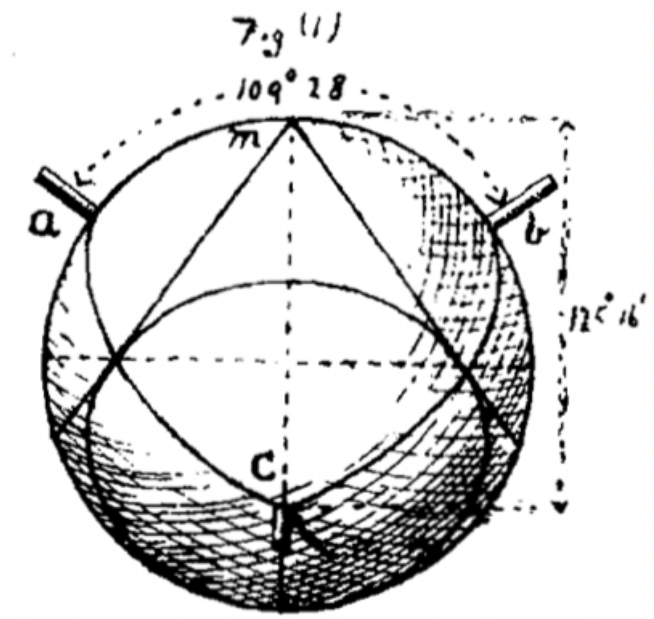
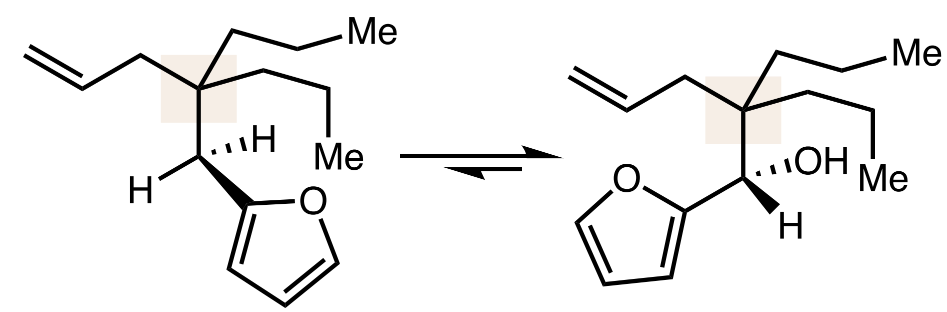
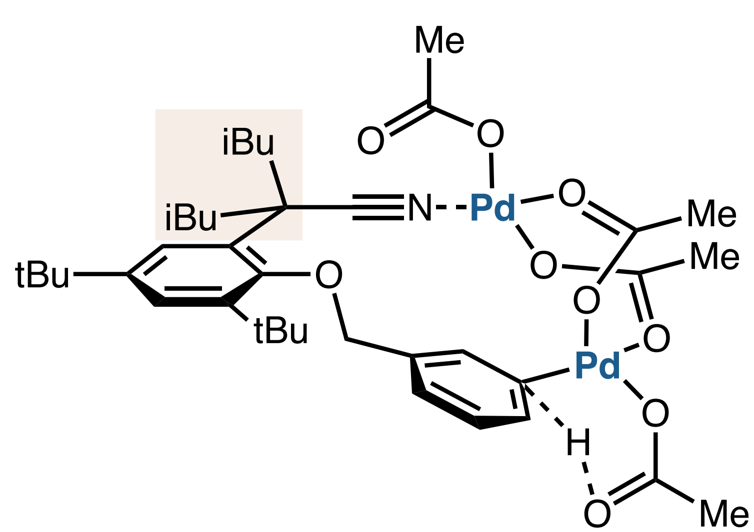
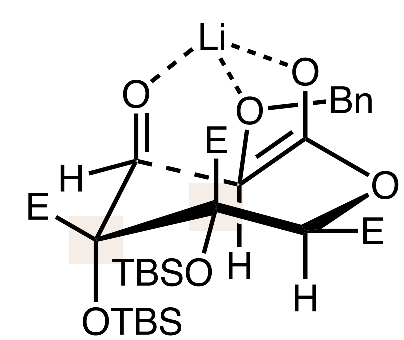
Conformational Effects of Fully Substituted Carbons









Nick Intermaggio

Group Meeting–Literature Review

June 1st, 2020

Conformational Effects of Fully Substituted Carbons

Outline

- Introduction and Evolution of Theory
    - – Thorpe–Ingold Effect
    - – Reactive Rotamer Effect
- Application in Modern Catalysis
    - – Directing groups in C–H Activation
- Complex Molecule Synthesis
    - – (–)-Indolizidine 223AB and Alkaloid (–)-250B
    - – Zaragozic acid C
    - – tricholomalide A and (–)-guanacastepene
- Drug Discovery

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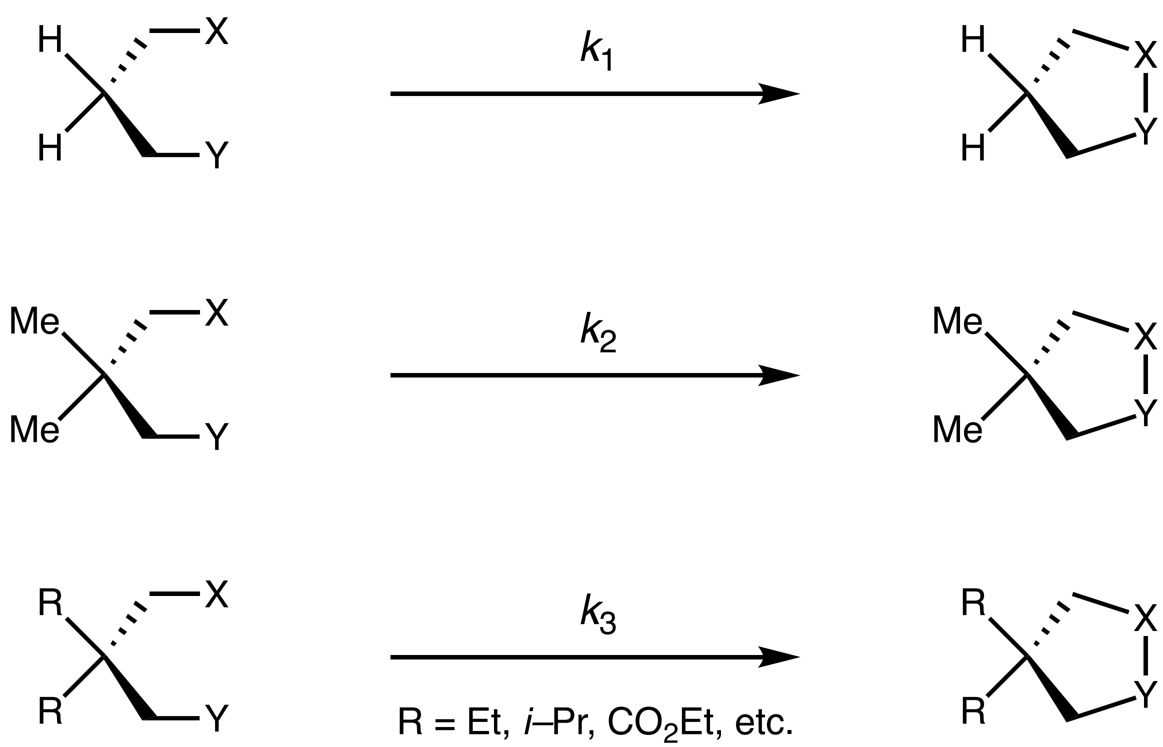
Conformational Effects of Fully Substituted Carbons

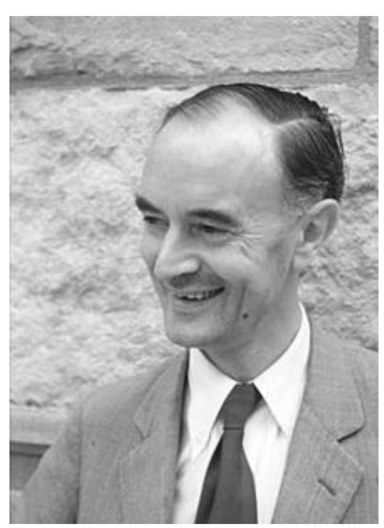
General Observation



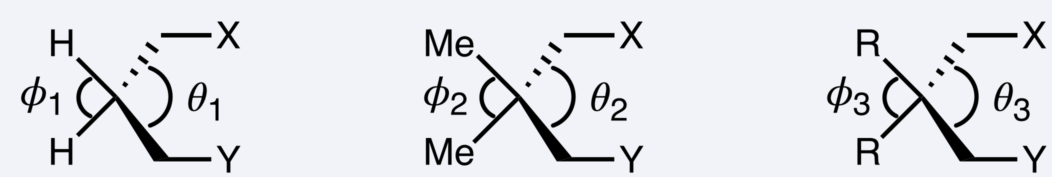
subsitition on carbon atoms tethering two reaction centers accelerates the rate of cyclization

$$k_1 < k_2 < k_3$$

Sir Jocelyn Field Thorpe
(1872 – 1940)



Christopher Kelk Ingold
(1893 – 1970)

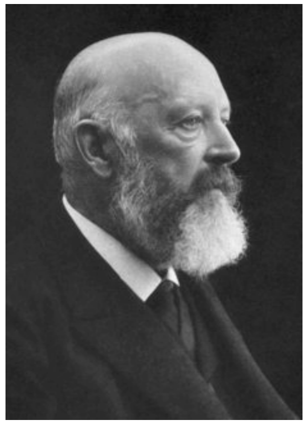


$\theta_1 > \theta_2 > \theta_3$ $\phi_1 < \phi_2 < \phi_3$

Thorpe–Ingold Effect
(1915)

Conformational Effects of Fully Substituted Carbons

Thorpe–Ingold Hypothesis: Baeyer's Strain Hypothesis



Adolf Von Baeyer

(1835 – 1917)

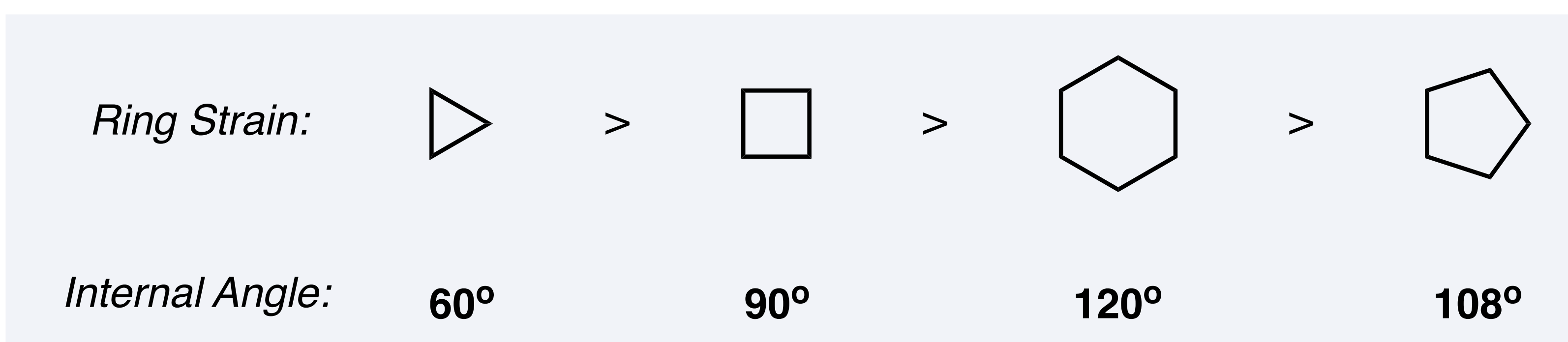
Baeyer's Ring Strain Hypothesis (1885)

VII. Die vier Valenzen des Kohlenstoffatoms wirken in den Richtungen, welche den Mittelpunkt der Kugel mit den Tetraederecken verbinden, und welche mit einander einen Winkel von 109° 28′ machen.

Die Richtung der Anziehung kann eine Ablenkung erfahren, die jedoch eine mit der Grösse der Letzteren wachsende Spannung zur Folge hat.

---

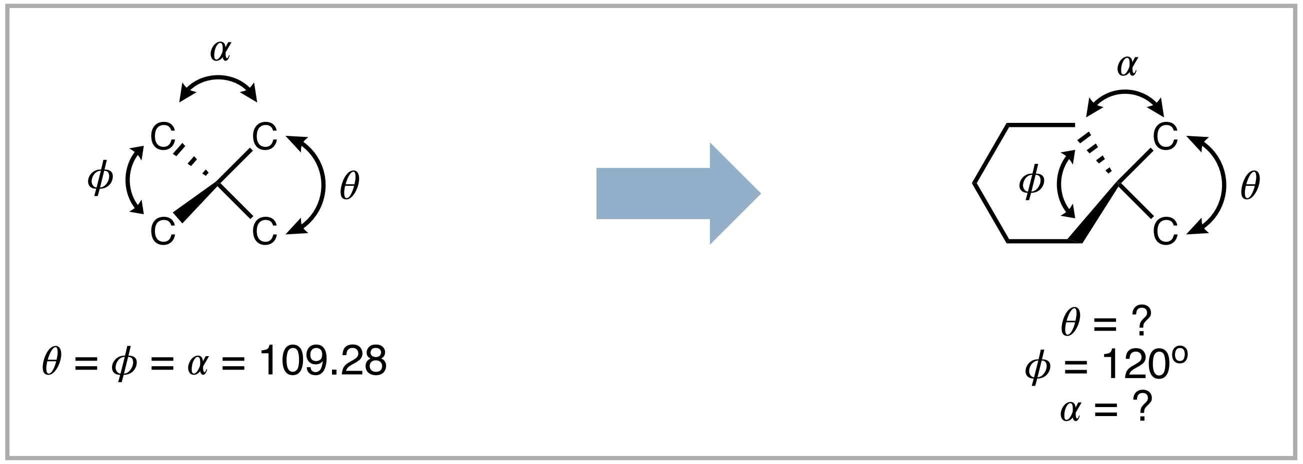
*"The four valences of the carbon atom act in the directions that connect the center of a sphere with the corners of a tetrahedron and that form an angle of **109° 28'** with each other. The direction of the attraction can experience a deviation that will, however, cause and increase in strain correlating with the degree of this deviation"*



Meijere, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 7836–7840
Von Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2269–2281

Conformational Effects of Fully Substituted Carbons

Thorpe–Ingold Hypothesis



How does restricting one angle effect the others?

Hypothesis A

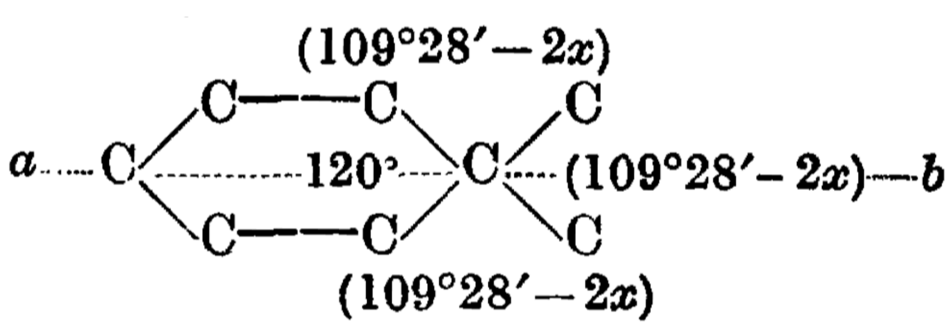


Fig. (*a*).

All other substituents distribute evenly in space

Hypothesis B

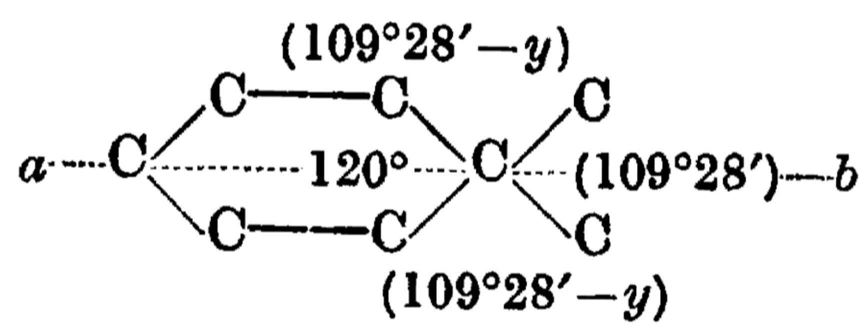


Fig. (*b*).

opposite angle (θ) remains constant and space distributed between remaining two angles (α)

Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080–1106

Conformational Effects of Fully Substituted Carbons

Thorpe–Ingold Hypothesis

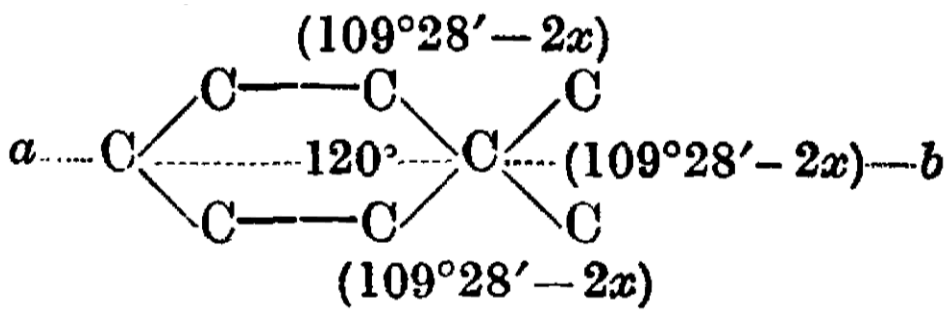


Fig. (a).

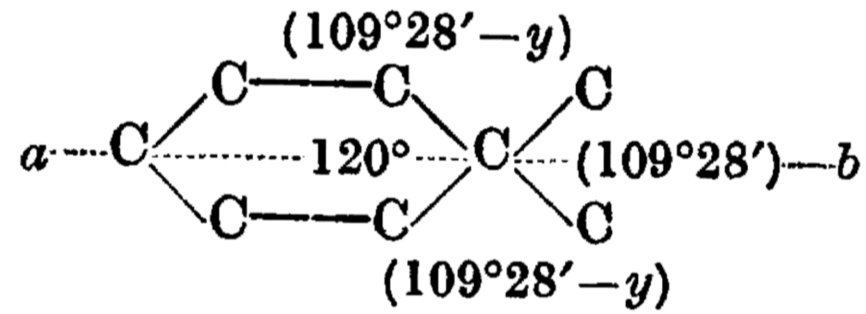
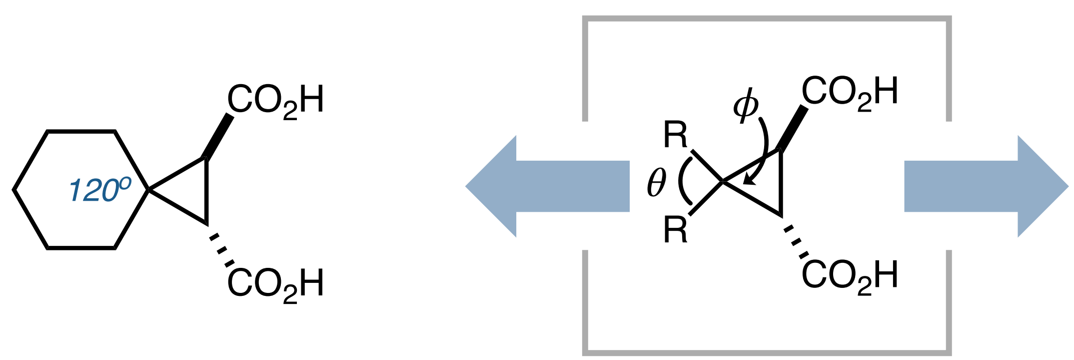


Fig. (b).

A = *All other substituents distribute evenly in space*

B = *opposite angle remains constant and space distributed between remaining two angles*



If θ is large, *ϕ will be small and small rings will be stabilized*

Stability of small ring systems

If θ = 109.28° small rings will not be stabilized

Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080–1106

Conformational Effects of Fully Substituted Carbons

Thorpe–Ingold Hypothesis

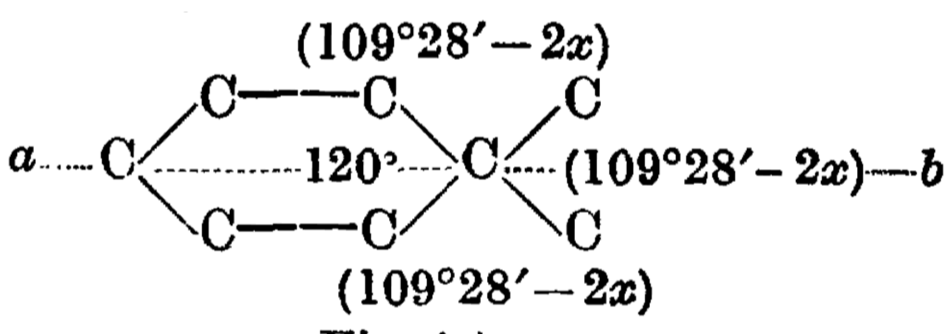


Fig. (a).

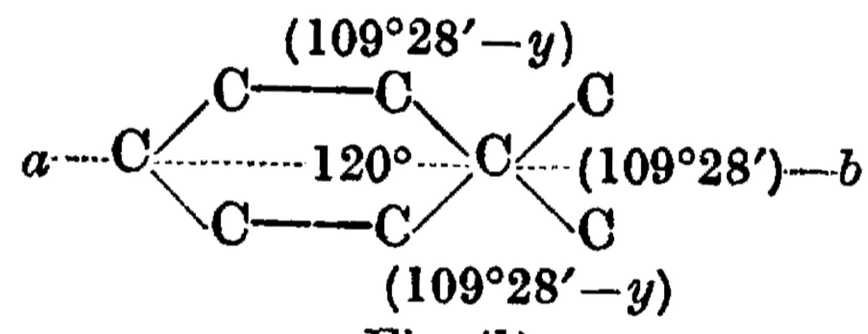
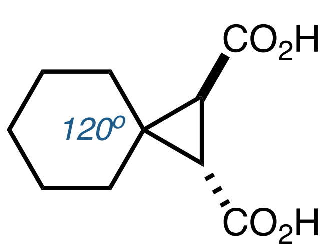
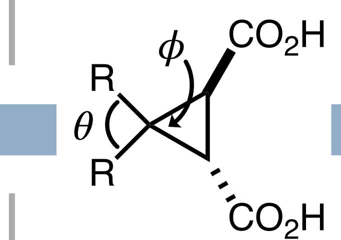


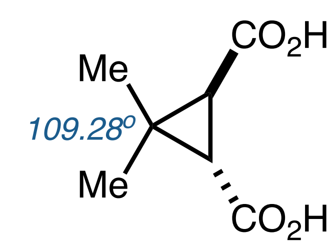
Fig. (b).

