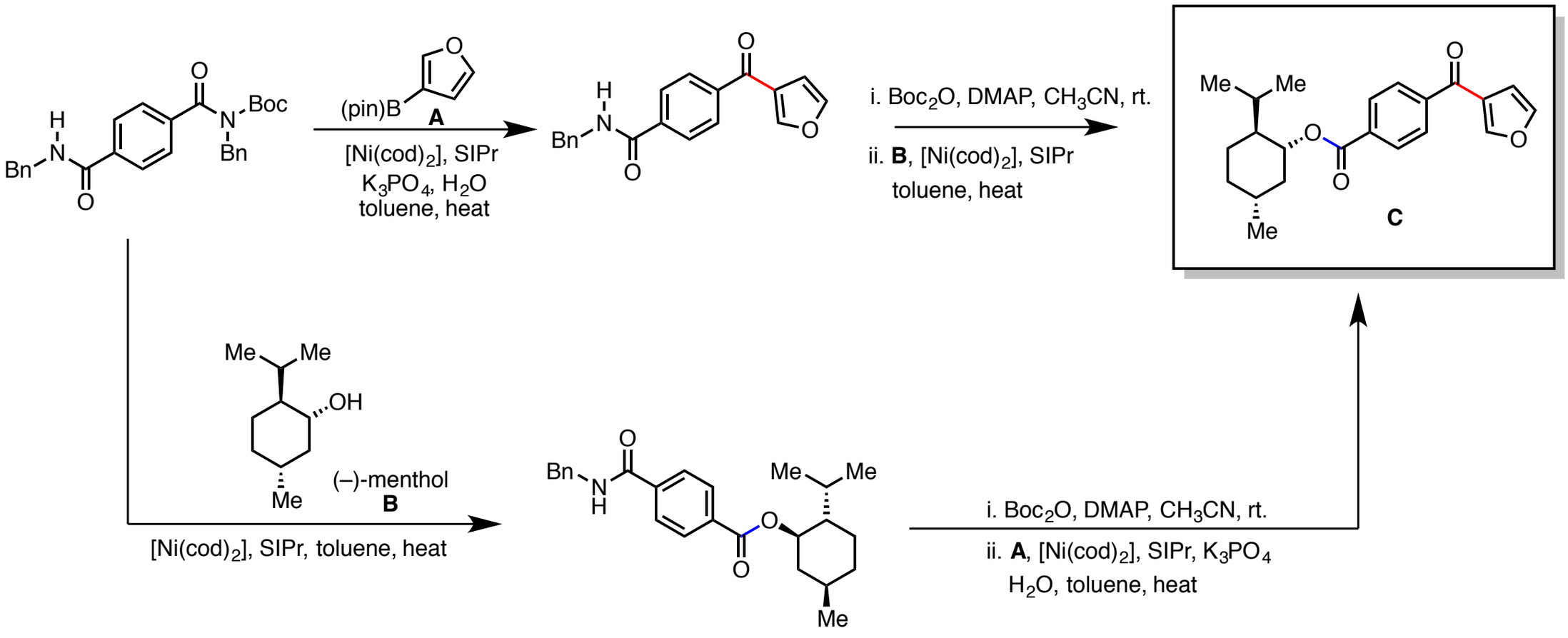
Hie, L.; Fine Nathel, N. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *524*, 79.