A = *All other substituents distribute evenly in space*

B = *opposite angle remains constant and space distributed between remaining two angles*







cyclohexane more stable supports hypothesis **A**

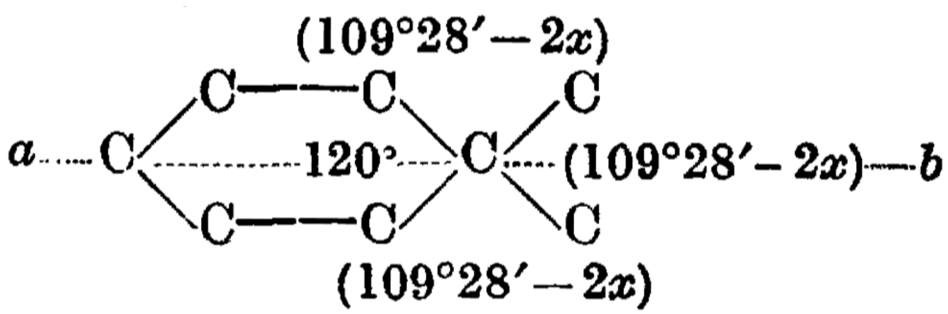
Stability of small ring systems

dimethyl equally as stable supports hypothesis **B**

Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080–1106

Conformational Effects of Fully Substituted Carbons

Thorpe–Ingold Hypothesis



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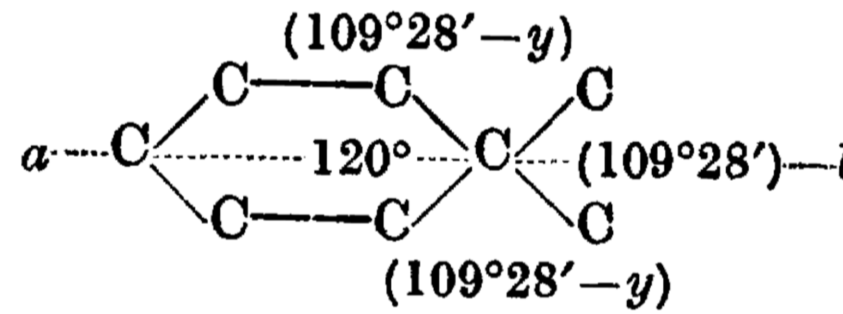

Fig. (b).

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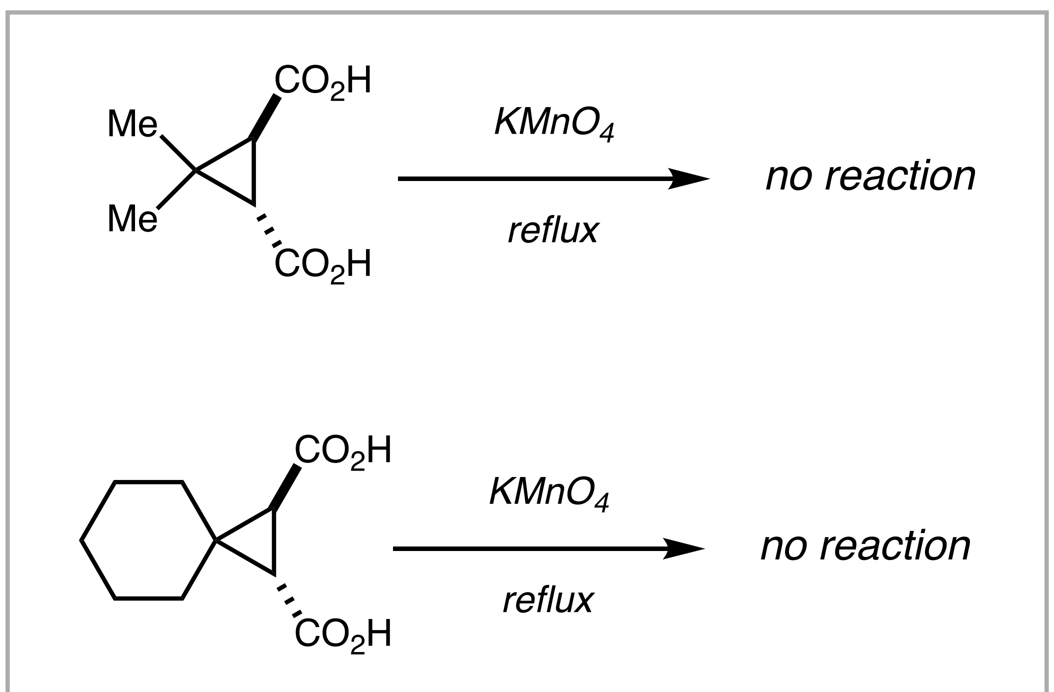

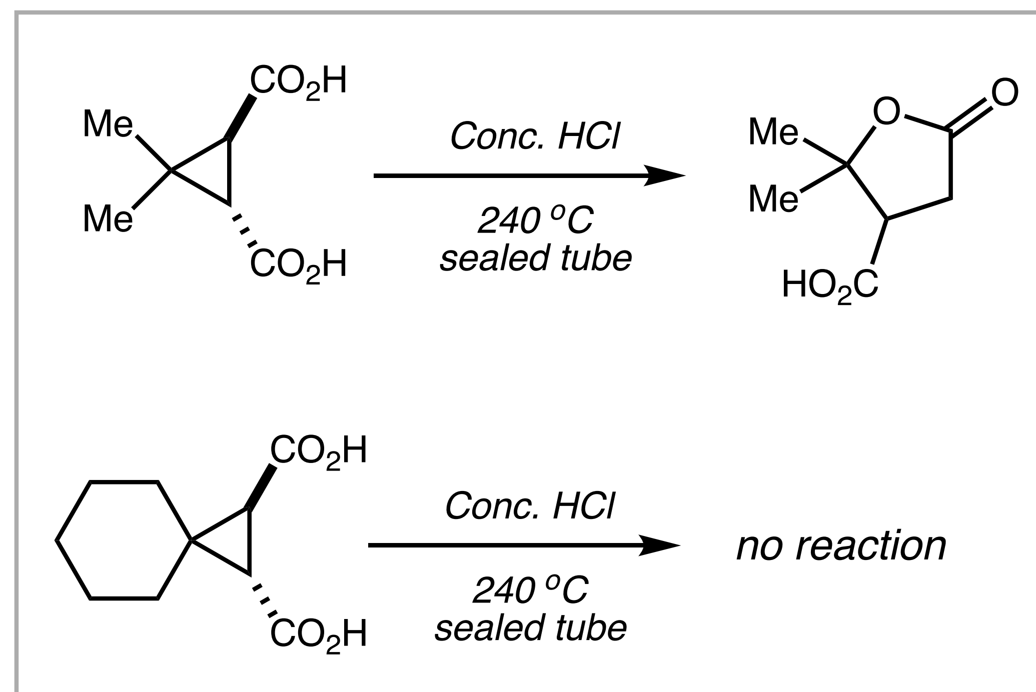

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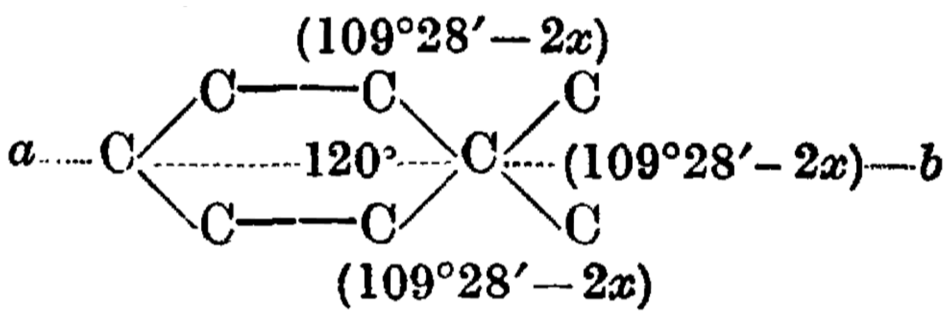

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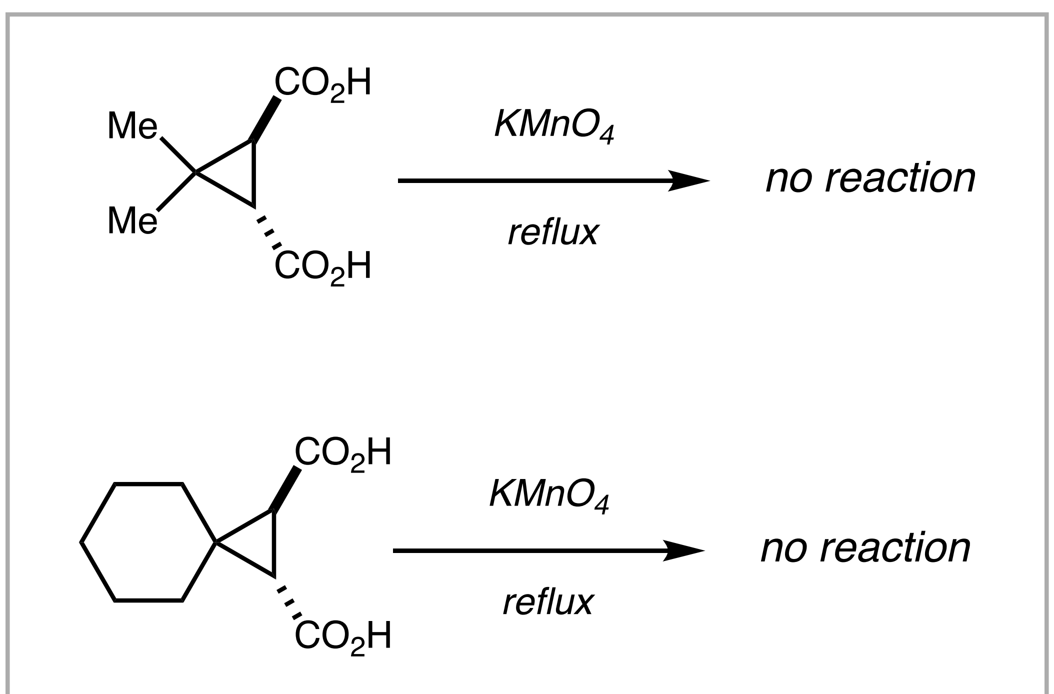
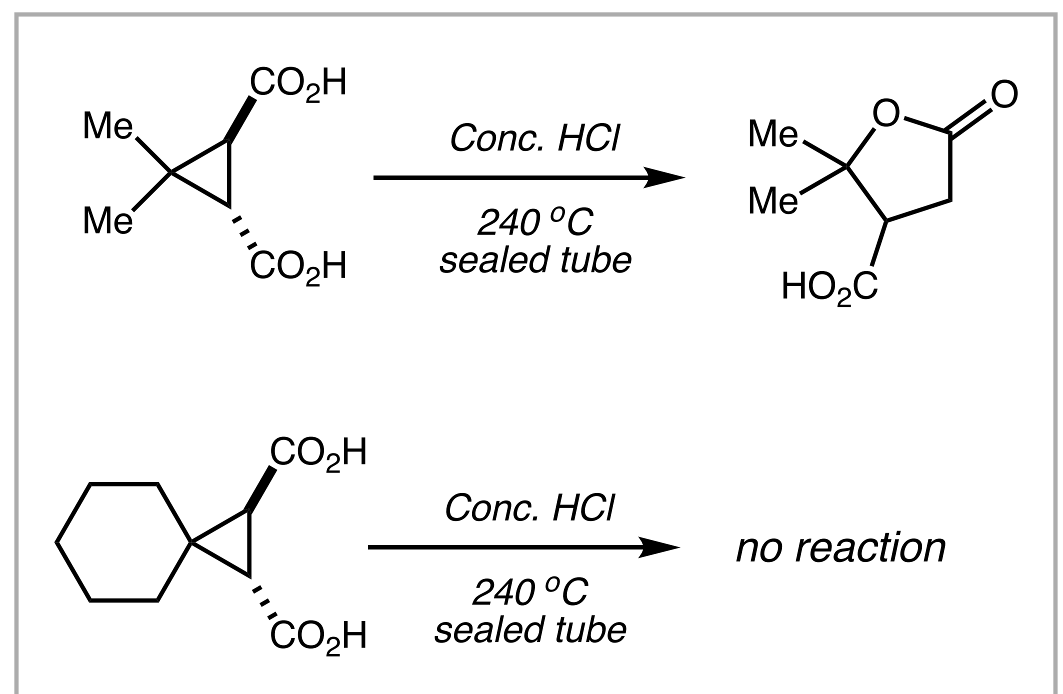




Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080–1106

Conformational Effects of Fully Substituted Carbons

Thorpe–Ingold Hypothesis

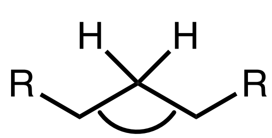
- Failure of Baeyer's strain theory:

Ring	*cyclo-* Propane.	*cyclo-* Butane.	*cyclo-* Pentane.	*cyclo-* Hexane.
Angle of strain (Baeyer) ...	24·7°	9·7°	0·7°	5·3°
Heat absorbed (S. and K.) ...	38·1	42·6	16·1	14·3 cals.

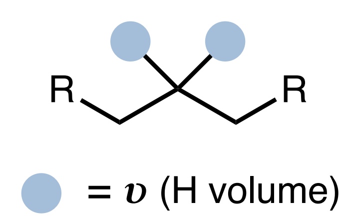
"The discordance is most pronounced" – Christopher Keller Ingold (1921)

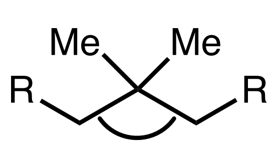
Baeyer's theory:

polymethylene chains will have the same bond angles as substituted methylene chains



θ = 109.28°





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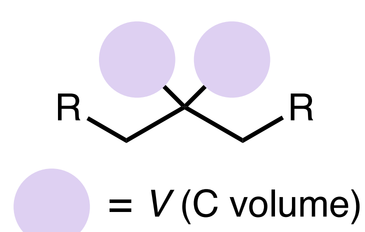
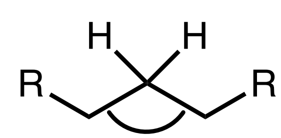
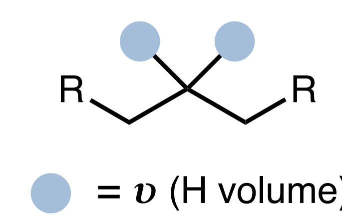


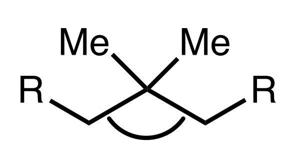
Ingold's atomic volume hypothesis

tetrahedrons will distribute subsituents evenly according to their atomic volume

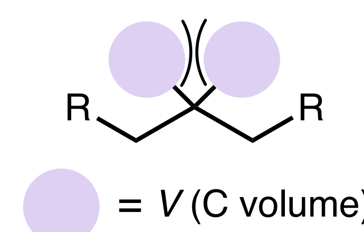


θ > 109.28°





θ = 109.28°



Ingold, C. K. *J. Chem. Soc., Trans.* **1921**, *119*, 305–329

Conformational Effects of Fully Substituted Carbons

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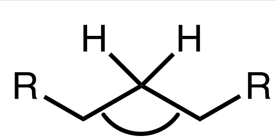
Heat absorbed (S. and K.) ...	38·1	42·6	16·1	14·3 cals.

"The discordance is most pronounced" – Christopher Keller Ingold (1921)

$$V^{\frac{1}{3}} \sin \phi - v^{\frac{1}{3}} \sin \theta = (V^{\frac{1}{3}} - v^{\frac{1}{3}}) \sin \theta \sin \phi$$

$$V^{\frac{1}{3}} \cot \theta + v^{\frac{1}{3}} \cot \phi = \sqrt{2}(Vv)^{\frac{1}{6}},$$

$$\operatorname{cosec} \theta = 1 + v^{\frac{1}{3}} \cdot \frac{\sqrt{6}(Vv)^{\frac{1}{6}} - (V^{\frac{1}{3}} + v^{\frac{1}{3}})}{2(Vv)^{\frac{1}{3}} - (V^{\frac{1}{3}} - v^{\frac{1}{3}})}.$$

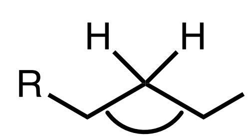


θ = 115.3°

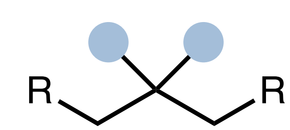
θ = 112.2° (*lit.*)

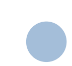
Ingold's atomic volume hypothesis

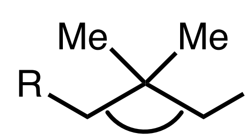
tetrahedrons will distribute subsituents evenly according to their atomic volume



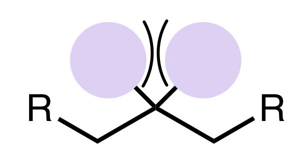
θ = 109.28°



 = v (H volume)



θ < 109.28°



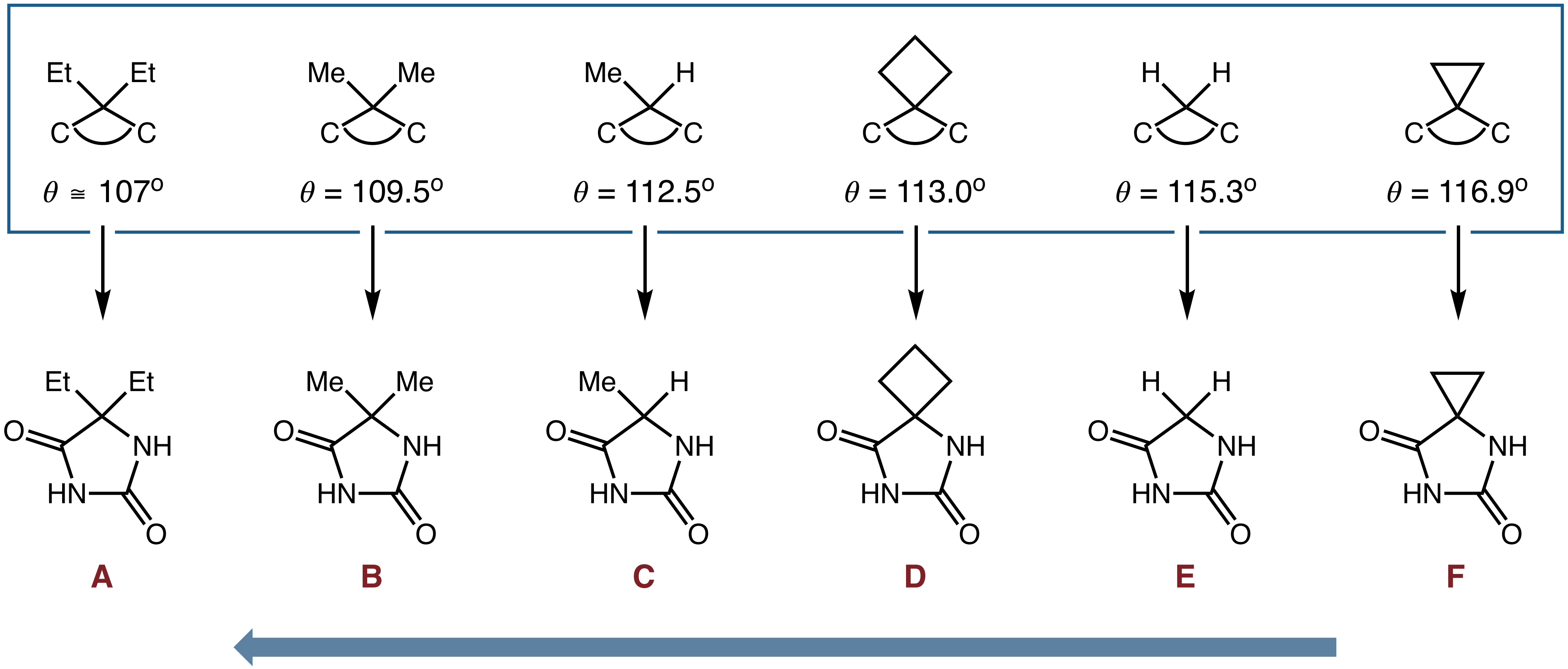
 = V (C volume)

Jung, M. E., Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735–1766

Ingold, C. K. *J. Chem. Soc., Trans.* **1921**, *119*, 305–329

Conformational Effects of Fully Substituted Carbons

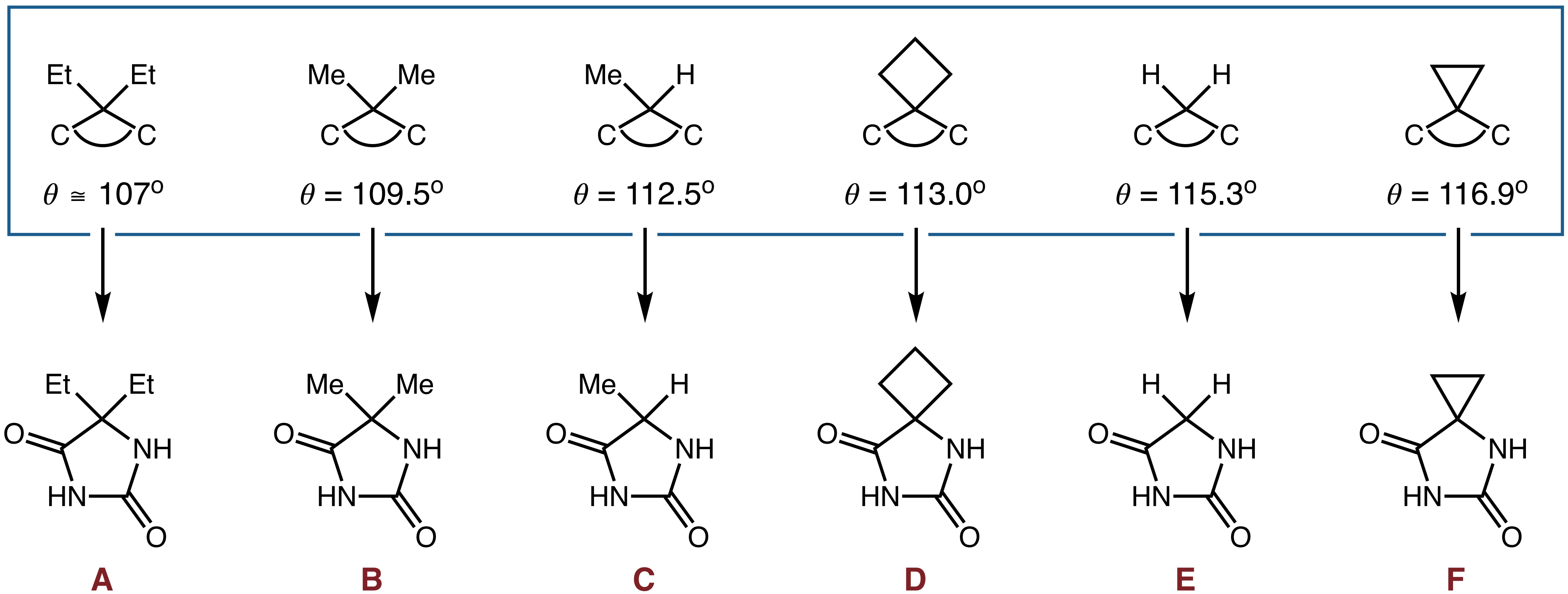
Thorpe–Ingold Hypothesis

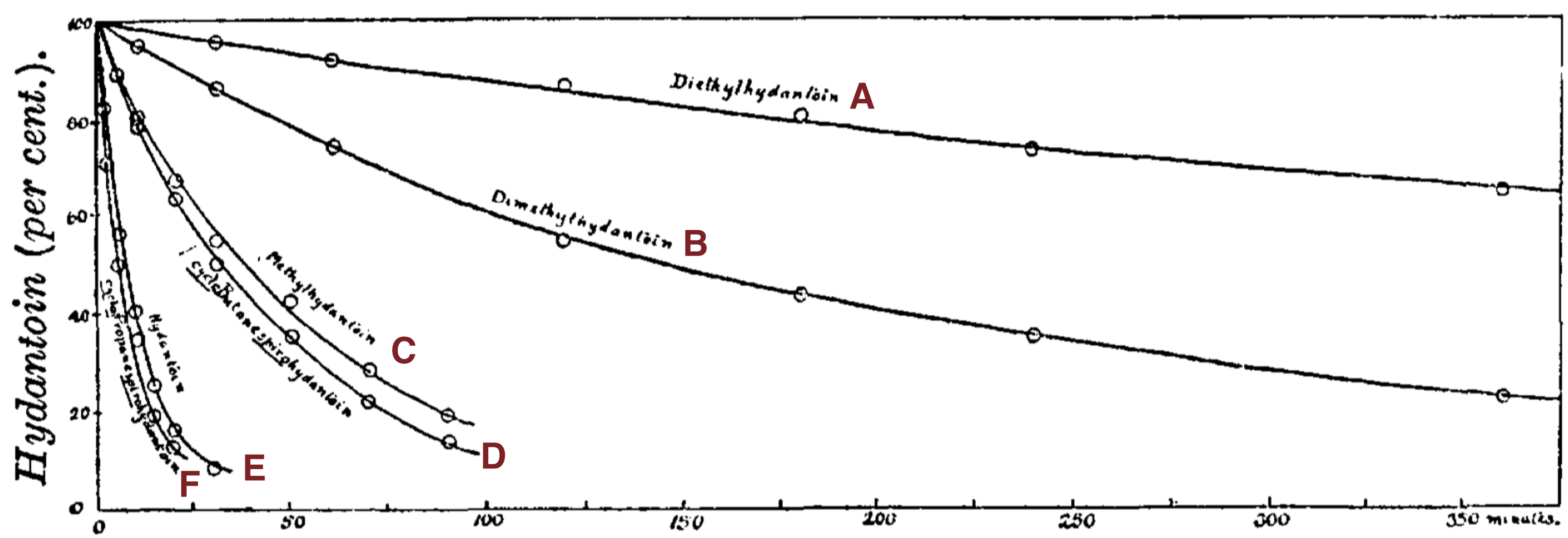


Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1922**, *121*, 1177–1198

Conformational Effects of Fully Substituted Carbons

Thorpe–Ingold Hypothesis





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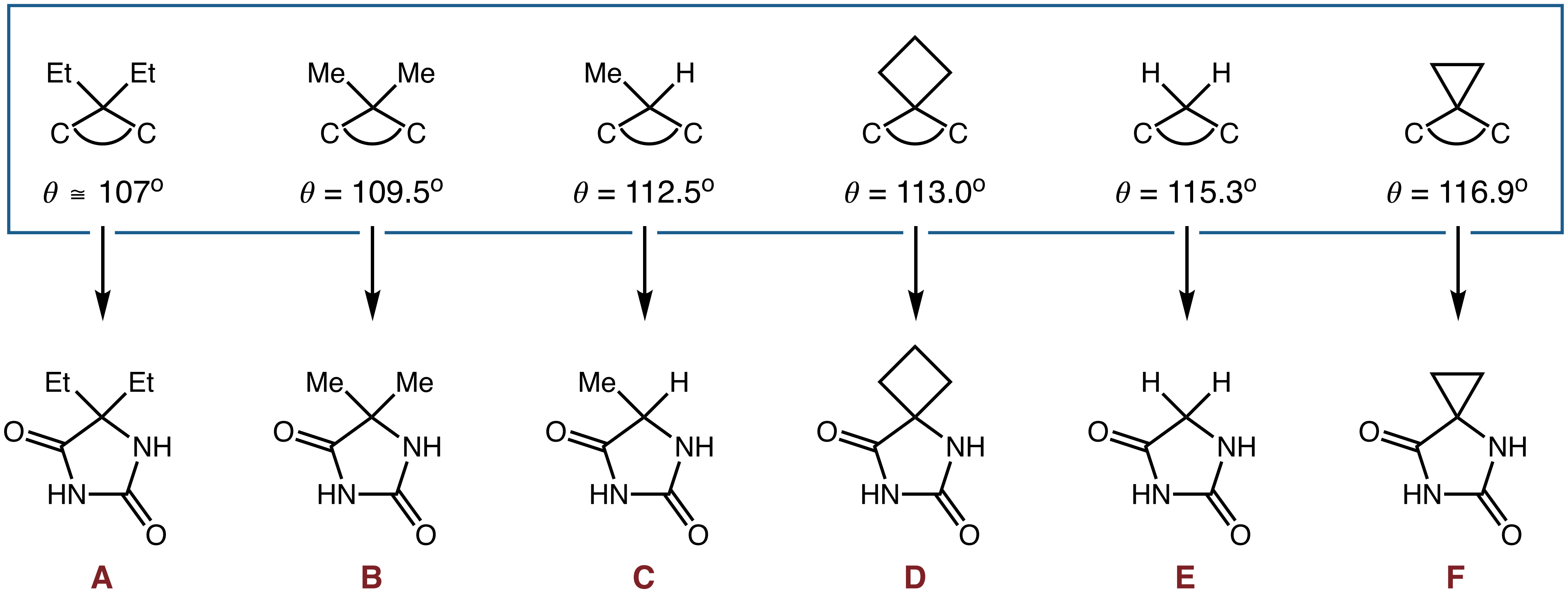
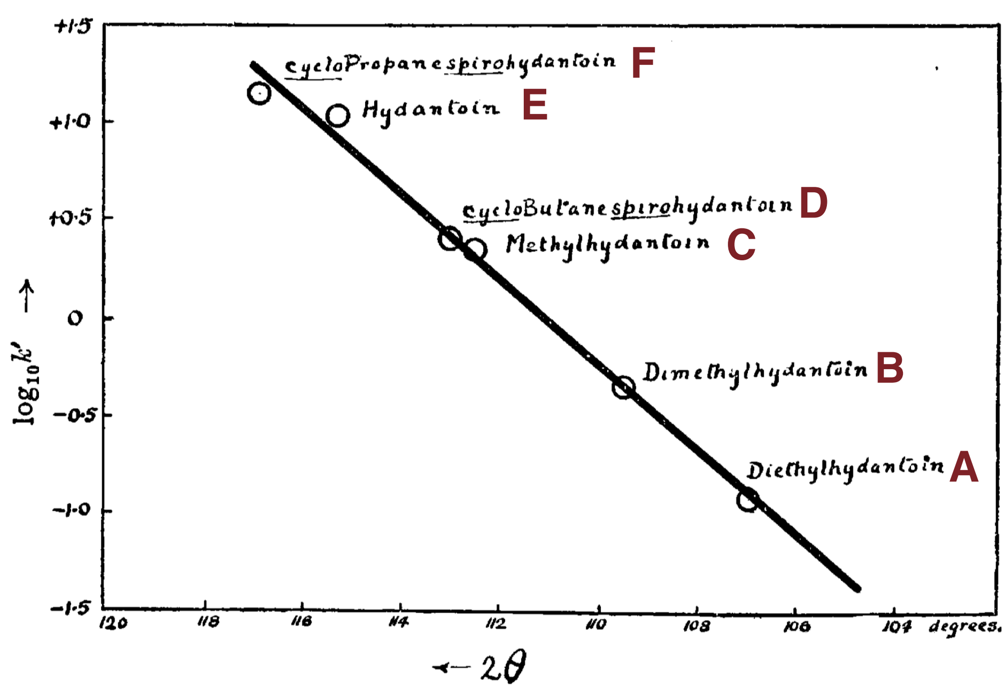
Thorpe–Ingold Hypothesis



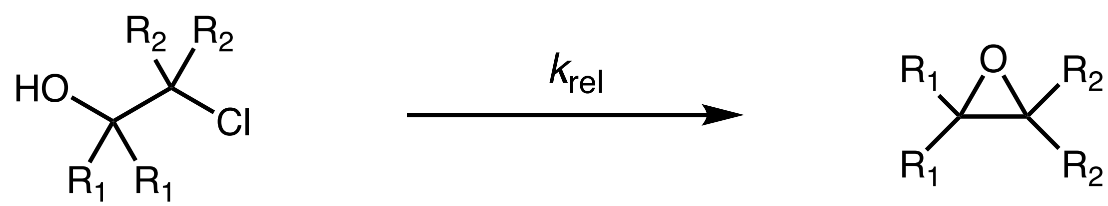


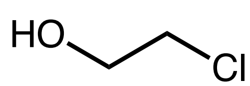
	2θ.	k'.	$\log_{10}k'$.
*cyclo*Propane*spiro*hydantoin ...	116·9	13·8	+1·14
Hydantoin	115·3	11·2	+1·05
*cyclo*Butane*spiro*hydantoin	113·0	2·63	+0·42
Methylhydantoin	112·5	2·28	+0·36
Dimethylhydantoin	109·5	0·551	−0·26
Diethylhydantoin	107·0	0·146	−0·84

Ingold, C. K.; Sako, S.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1922**, *121*, 1177–1198

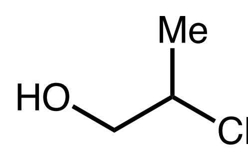
Conformational Effects of Fully Substituted Carbons

Early Experimental Evidence

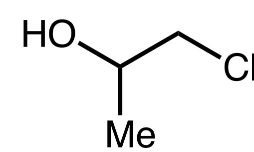




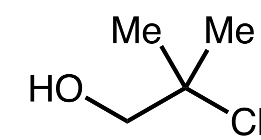
k_{rel} = 1



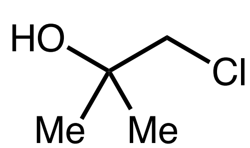
k_{rel} = 5.5



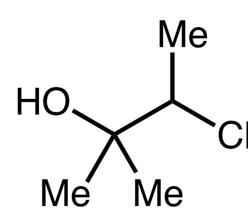
k_{rel} = 21



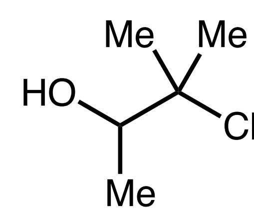
k_{rel} = 248



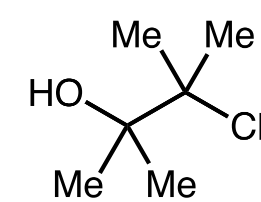
k_{rel} = 252



k_{rel} = 1360



k_{rel} = 2040



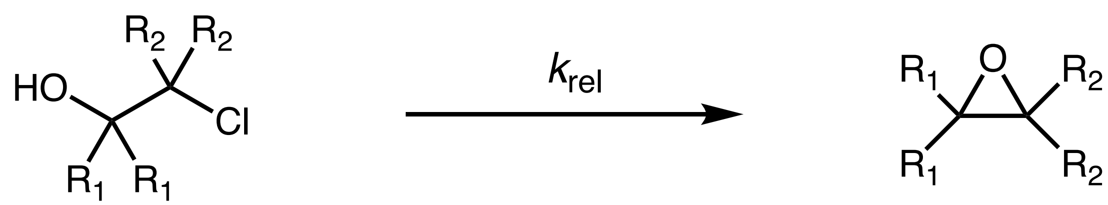
k_{rel} = 11,600

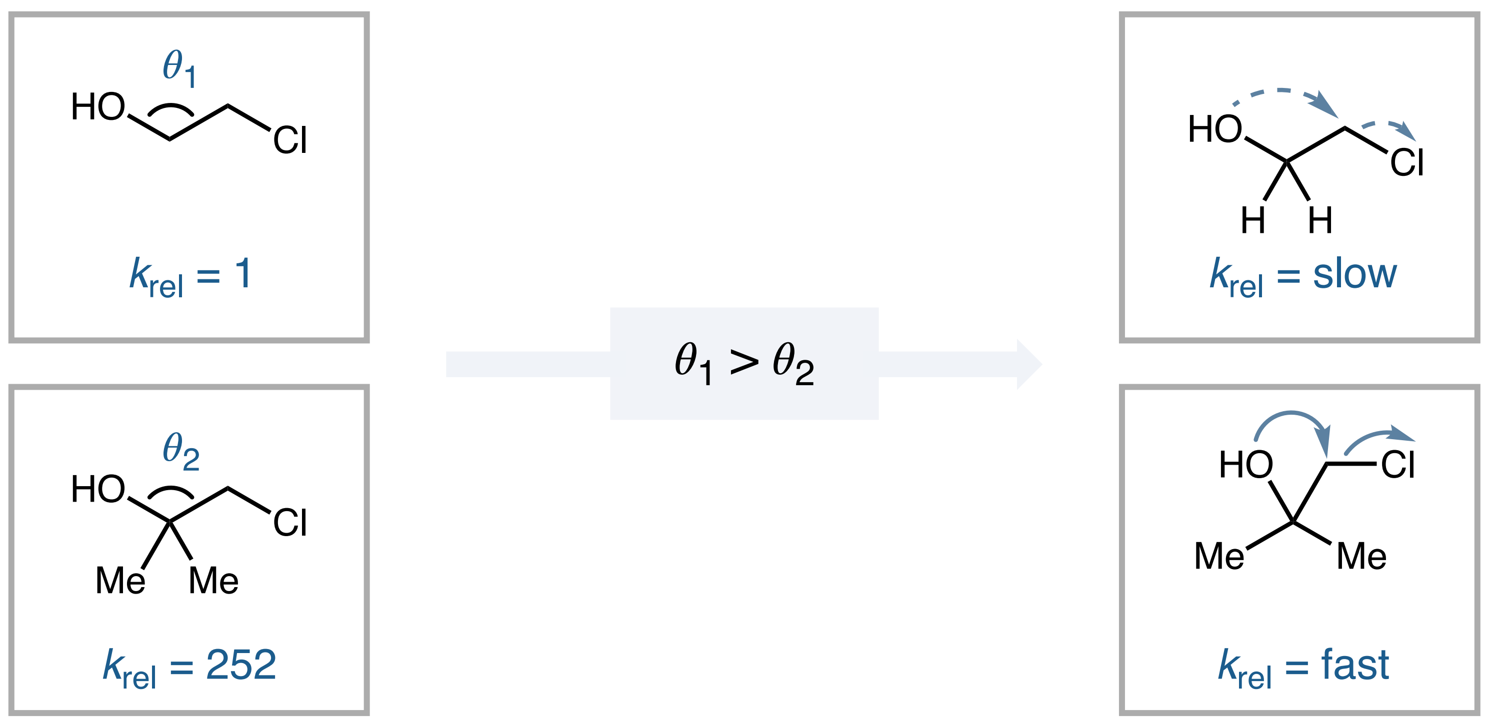
substitution provides >10^4 rate enhancement

Nilsson, H.; Smith, L. Z. *Phys. Chem.* **1933**, *166A*, 136

Conformational Effects of Fully Substituted Carbons

Early Experimental Evidence



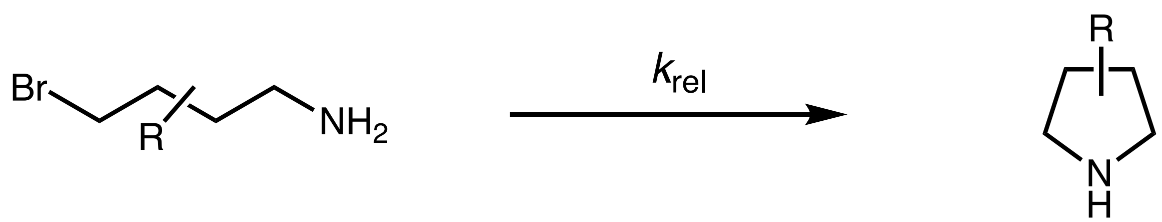


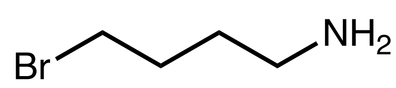
OH and R–Cl forced in close proximity
by dimethyl induced valency deviation

Nilsson, H.; Smith, L. Z. *Phys. Chem.* **1933**, *166A*, 136

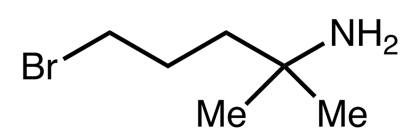
Conformational Effects of Fully Substituted Carbons

Early Experimental Evidence

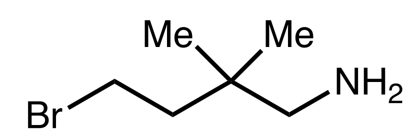




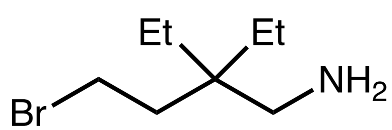
k_{rel} = 1



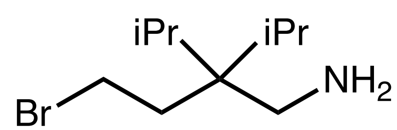
k_{rel} = 2.19



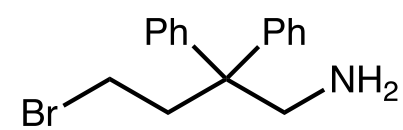
k_{rel} = 158



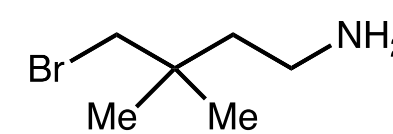
k_{rel} = 594



k_{rel} = 9190



k_{rel} = 5250



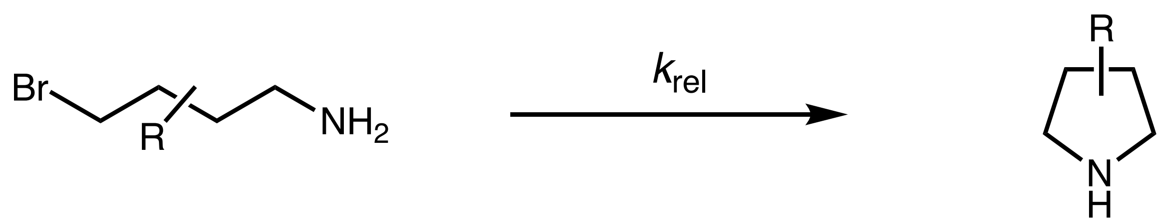
k_{rel} = 0.158

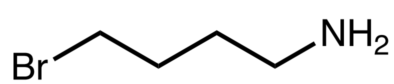
substitution provides >10^4 rate enhancement

Brown, R. F.; Van Gulick, N. M. *J. Org. Chem.* **1956**, *21*, 1046

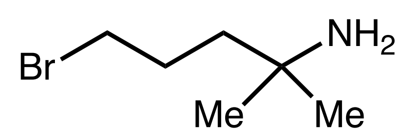
Conformational Effects of Fully Substituted Carbons

Early Experimental Evidence

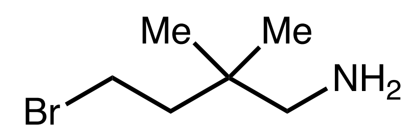




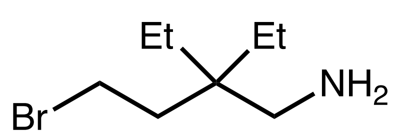
k_{rel} = 1



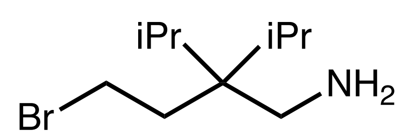
k_{rel} = 2.19



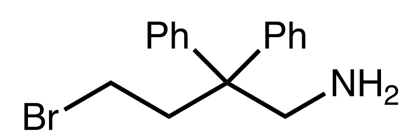
k_{rel} = 158



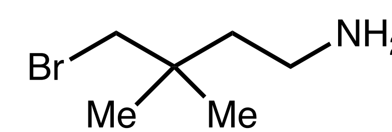
k_{rel} = 594



k_{rel} = 9190



k_{rel} = 5250



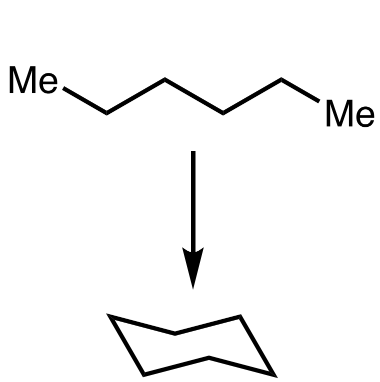
k_{rel} = 0.158

Can a 2-3^{o} tetrahedral angle change account for a rate enhancement of >5000?