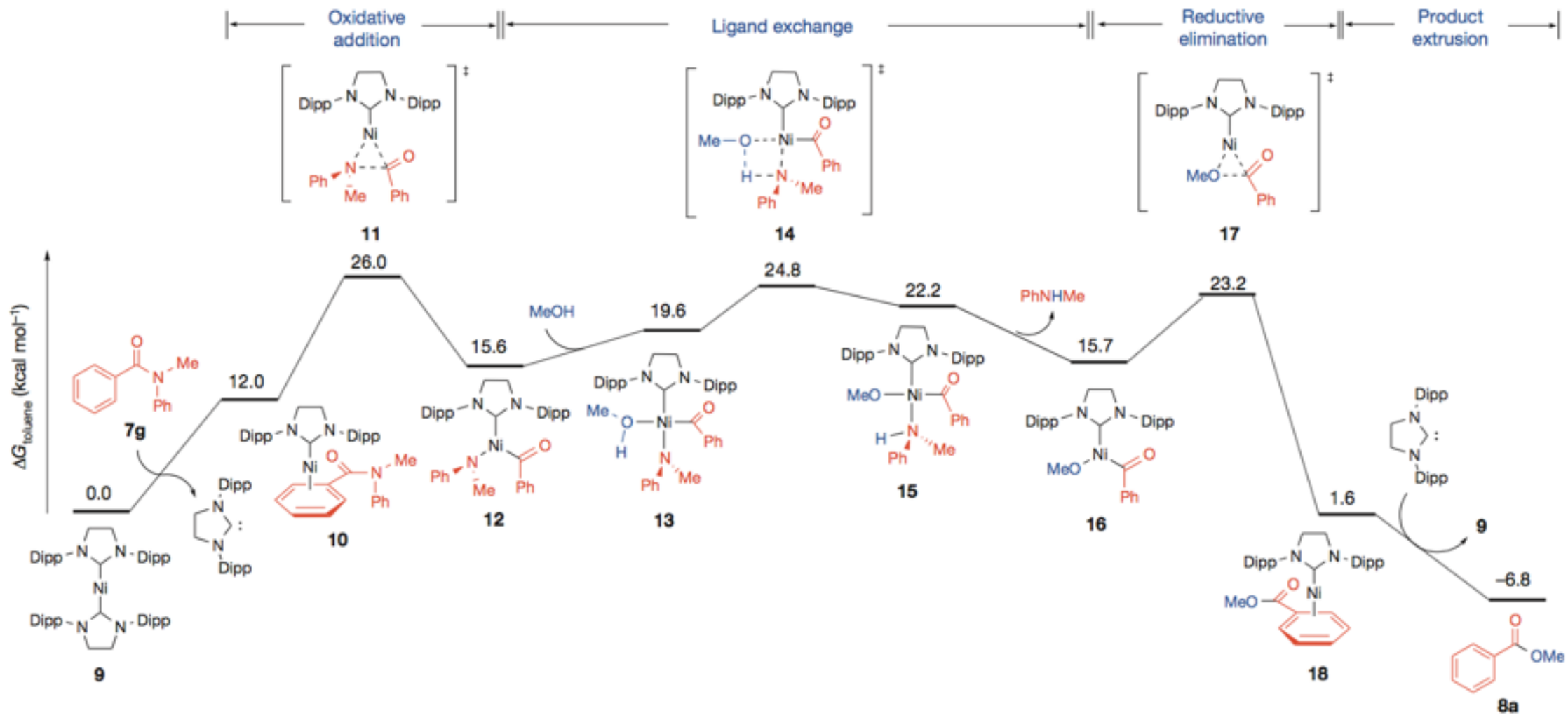
R = Me or Bn

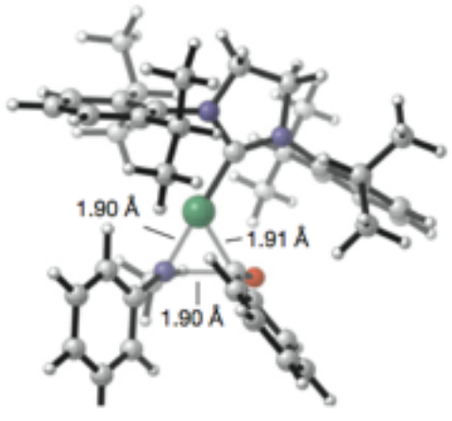
Weires, N. A.; Baker, E. L.; Garg, N. K. *Nat. Chem.* **2016**, *8*, 75.

C–N Bond Activation

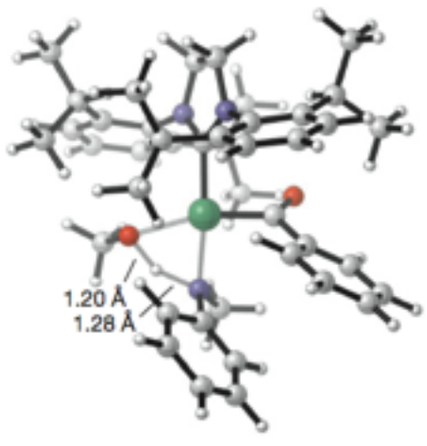


C–N Bond Activation

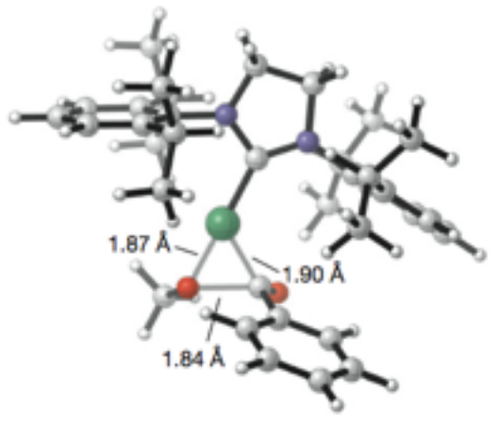




11 (oxidative addition transition state)