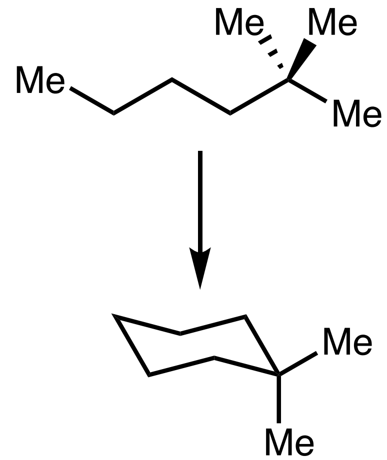
Brown, R. F.; Van Gulick, N. M. *J. Org. Chem.* **1956**, *21*, 1046

Conformational Effects of Fully Substituted Carbons

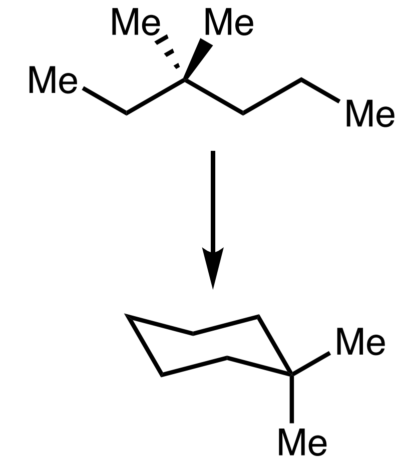
Allinger–Zalkow Thermodynamic Analysis



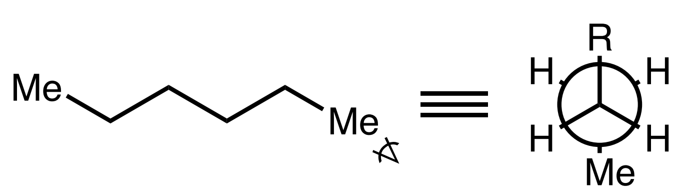
Δ H° = 10.53 kcal/mol
Δ S° = 9.66 cal/K
K_{eq} ~ 10^{-7}



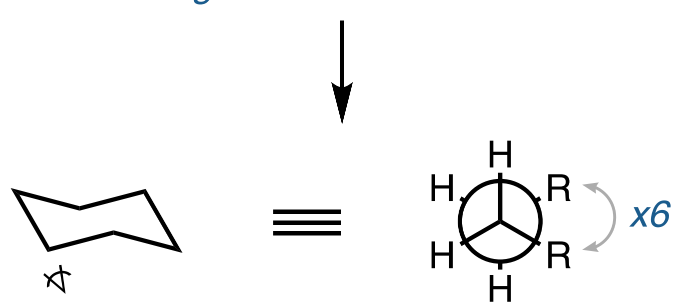
Δ H° = 10.45 kcal/mol
Δ S° = 15.39 cal/K
K_{eq} ~ 10^{-5}



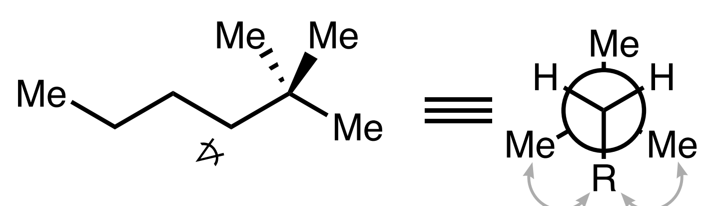
Δ H° = 9.35 kcal/mol
Δ S° = 13.85 cal/K
K_{eq} ~ 10^{-4}



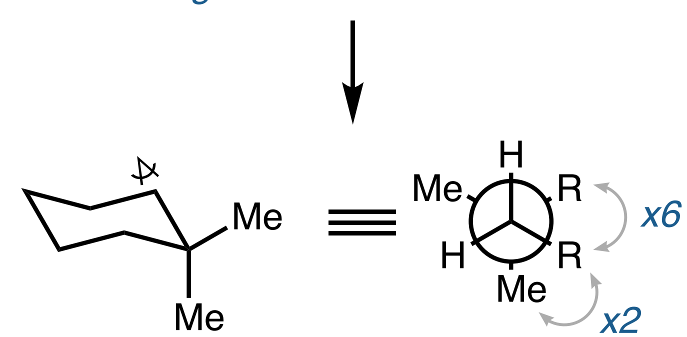
0 gauche interactions



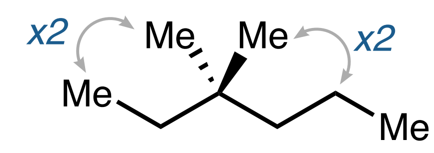
6 gauche interactions (Δ = 6)



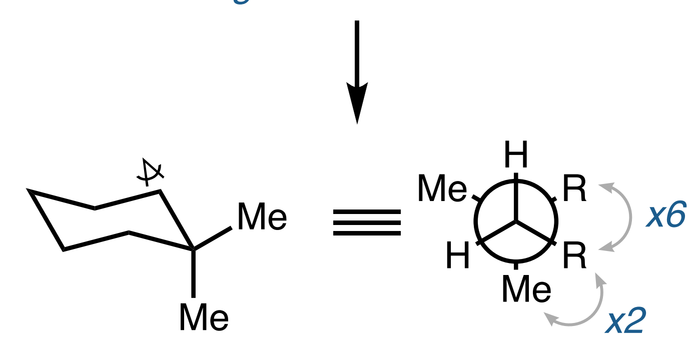
2 gauche interactions



8 gauche interactions (Δ = 6)



4 gauche interactions

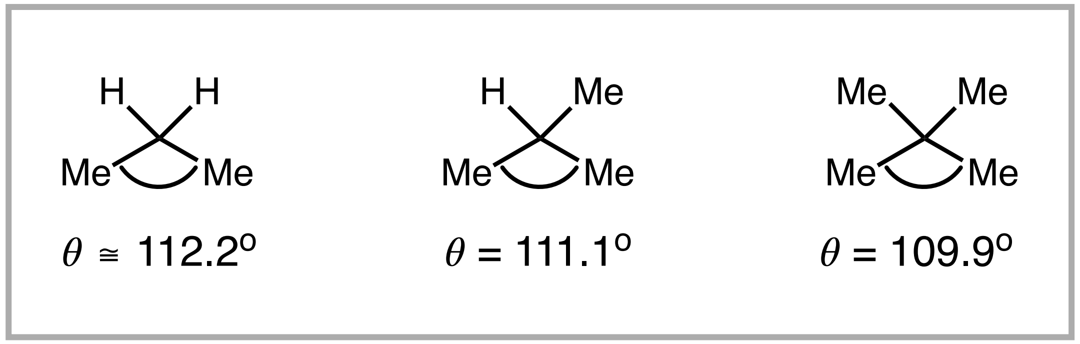


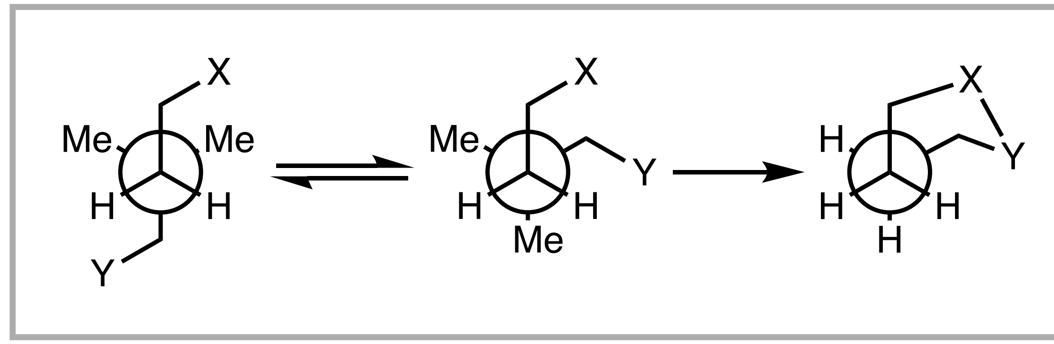
8 gauche interactions (Δ = 4)

Allinger, N. L.; Zalkow, V. *J. Org. Chem.* **1960**, *25*, 701

Conformational Effects of Fully Substituted Carbons

Deconvoluting the Thorpe–Ingold and Reactive Rotamer Hypotheses





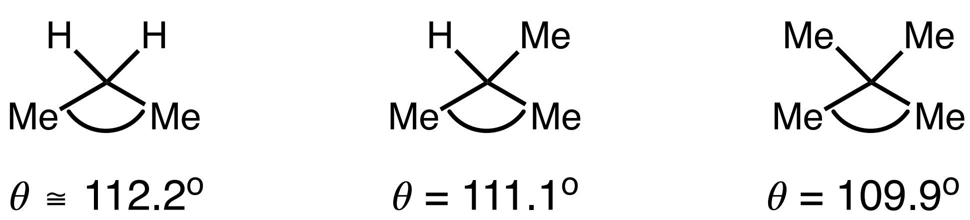
Thorpe–Ingold Valency Deviation

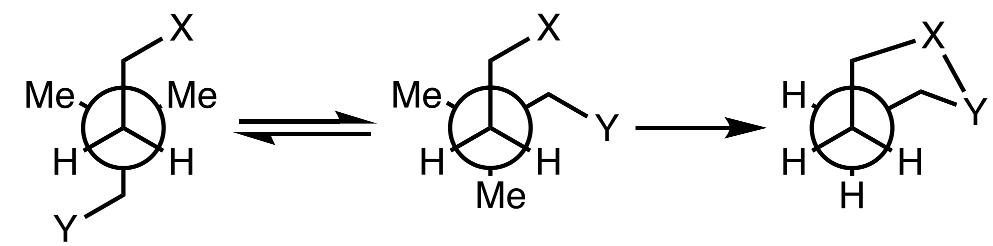
Reactive Rotamer Hypothesis

Is it possible to test each independently?

Conformational Effects of Fully Substituted Carbons

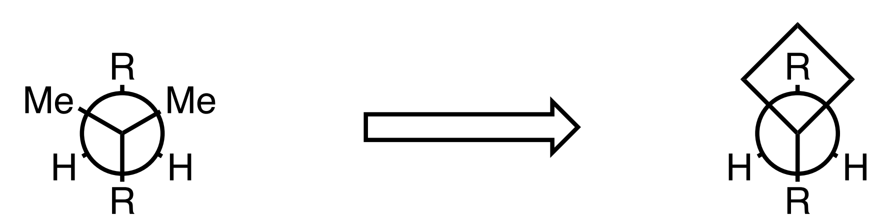
Deconvoluting the Thorpe–Ingold and Reactive Rotamer Hypotheses





Thorpe–Ingold Valency Deviation

Reactive Rotamer Hypothesis



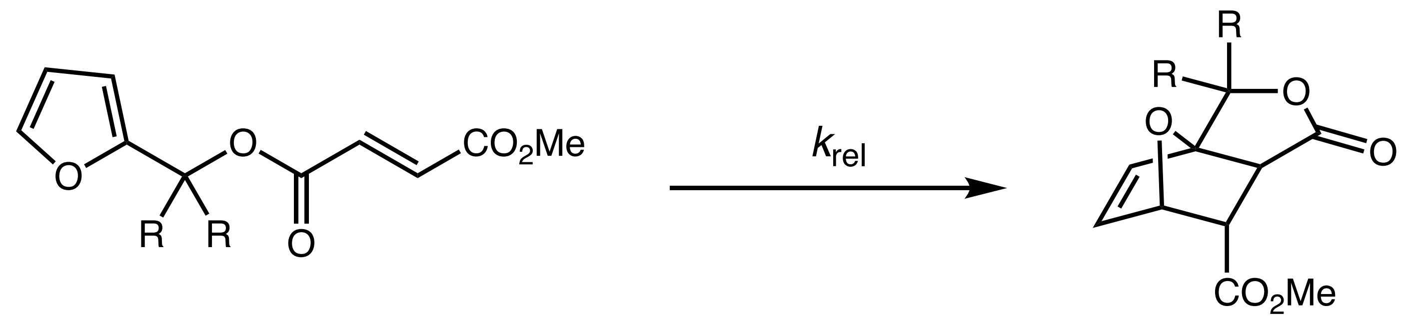
strain of cyclobutane ring forces internal angle to be larger than polymethylene

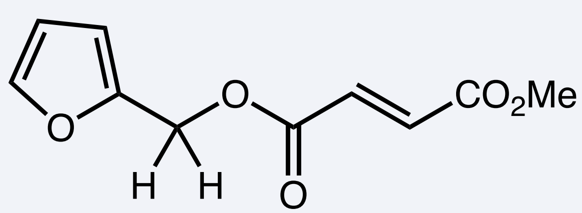
cyclobutane confers similar gouche effects as gem–dimethyl

Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224

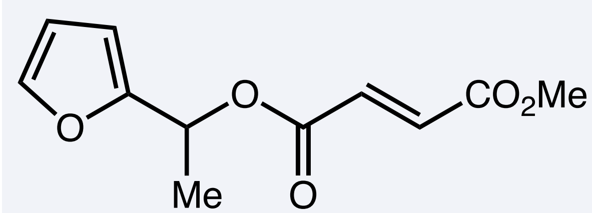
Conformational Effects of Fully Substituted Carbons

Deconvoluting the Thorpe–Ingold and Reactive Rotamer Hypotheses

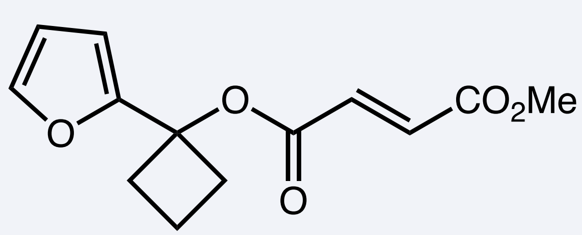




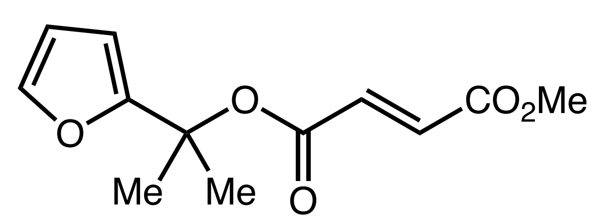
k_{rel} = 1
θ **~ 112.2°**



k_{rel} = 8.35
θ **~ 111.1**

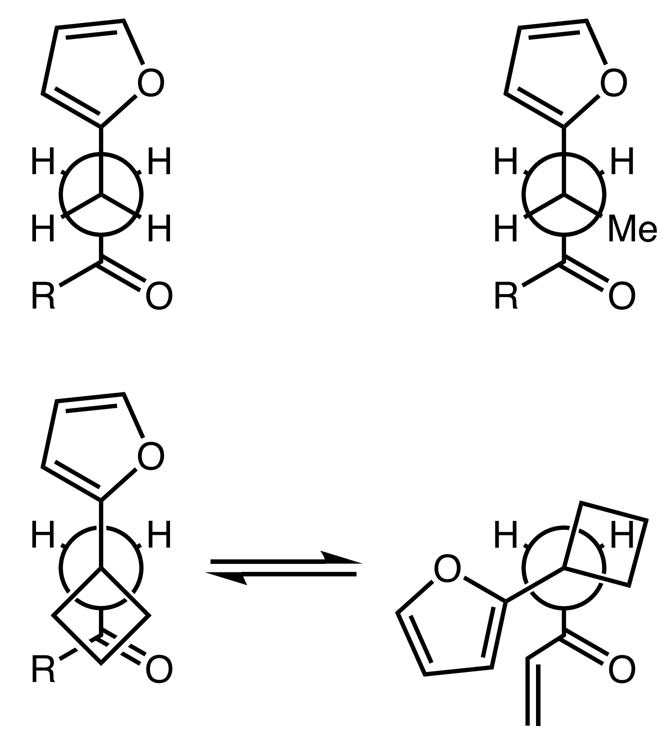


k_{rel} = 208
θ **~ 112.7°**



k_{rel} = 2123
θ ~ 109.5°

rate enhancement is due primarily to Reactive Rotamer Hypothesis

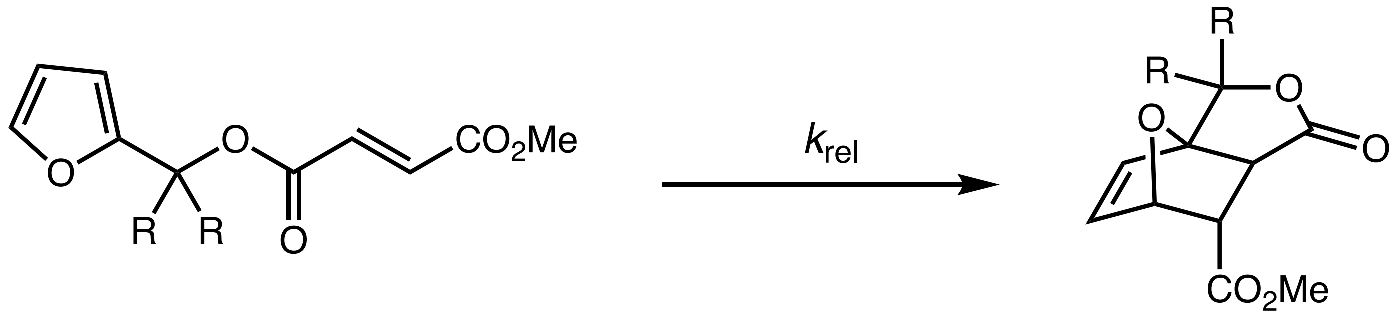


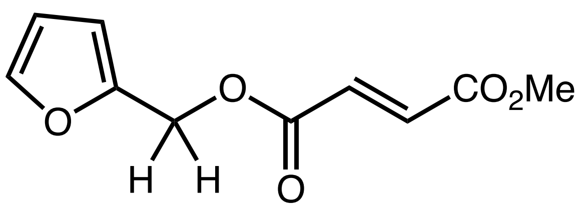
reactive conformer

Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224

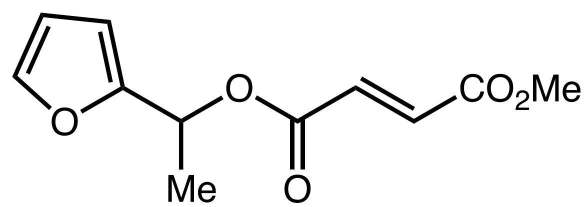
Conformational Effects of Fully Substituted Carbons

Deconvoluting the Thorpe–Ingold and Reactive Rotamer Hypotheses



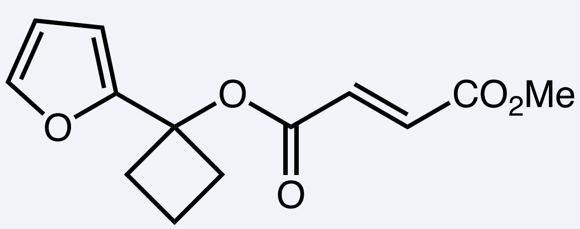


k_{rel} = 1
θ ~ 112.2°

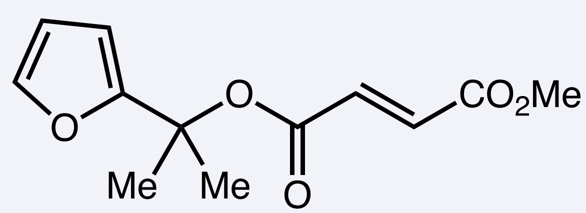


k_{rel} = 8.35
θ ~ 111.1

Rate enhancement for 5 member ring formation is due primarily to reactive rotamer effect



k_{rel} = 208
θ ~ 112.7°



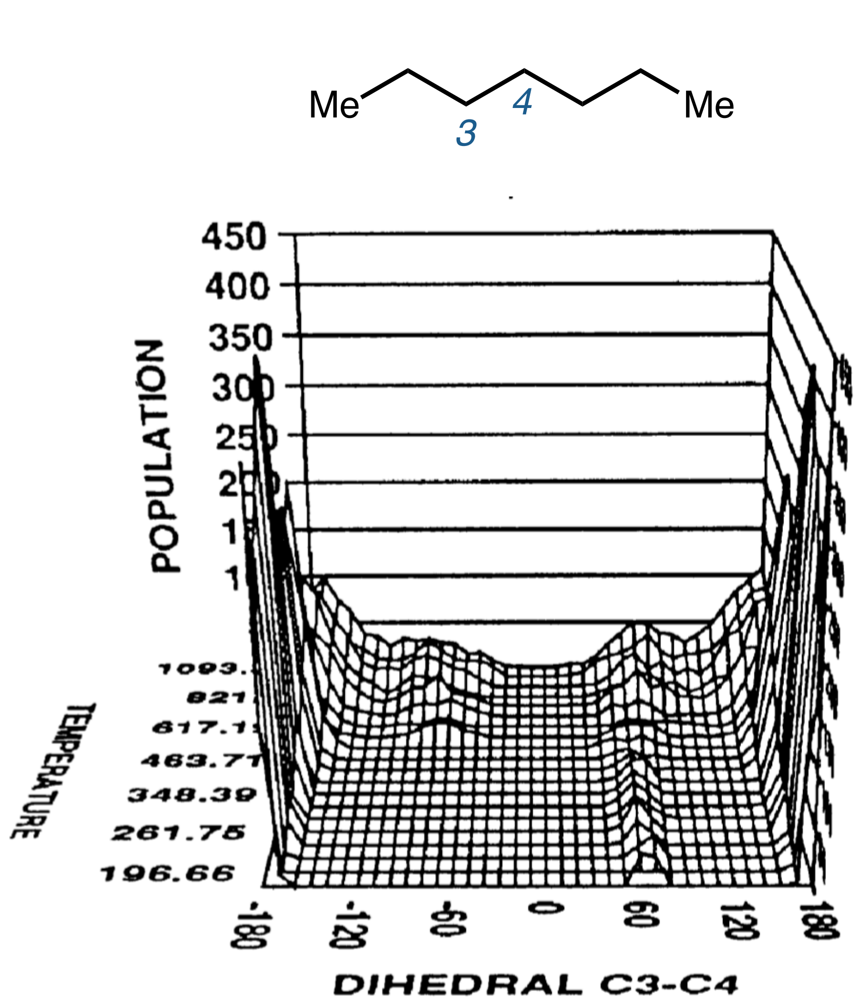
k_{rel} = 2123
θ ~ 109.5°

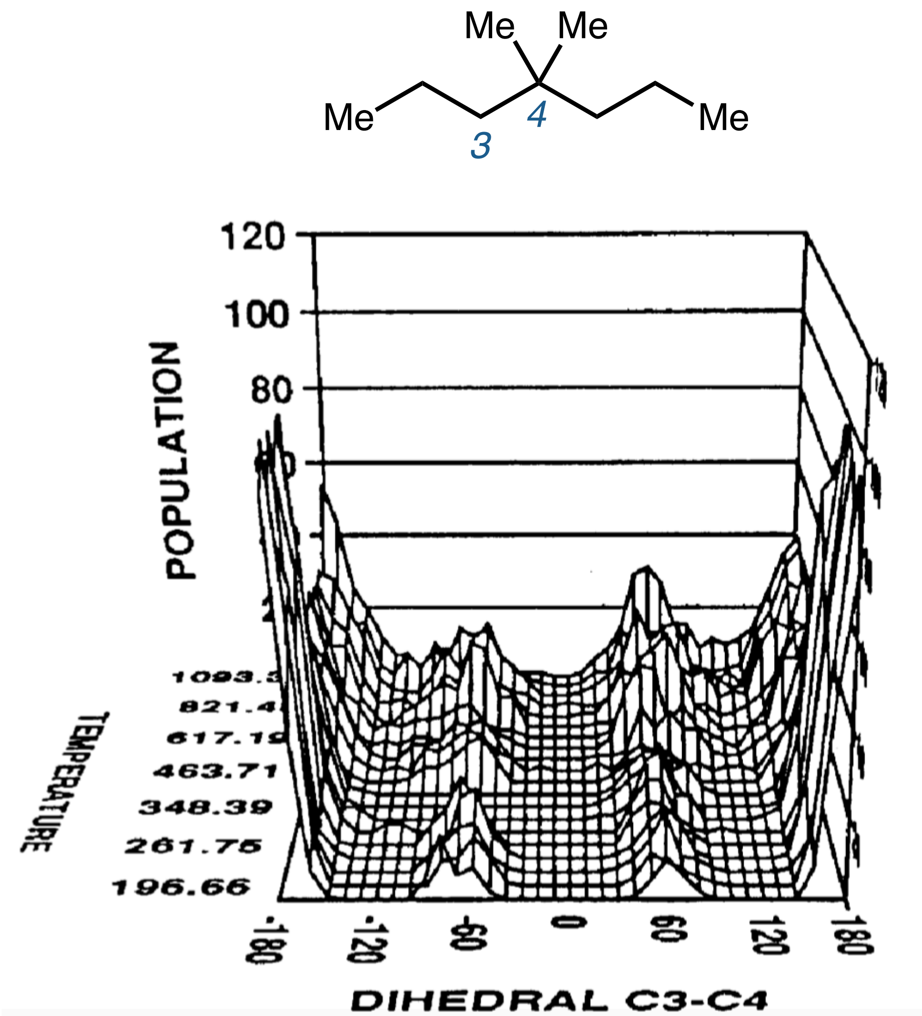
rate difference is said to be the result of cyclobutyl ring strain and not Thorpe–Ingold angle contraction

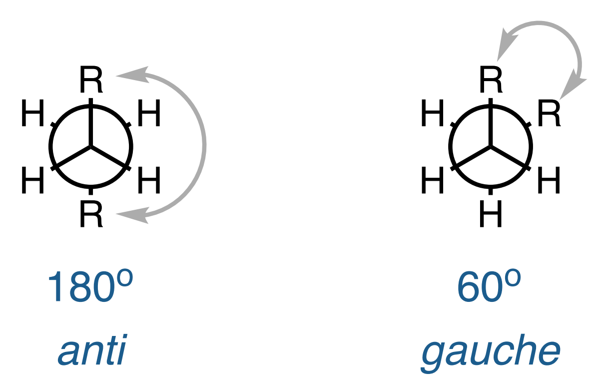
Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224

Conformational Effects of Fully Substituted Carbons

Deconvoluting the Thorpe–Ingold and Reactive Rotamer Hypotheses



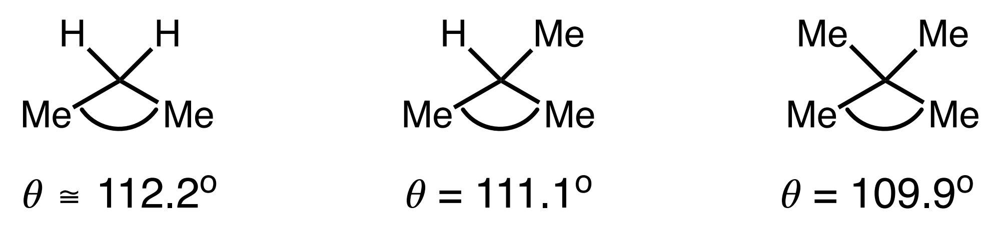


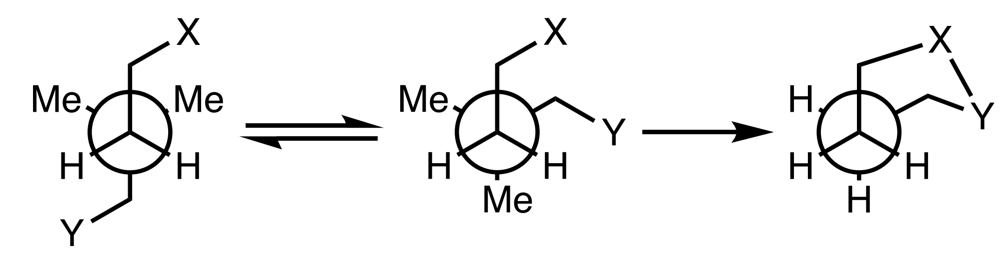


Wilson, S. R.; Cui, W.; Moskowitz, J. W.; Schmidt, K. E. *J. Comput. Chem.* **1991**, *12*, 342

Conformational Effects of Fully Substituted Carbons

General Consensus





Thorpe–Ingold Valency Deviation

Reactive Rotamer Hypothesis

Facilitated Transition Hypothesis

Stereopopulation Control

Relief of Ground–State Strain

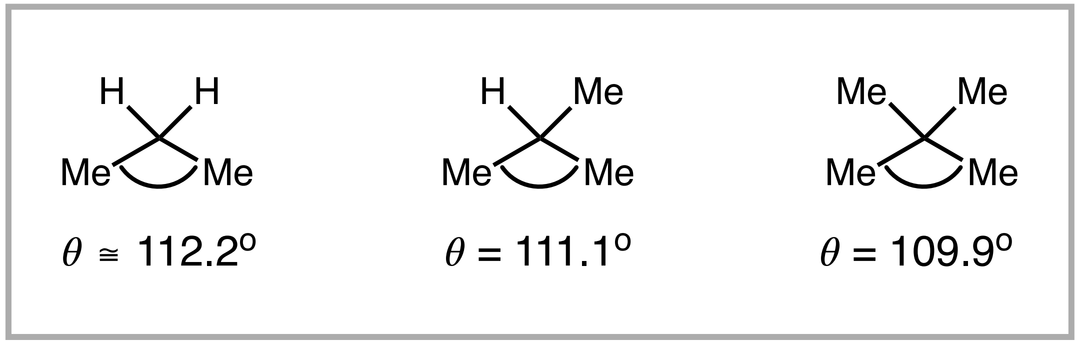
Origin of rate acceleration is believed to be largely system dependant

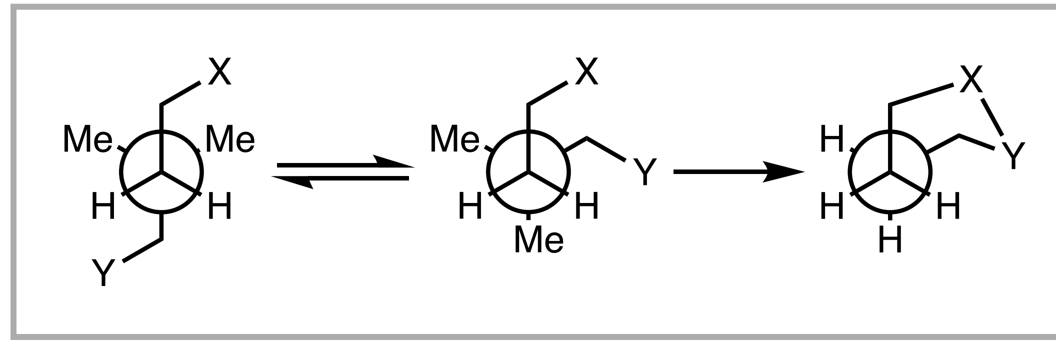
⇒ ***gem*–disubstituent effect**

Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735

Conformational Effects of Fully Substituted Carbons

General Consensus





Thorpe–Ingold Valency Deviation

Reactive Rotamer Hypothesis

Facilitated Transition Hypothesis

Stereopopulation Control

Relief of Ground–State Strain

Origin of rate acceleration is believed to be largely system dependant ⇒ **"Thorpe–Ingold Effect"**

Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735

Conformational Effects of Fully Substituted Carbons

Outline

- Introduction and Evolution of Theory
  - – Thorpe–Ingold Effect
  - – Reactive Rotamer Effect
- Application in Modern Catalysis
  - – Directing groups in C–H Activation
- Complex Molecule Synthesis
  - – (–)-Indolizidine 223AB and Alkaloid (–)-250B
  - – Zaragozic acid C
  - – tricholomalide A and (–)-guanacastepene
- Drug Discovery

Conformational Effects of Fully Substituted Carbons

Outline

- Introduction and Evolution of Theory
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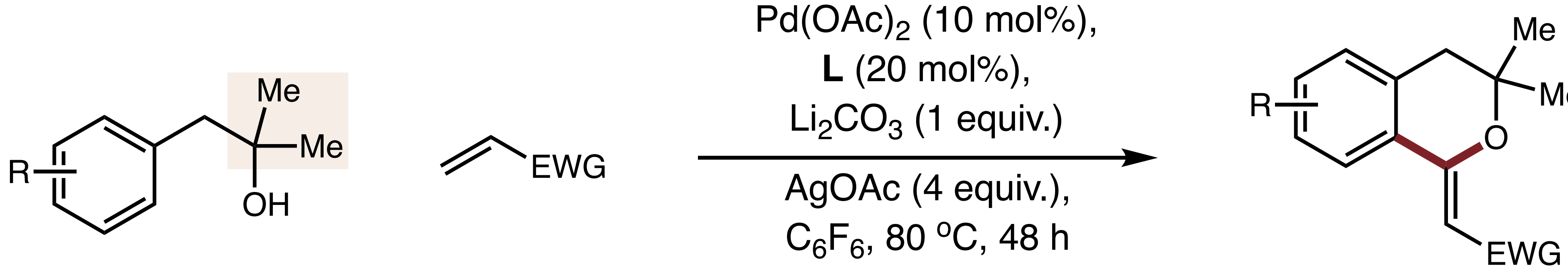
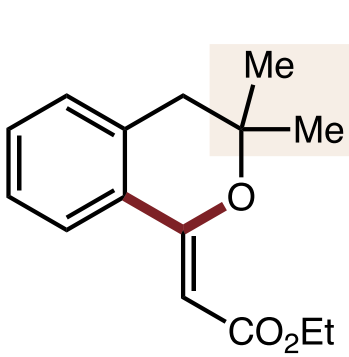
- Drug Discovery

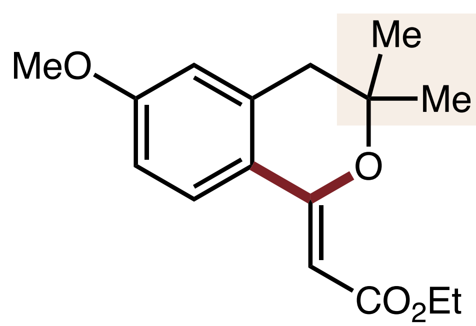
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in C–H Functionalization

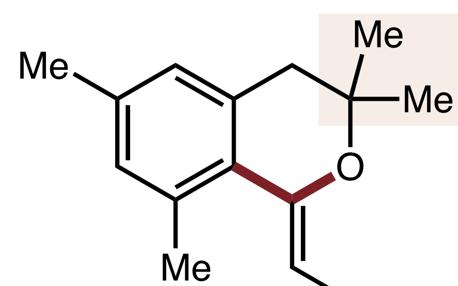




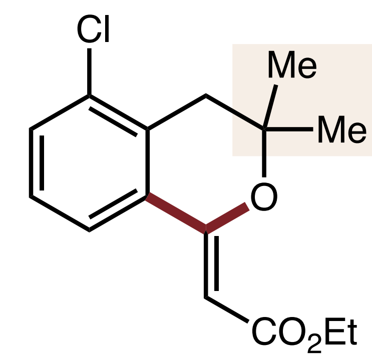
67% yield



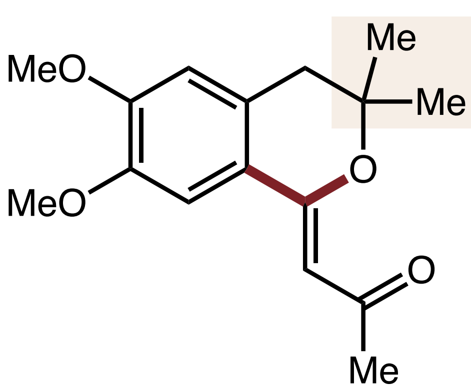
92% yield



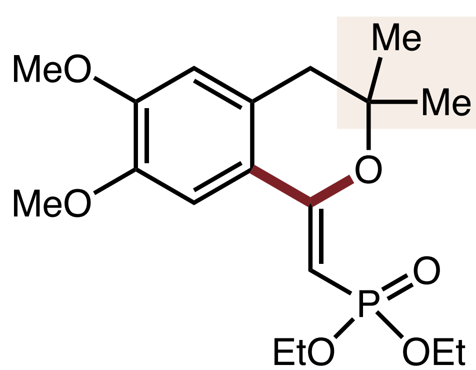
80% yield



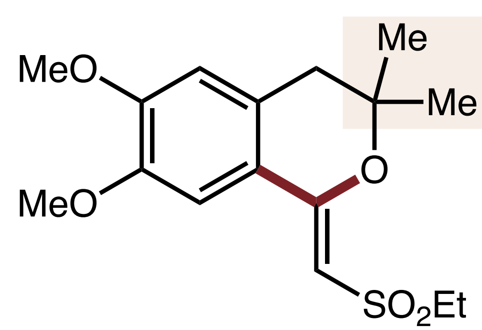
59% yield



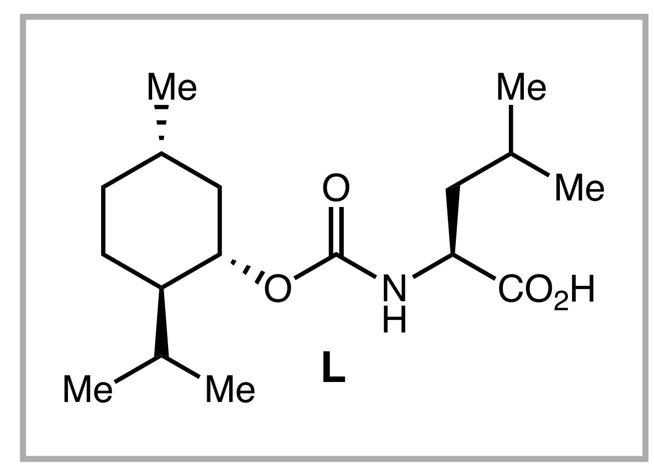
53% yield



89% yield



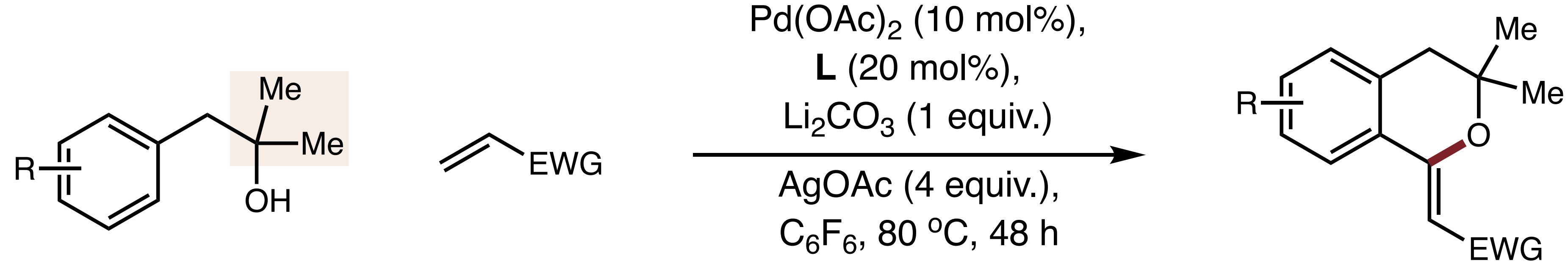
66% yield

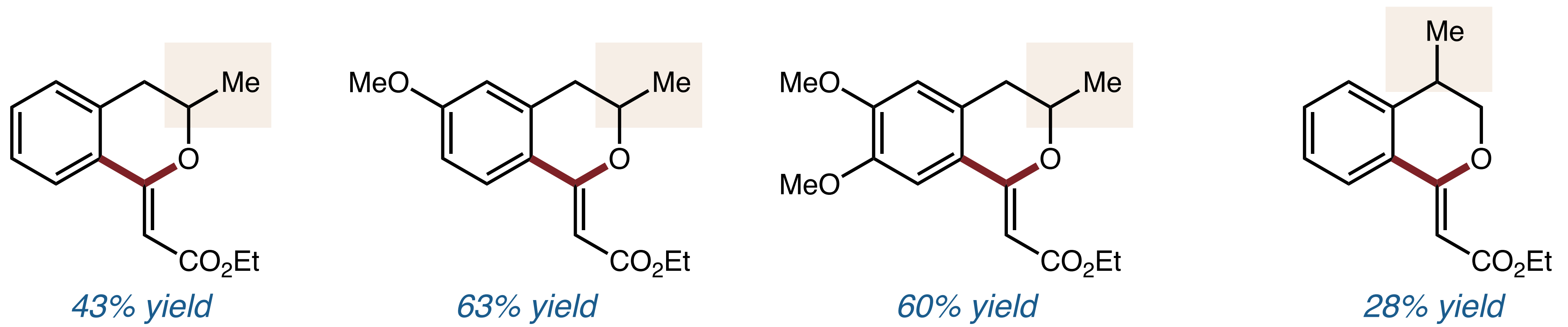


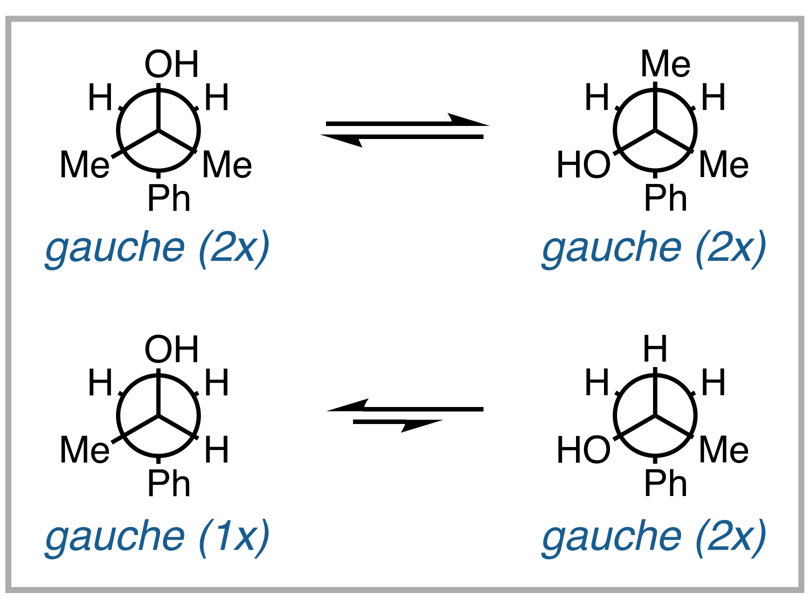
Lu, Y.; Wang, D.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916

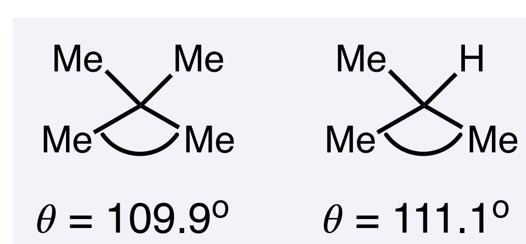
Conformational Effects of Fully Substituted Carbons

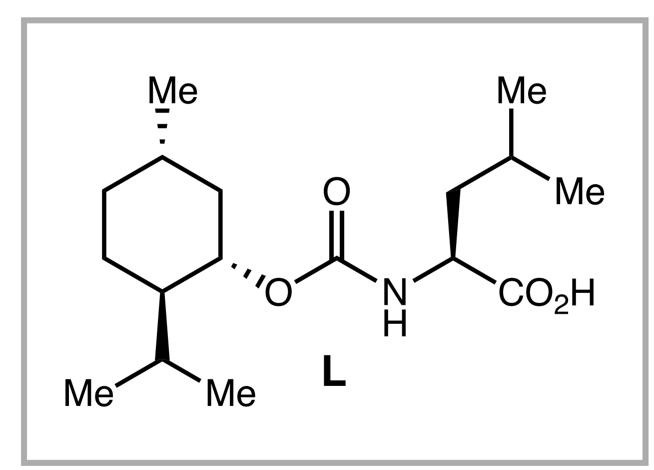
"Thorpe–Ingold" Effect in C–H Functionalization