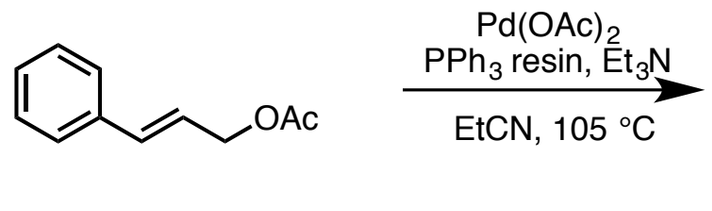


14 (ligand exchange transition state)



17 (reductive elimination transition state)

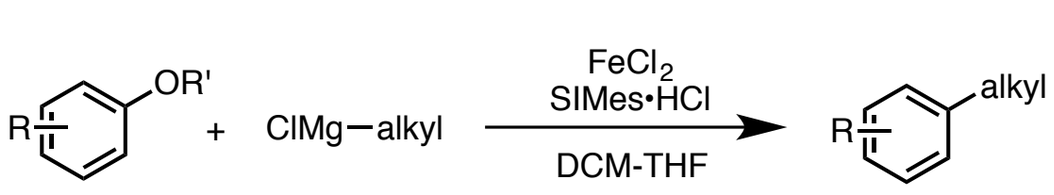
Other Metal-catalyzed Coupling Reactions



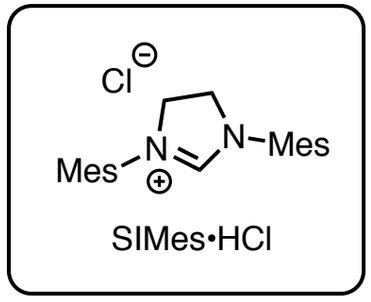
- *gram scale*
- *useful compound (fluorescent probes)*

diphenylhexatriene

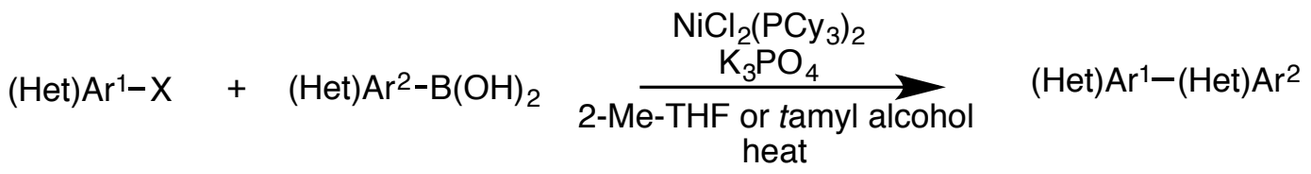
Mesganaw, T.; Im, G-Y. J.; Garg, N. K. *J. Org. Chem.* **2013**, *78*, 3391.



R' = $OCONEt_2$ or OSO_2NMe_2



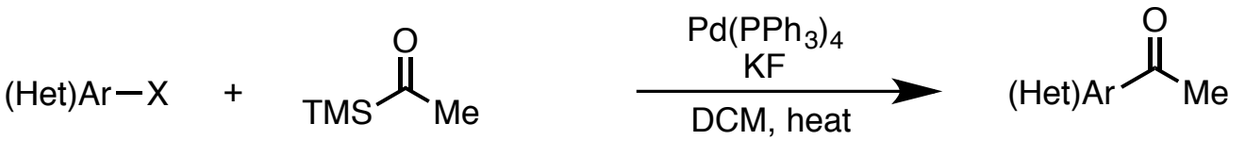
Silberstein, A. L.; Ramgren, S. D.; Garg, N. K. *Org. Lett.* **2012**, *14*, 3796.



X = Br, I, Cl or OSO_2NMe_2

green solvent

Ramgren, S. D.; Hie, L.; Ye, Y.; Garg, N. K. *Org. Lett.* **2013**, *15*, 3950.



X = Br, I or OTf

Ramgren, S. D.; Garg, N. K. *Org. Lett.* **2014**, *16*, 824.

Summary

– Aryne Chemistry

- Aryne Distortion Model
- Alkaloid Total Synthesis (e.g., *(–)-N-methylwelwitindolinone C Isothiocyanate*)

– Interrupted Fischer Indolization

- Methodology Development
- Alkaloid Total Synthesis (e.g., *(±)-Aspidophylline A*)

– Metal-catalyzed Cross Coupling Reactions

- C–O Bond Activation
- C–N Bond Activation

Outlook and Possible Future Directions

- Total Synthesis and Drug Development
- Develop Ni(II)-Catalyzed C–N Bond Activation Reactions
- Kinetic Study of the C–N Bond Activation Reactions
- Photoredox Chemistry

Acknowledgements

- *Keary*
- *All Group members*