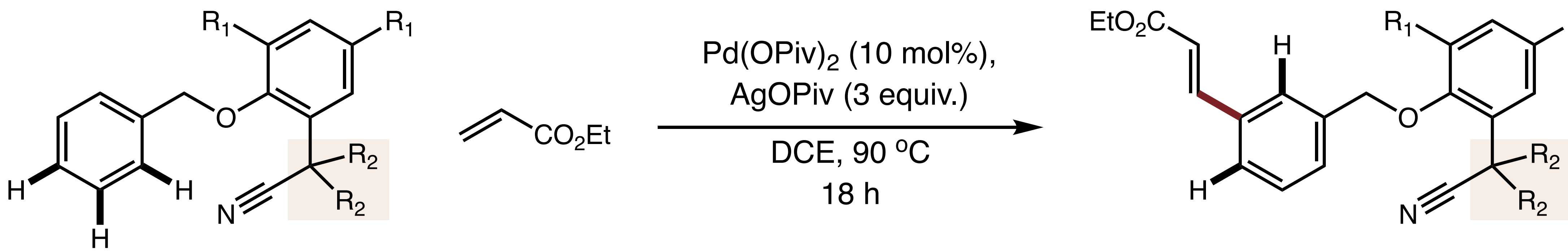


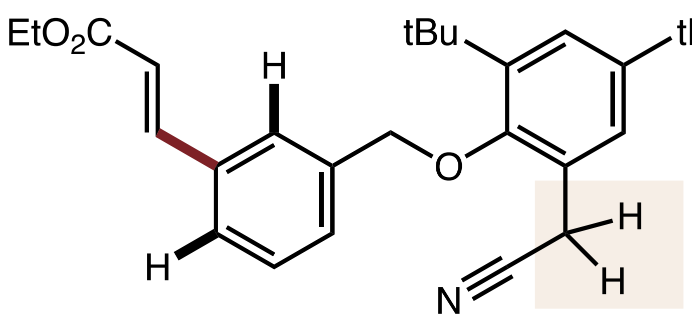


Lu, Y.; Wang, D.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916

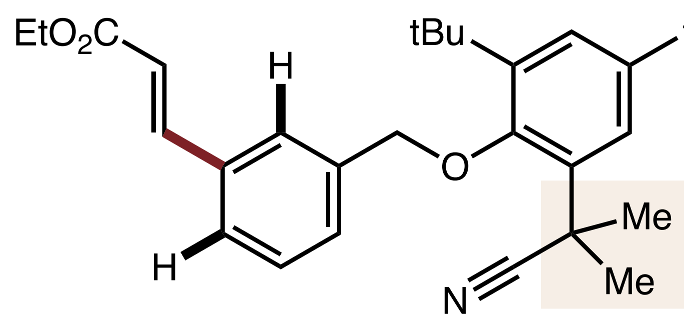
Conformational Effects of Fully Substituted Carbons

“Thorpe–Ingold” Effect in C–H Functionalization

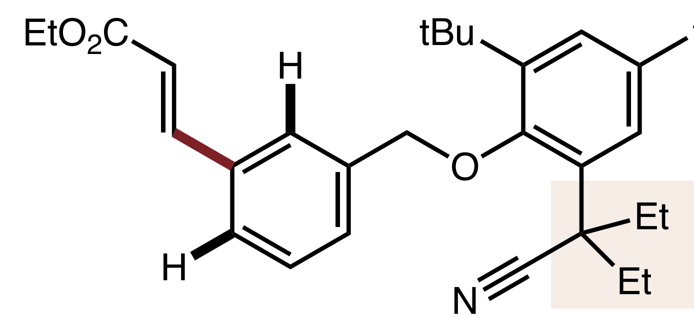




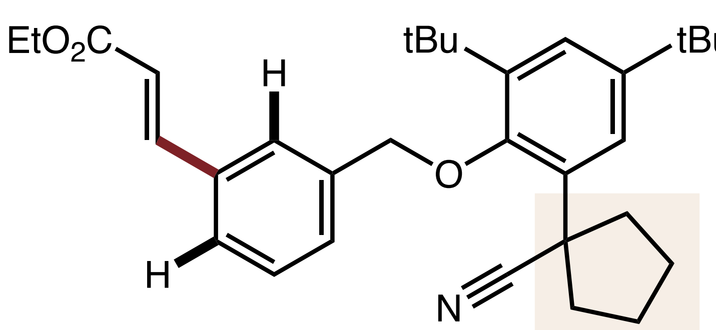
15% yield
*(**meta**:para:ortho) = (**59**:33:8)*



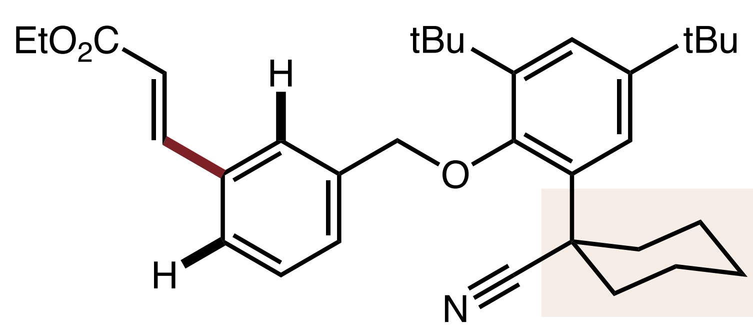
60% yield
*(**meta**:para:ortho) = (**91**:7:2)*



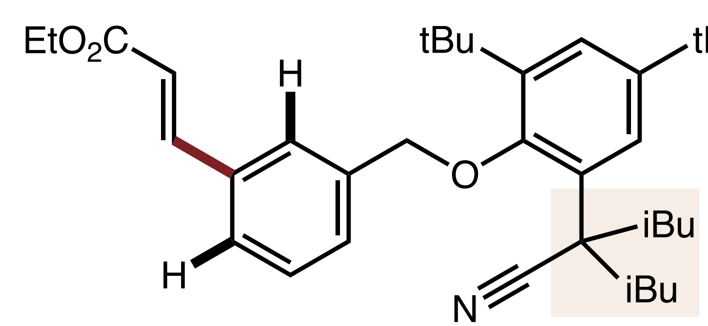
52% yield
*(**meta**:para:ortho) = (**93**:6:1)*



50% yield
*(**meta**:para:ortho) = (**88**:7:5)*



51% yield
*(**meta**:para:ortho) = (**91**:5:4)*

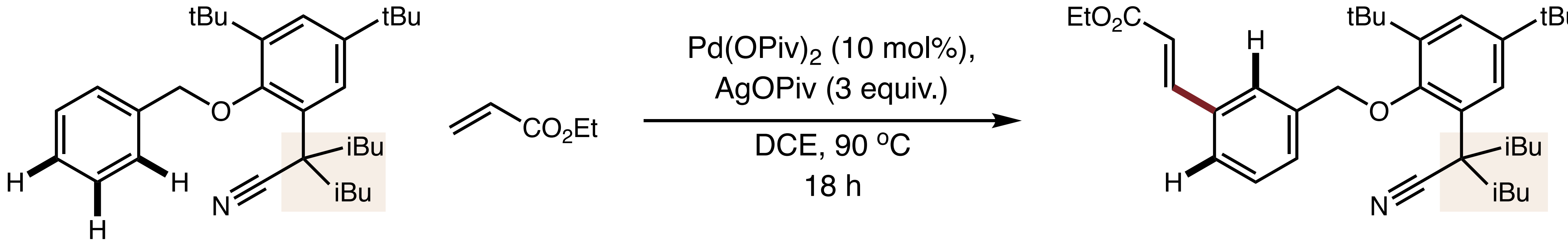


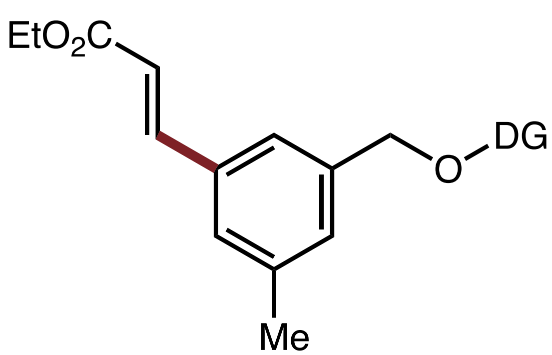
63% yield
*(**meta**:para:ortho) = (**95**:4:1)*

Leow, D.; Li, G.; Mei, T.-S.; Yu, J. -Q. *Nature* **2012**, *486*, 518

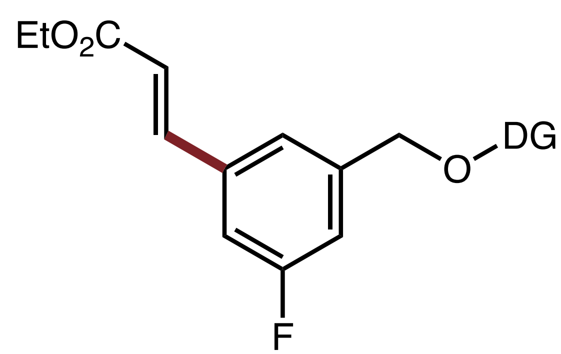
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in C–H Functionalization

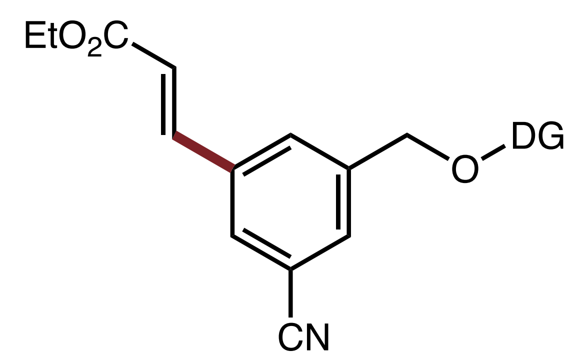




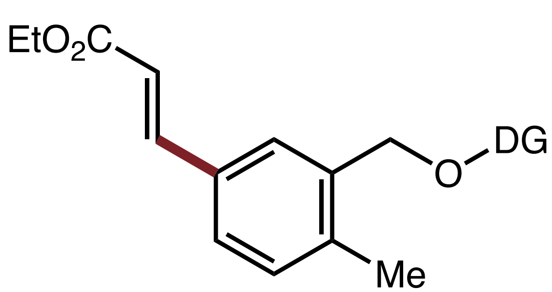
86% yield
*(**meta**:other) = (**94**:6)*



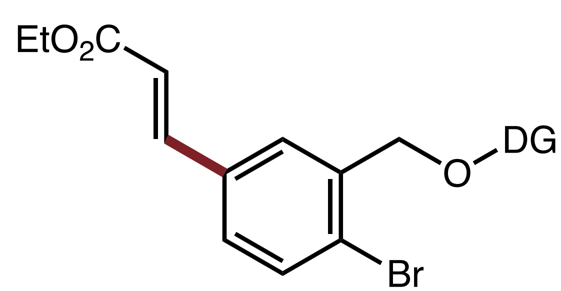
52% yield
*(**meta**:other) = (**75**:25)*



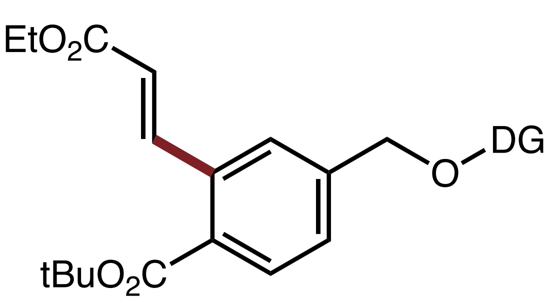
54% yield
*(**meta**:other) = (**98**:2)*



89% yield
*(**meta**:other) = (**91**:9)*



77% yield
*(**meta**:other) = (**90**:10)*

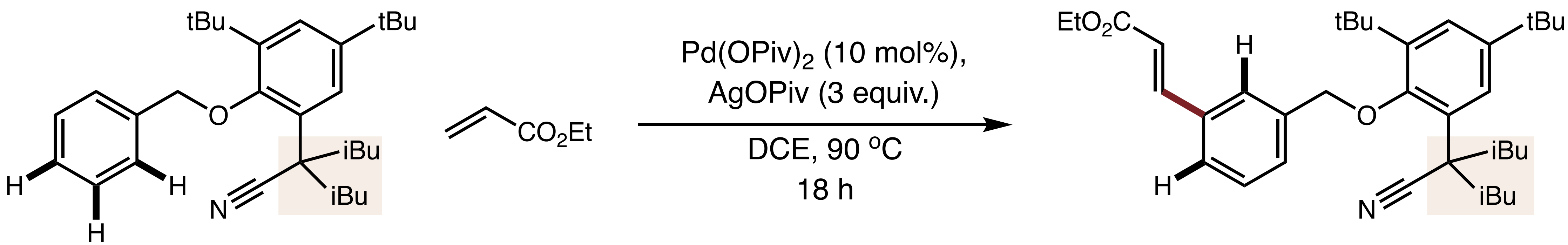


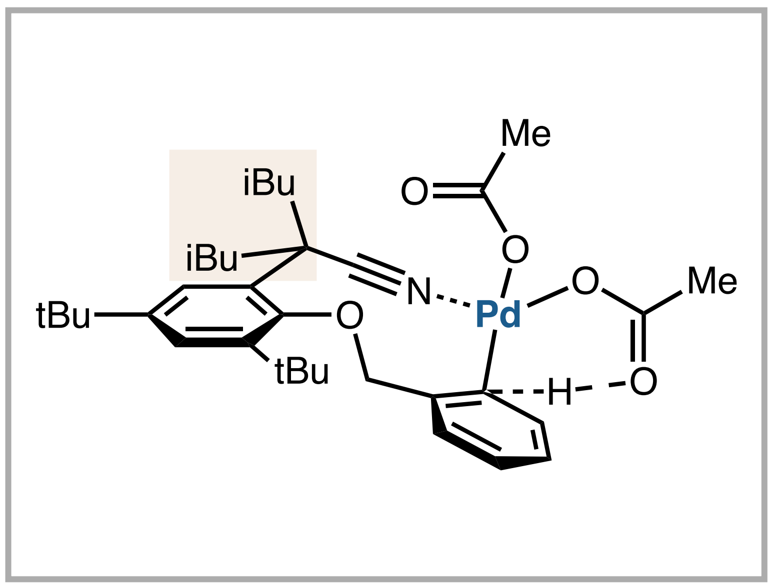
42% yield
*(**meta**:other) = (**98**:2)*

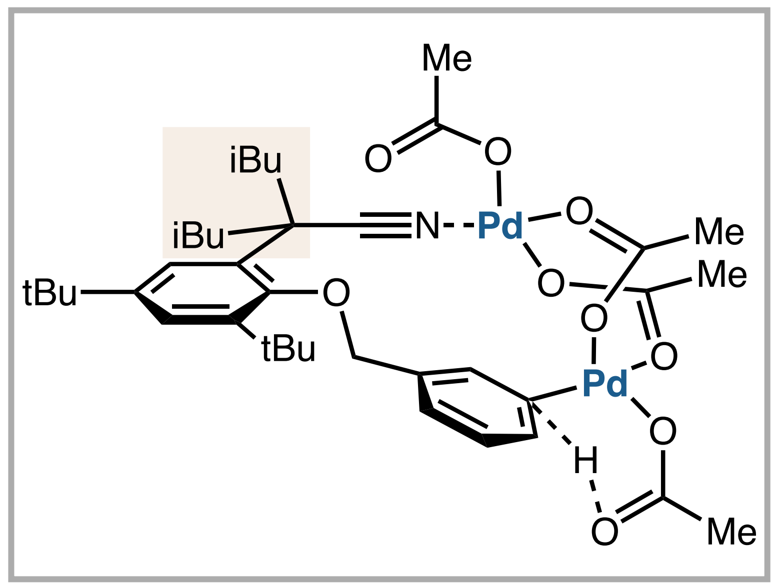
Leow, D.; Li, G.; Mei, T.-S.; Yu, J. -Q. *Nature* **2012**, *486*, 518

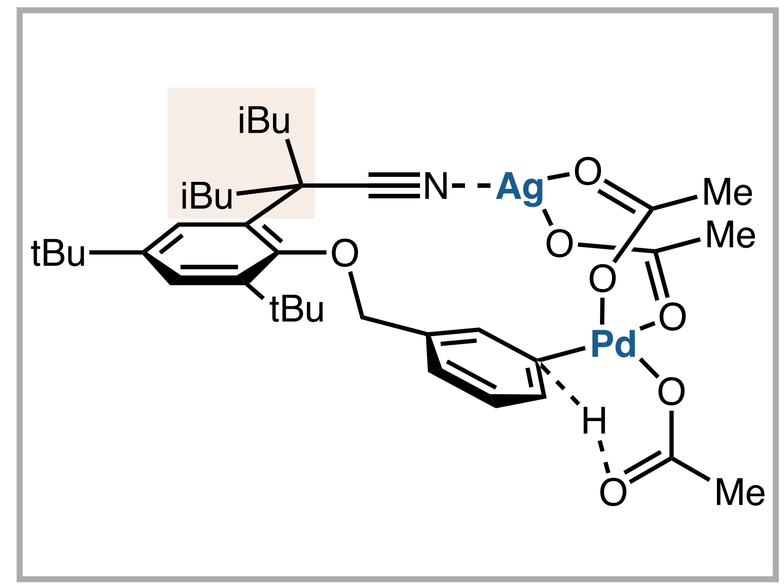
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in C–H Functionalization









Monomeric Pd T.S. is selective for ortho–functionalization

Dimeric Pd T.S. is selective for meta–functionalization

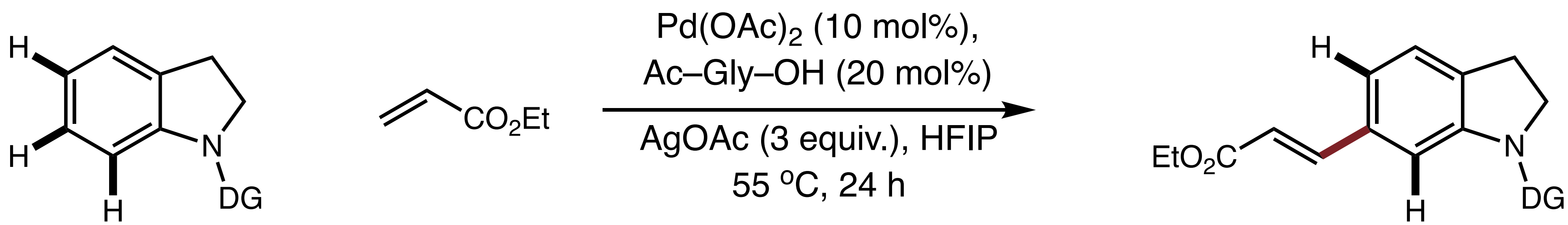
Pd–Ag T.S. also selective for meta–functionalization

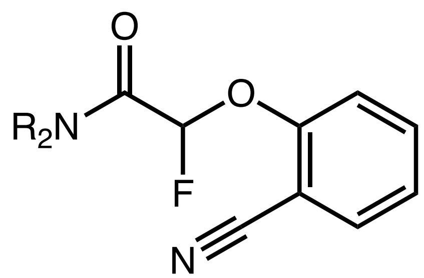
gem–diisobutyl groups likely play a role in stabilizing the larger ring T.S

Yang, Y. -F.; Cheng, G. -J.; Liu, P.; Leow, D.; Sun, T. -Y.; Chen, P.; Zhang, X.; Yu, J. -Q.; Wu, Y. -D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344

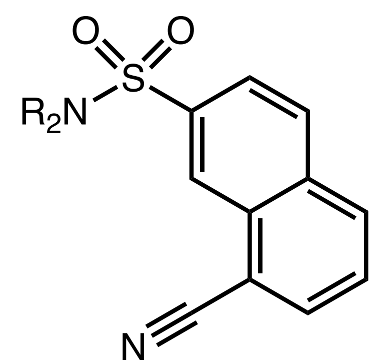
Conformational Effects of Fully Substituted Carbons

“Thorpe–Ingold” Effect in C–H Functionalization

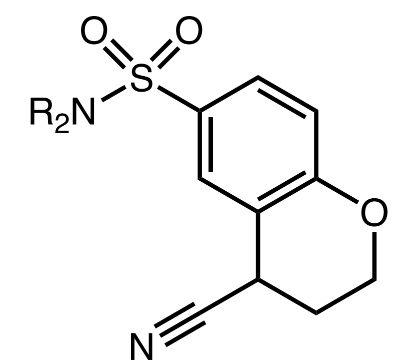




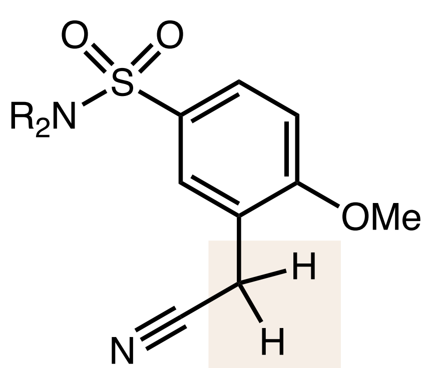
20% yield
*(**meta**:other) = (**1**:1.6)*



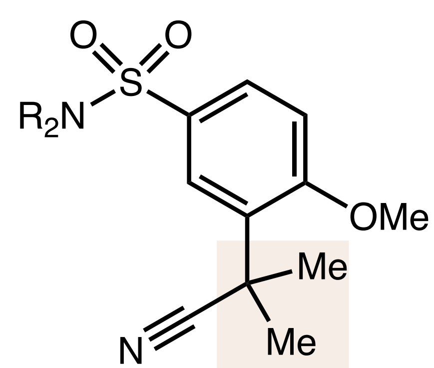
80% yield
*(**meta**:para:ortho) = (**1**:1.4:1)*



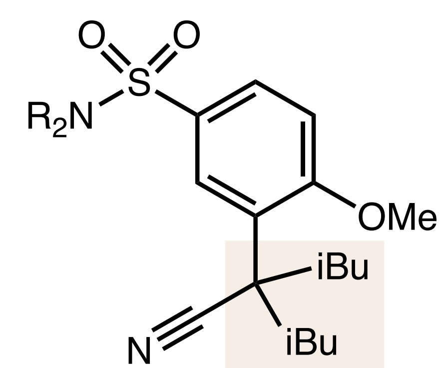
82% yield
*(**meta**:para:ortho) = (**1**:4:1)*



86% yield
*(**meta**:para:ortho) = (**1**:3.1:3)*



81% yield
*(**meta**:para:ortho) = (**13**:3.2:1)*

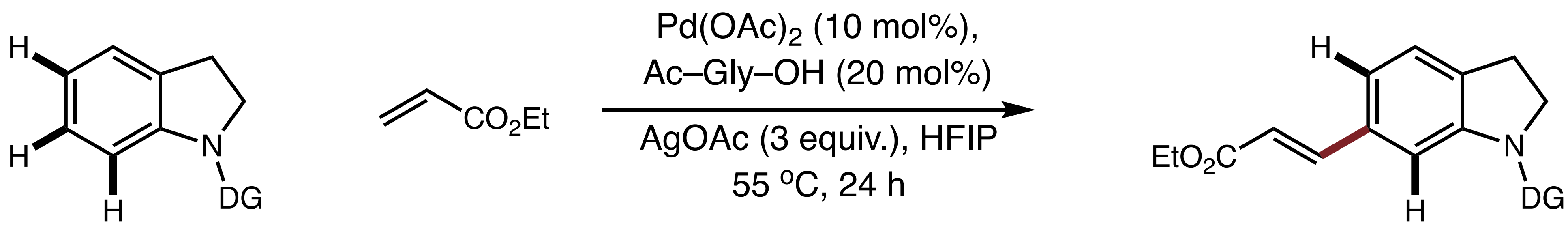


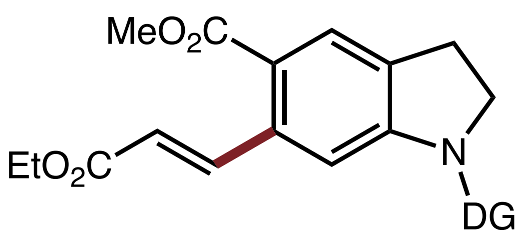
78% yield
(**meta**:other) = (**>20**:1)

Yang, G.; Lindovsa, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R. -Y.; Movassaghi, M.; Yu, J. -Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807

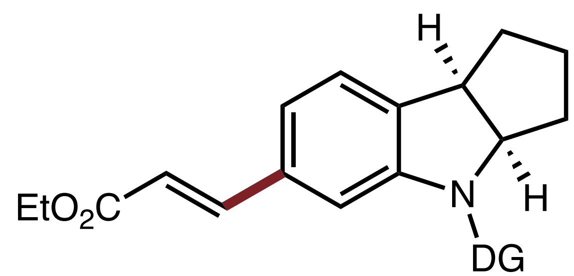
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in C–H Functionalization

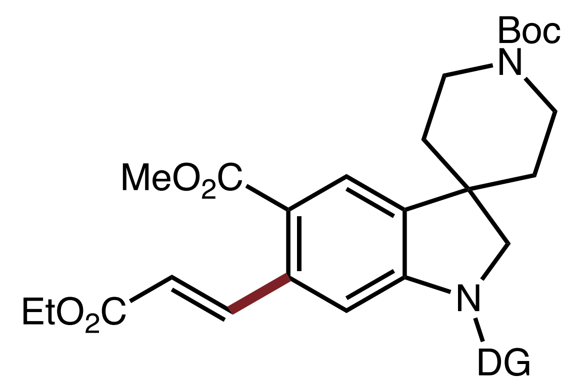




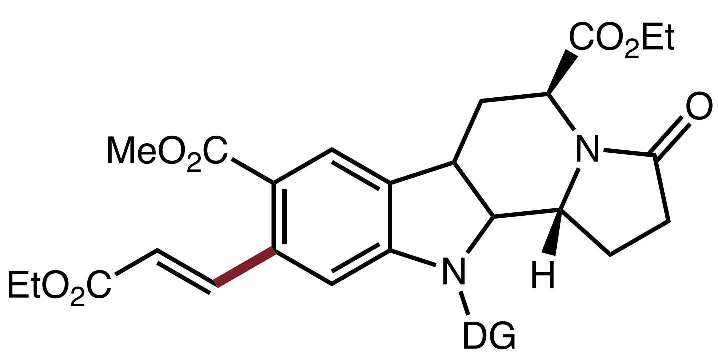
76% yield
*(**meta**:other) = (**>20**:1)*



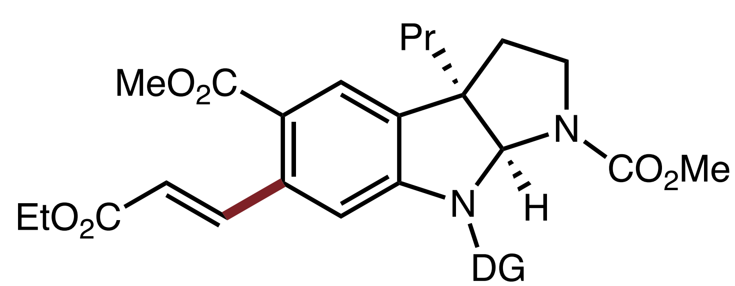
60% yield
*(**meta**:other) = (**>20**:1)*



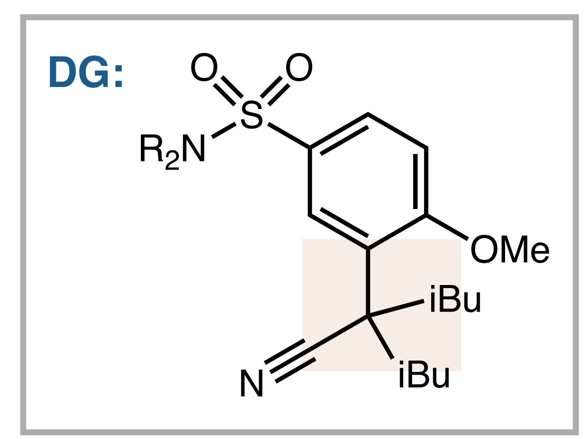
82% yield
*(**meta**:other) = (**>20**:1)*



49% yield
*(**meta**:other) = (**16**:1)*



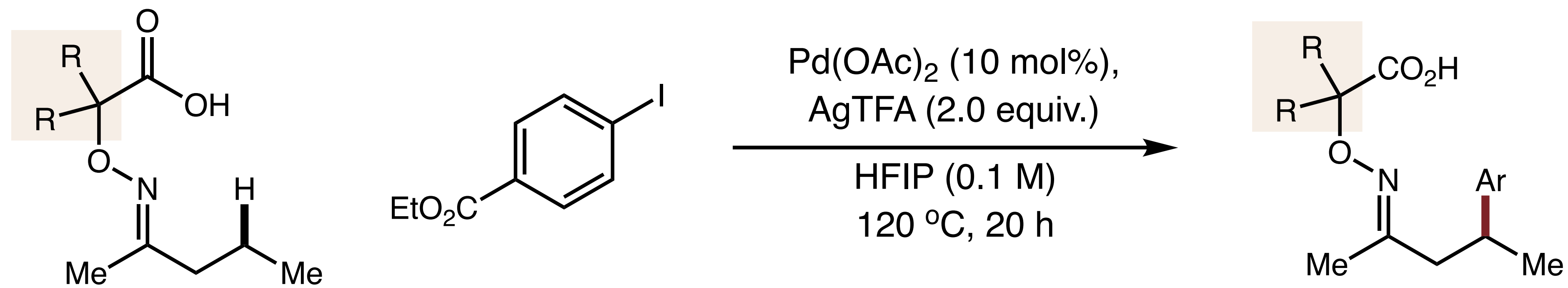
75% yield
*(**meta**:other) = (**>20**:1)*

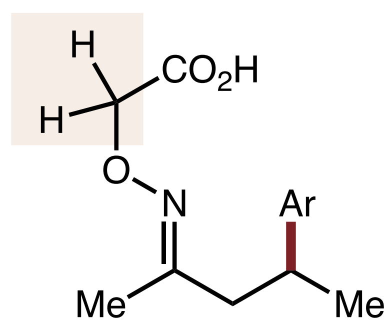


Yang, G.; Lindovsa, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R. -Y.; Movassaghi, M.; Yu, J. -Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807

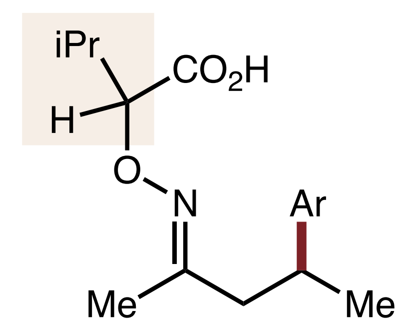
Conformational Effects of Fully Substituted Carbons

“Thorpe–Ingold” Effect in C–H Functionalization

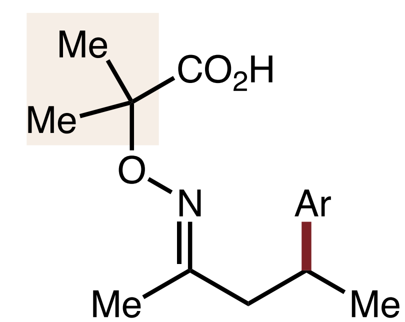




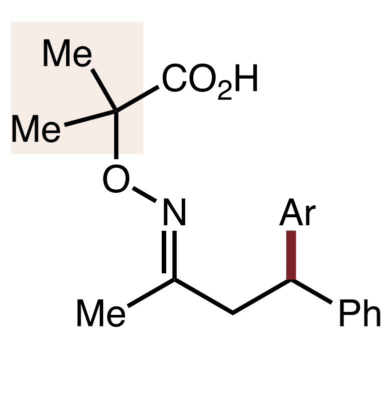
10% yield



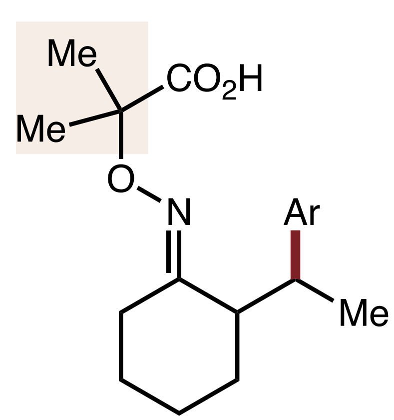
8% yield



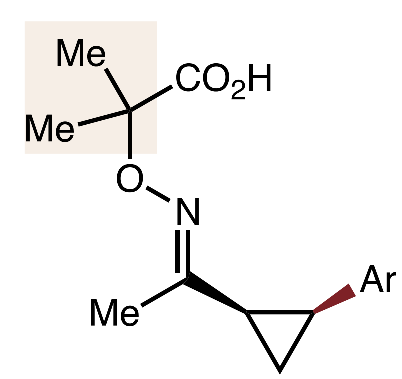
80% yield



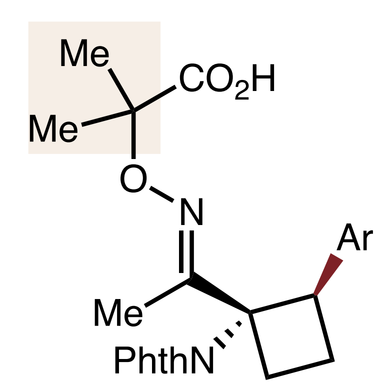
52% yield



68% yield



45% yield

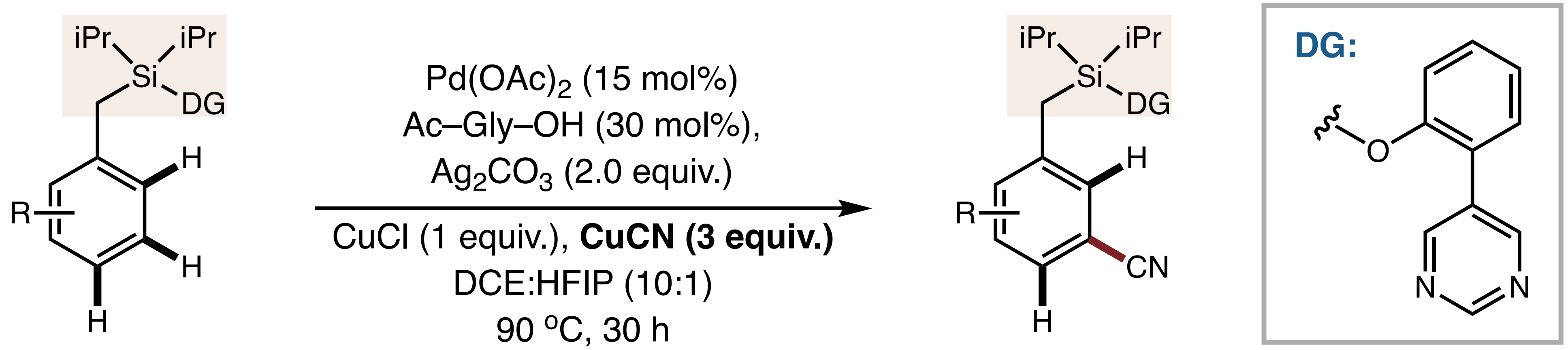


80% yield (1:1.6 mono:di)

Zhu, Ru, -Y.; Liu, L. -Y.; Park, H. S.; Hong. K.; Wu, Y.; Senayake, C. H.; Yu, J. -Q. *J. Am. Chem. Soc.* **2017**, *139*, 16080

Conformational Effects of Fully Substituted Carbons

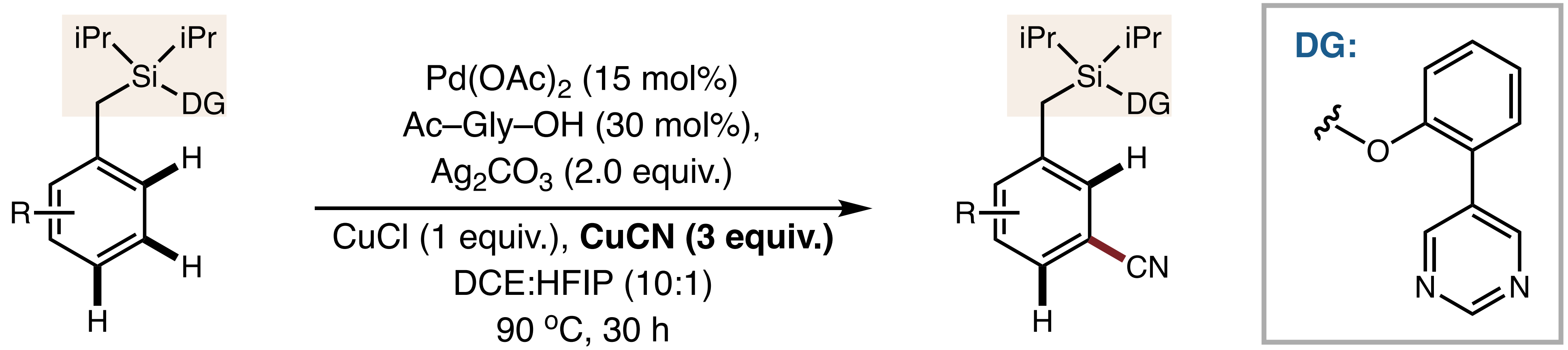
"Thorpe–Ingold" Effect in C–H Functionalization

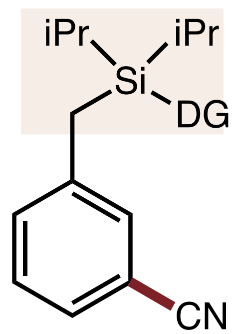


Bag, S.; Jayarajan, R.; Dutta, U.; Chowdhury, R.; Mondal, R.; Maiti, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 12538

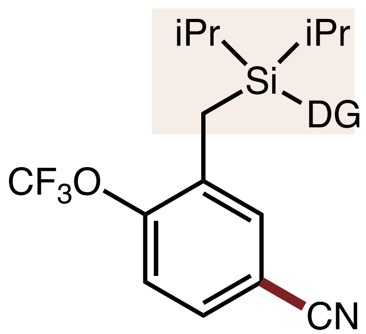
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in C–H Functionalization

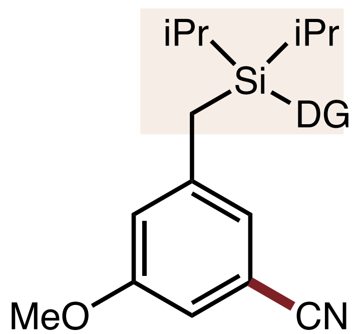




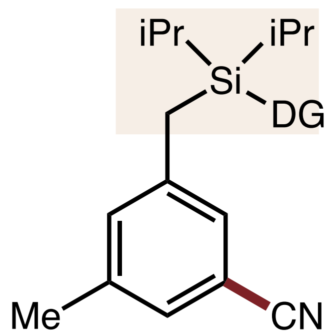
78% yield
*(**meta**:other) = (**20**:1)*



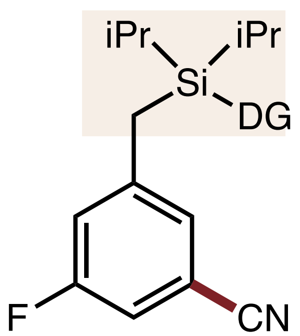
71% yield
*(**meta**:other) = (**16**:1)*



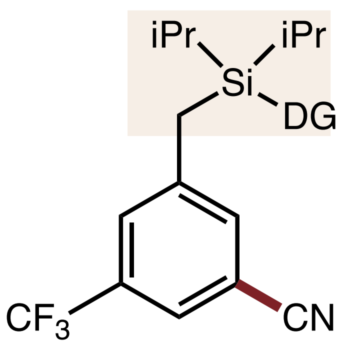
74% yield
*(**meta**:other) = (**18**:1)*



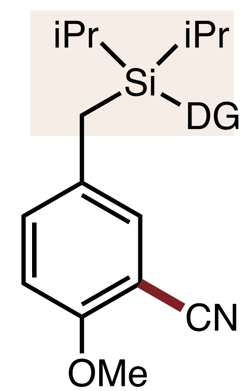
75% yield
*(**meta**:other) = (**20**:1)*



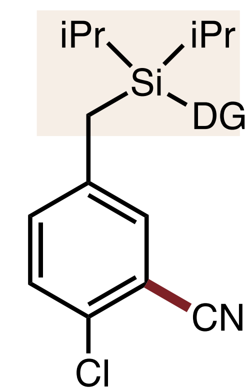
63% yield
*(**meta**:other) = (**>20**:1)*



65% yield
*(**meta**:other) = (**20**:1)*



81% yield
*(**meta**:other) = (**20**:1)*

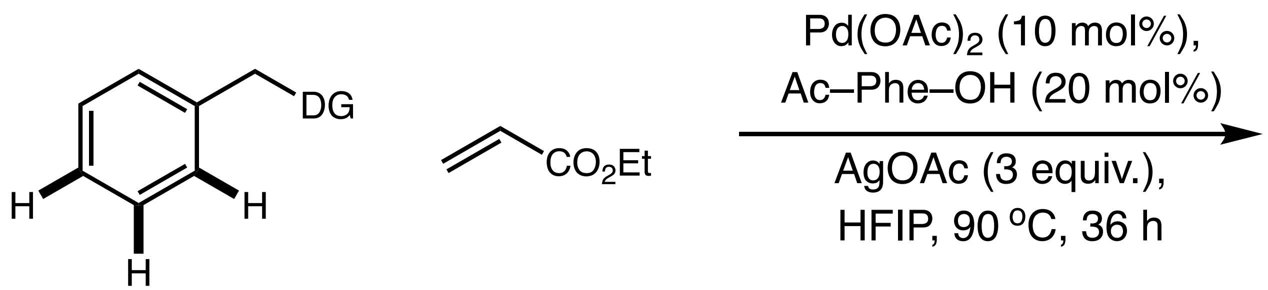


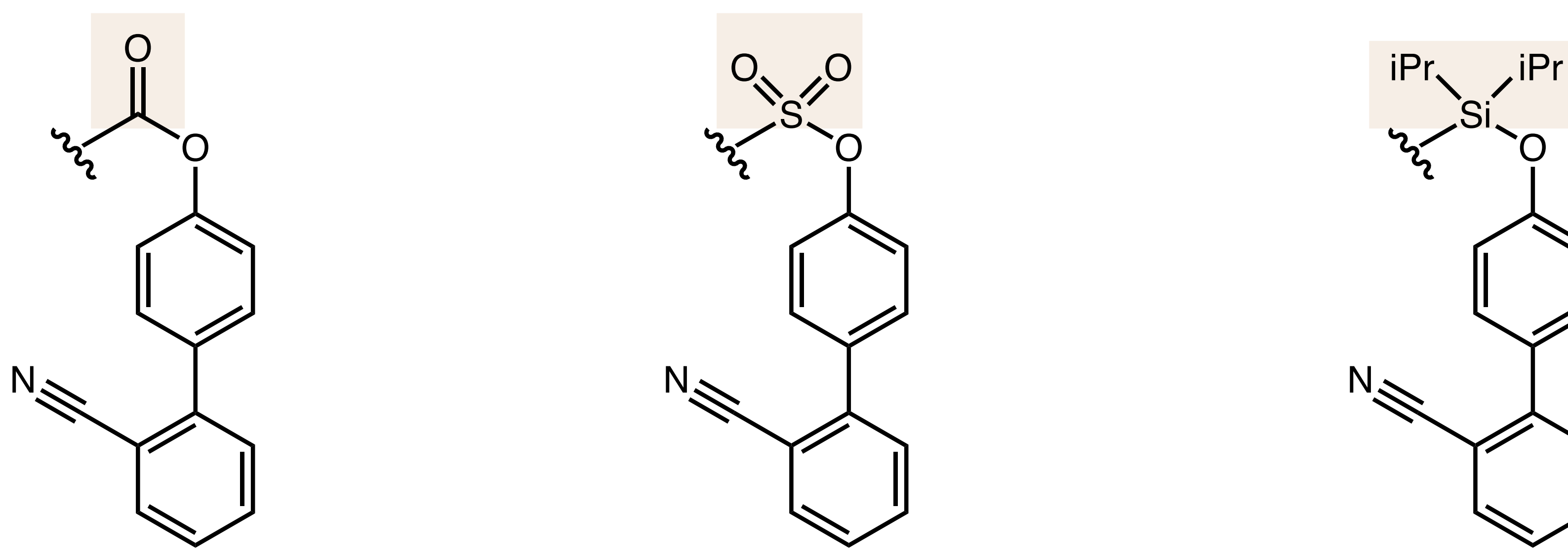
71% yield
*(**meta**:other) = (**>20**:1)*

Bag, S.; Jayarajan, R.; Dutta, U.; Chowdhury, R.; Mondal, R.; Maiti, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 12538

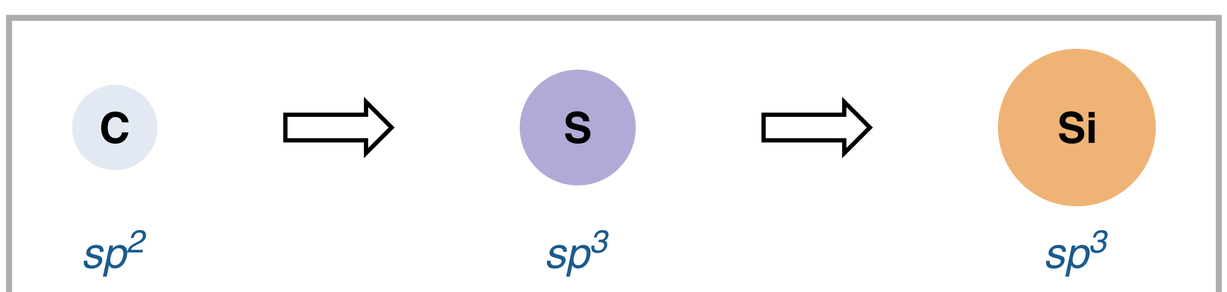
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in C–H Functionalization





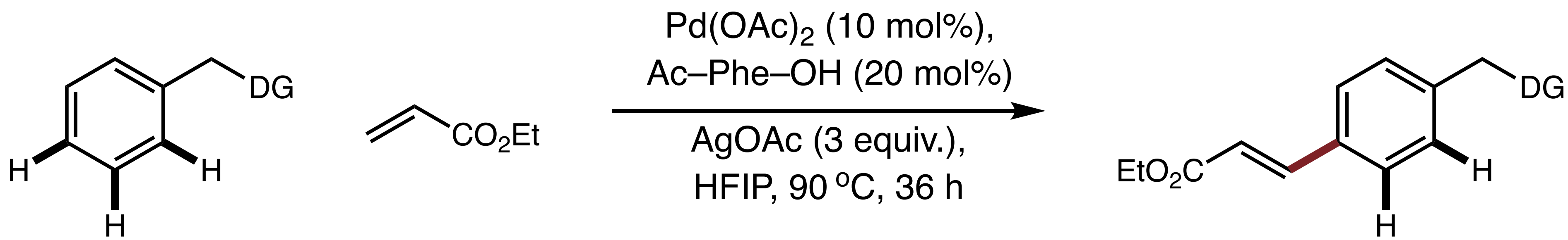
43% yield	*55% yield*	*82% yield*
multiple products	*(**para**:other) = (**1**:1)*	*(**para**:other) = (**20**:1)*

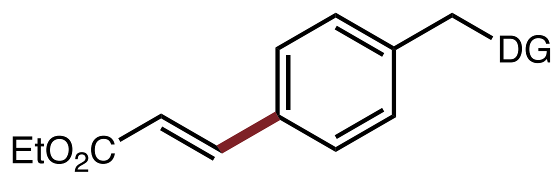


Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.;
Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D.; *J. Am. Chem. Soc.* **2015**, *137*, 11888

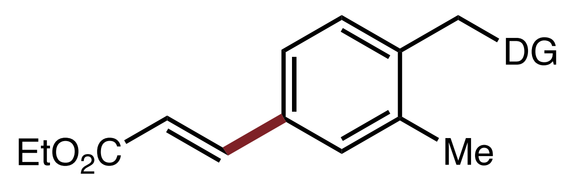
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in C–H Functionalization

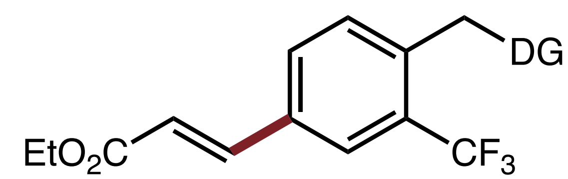




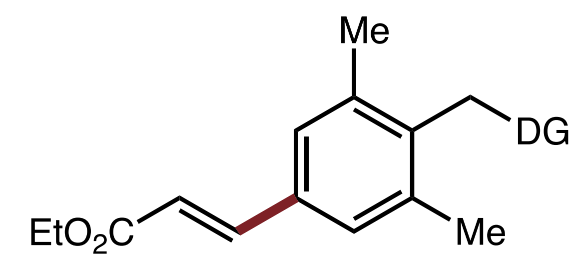
71% yield
*(**para**:other) = (**8**:1)*



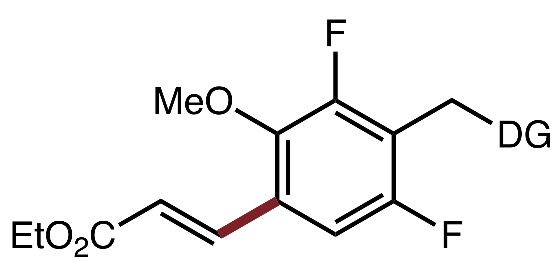
96% yield
*(**para**:other) = (**7**:1)*



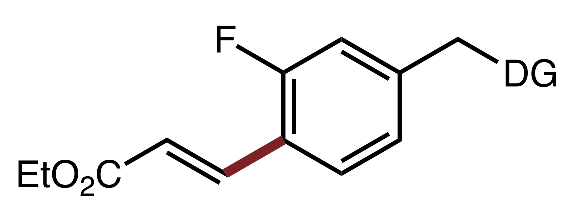
55% yield
*(**para**:other) = (**6**:1)*



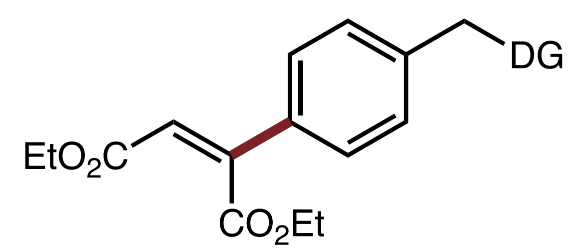
63% yield
*(**para**:other) = (**16**:1)*



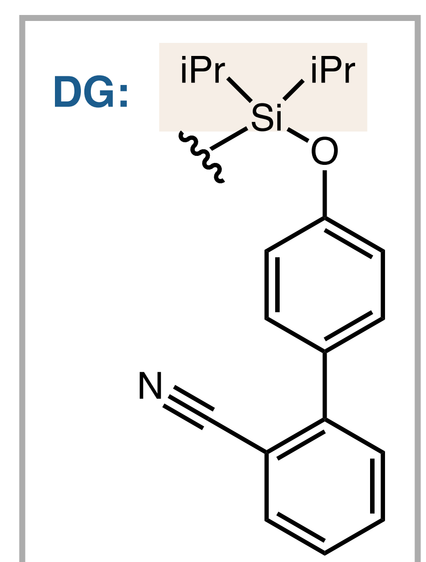
49% yield
*(**para**:other) = (**9**:1)*



76% yield
*(**para**:other) = (**8**:1)*



70% yield
*(**para**:other) = (**15**:1)*



Bag, S.; Patra, T.; Modak, A.; Deb, A.; Maity, S.; Dutta, U.;
Dey, A.; Kancherla, R.; Maji, A.; Hazra, A.; Bera, M.; Maiti, D.; *J. Am. Chem. Soc.* **2015**, *137*, 11888

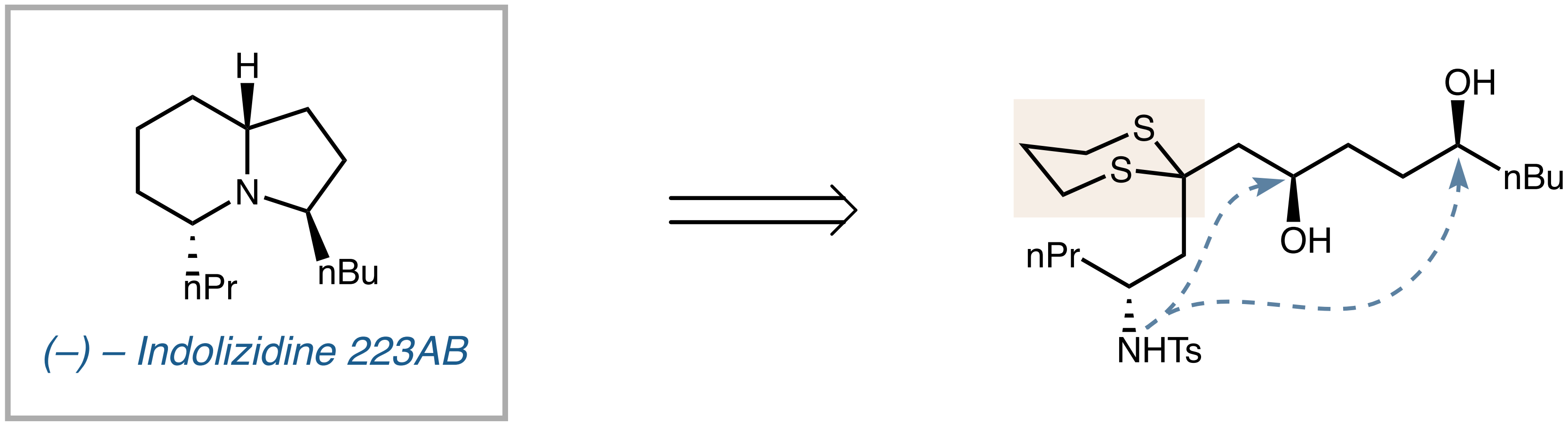
Conformational Effects of Fully Substituted Carbons

Outline

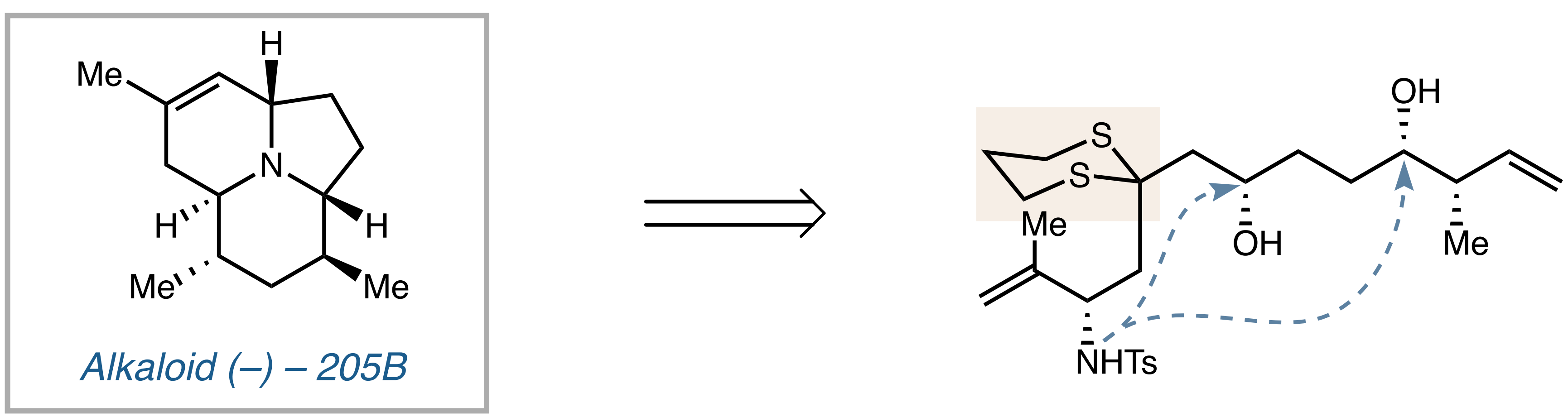
- Introduction and Evolution of Theory
  - – Thorpe–Ingold Effect
  - – Reactive Rotamer Effect
- Application in Modern Catalysis
  - – Directing groups in C–H Activation
- Complex Molecule Synthesis
  - – (–)-Indolizidine 223AB and Alkaloid (–)-250B
  - – Zaragozic acid C
  - – tricholomalide A and (–)-guanacastepene
- Drug Discovery

Conformational Effects of Fully Substituted Carbons

“Thorpe–Ingold” Effect in Complex Molecule Synthesis



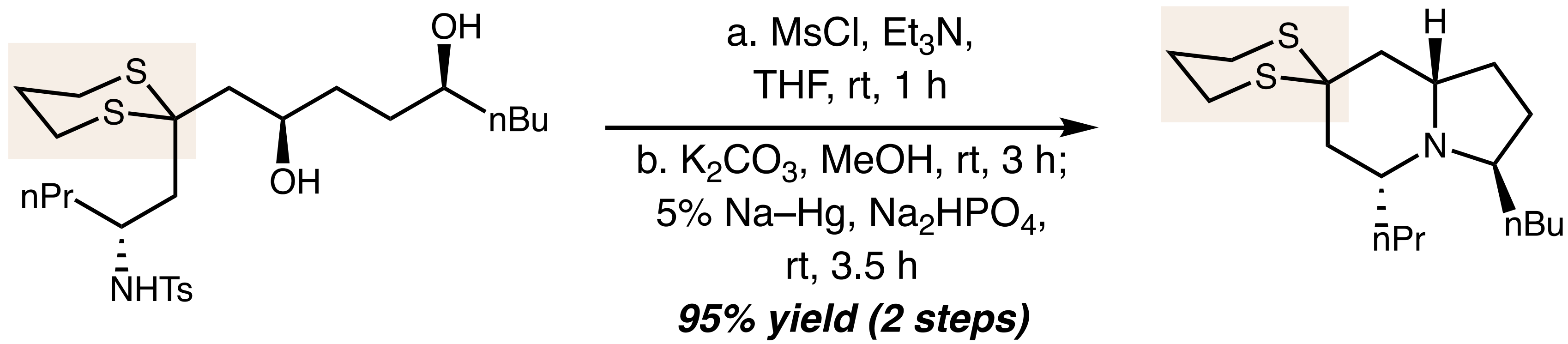
Key Step:
One Pot Double Cyclization

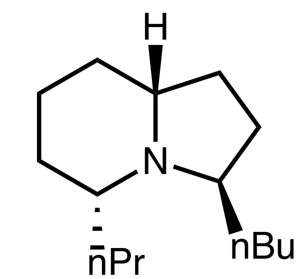


Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547

Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in Complex Molecule Synthesis



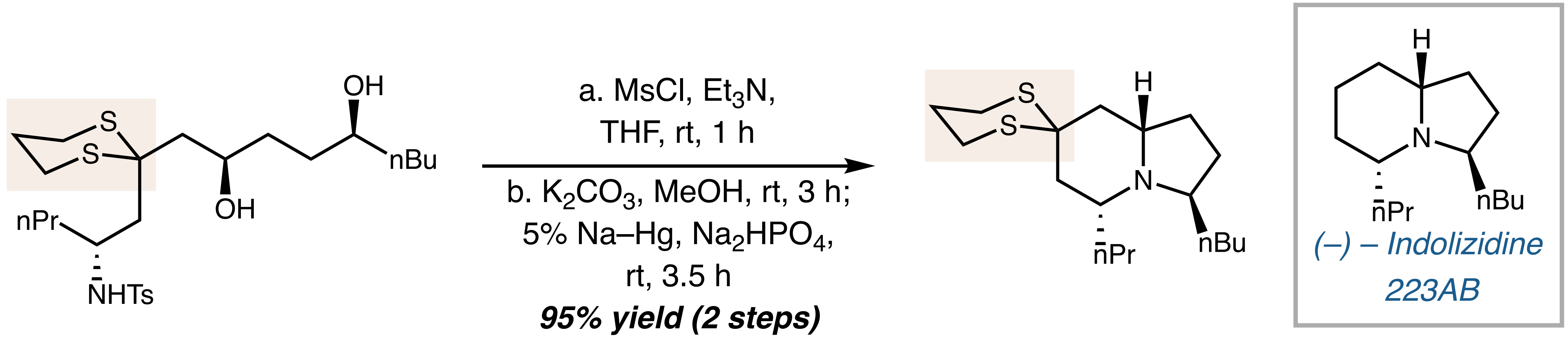


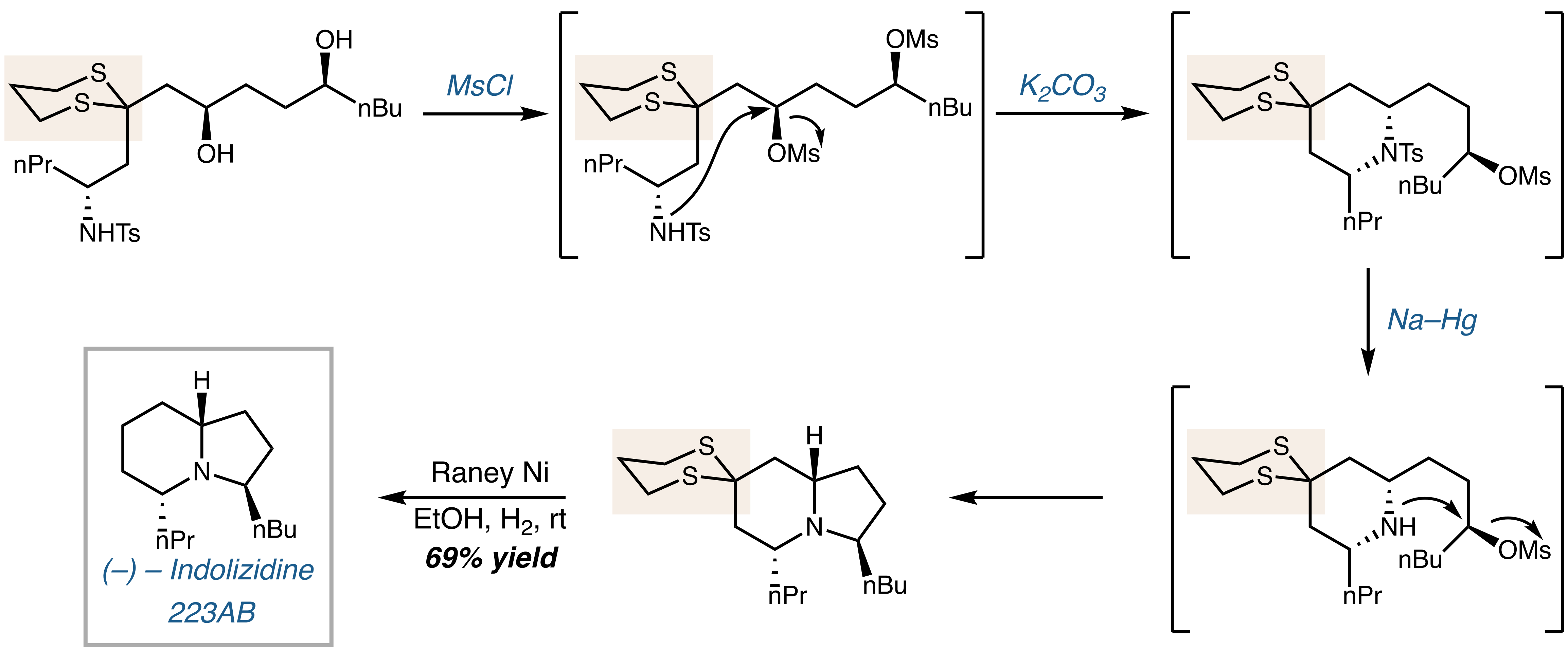
(–) – Indolizidine 223AB

Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547

Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in Complex Molecule Synthesis

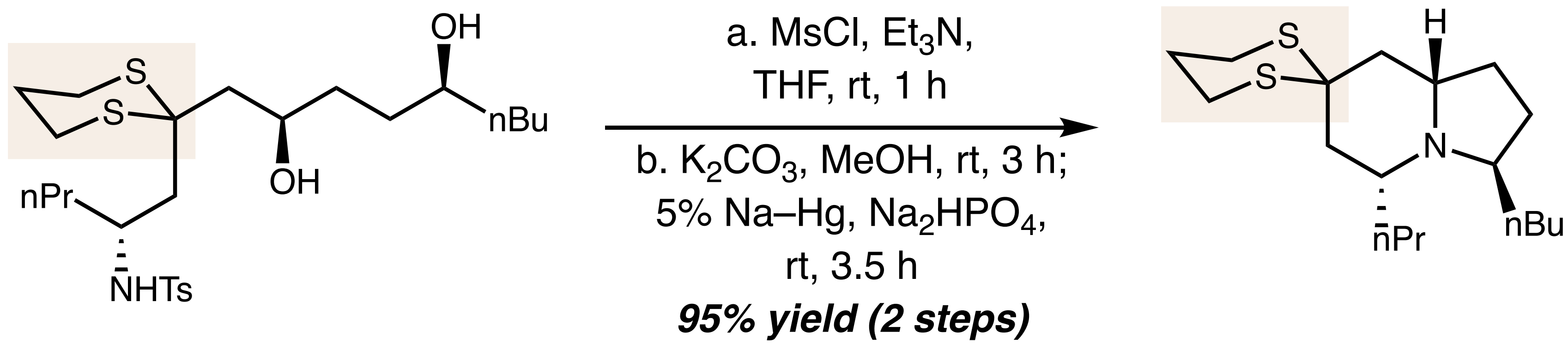


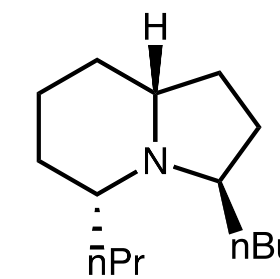


Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547

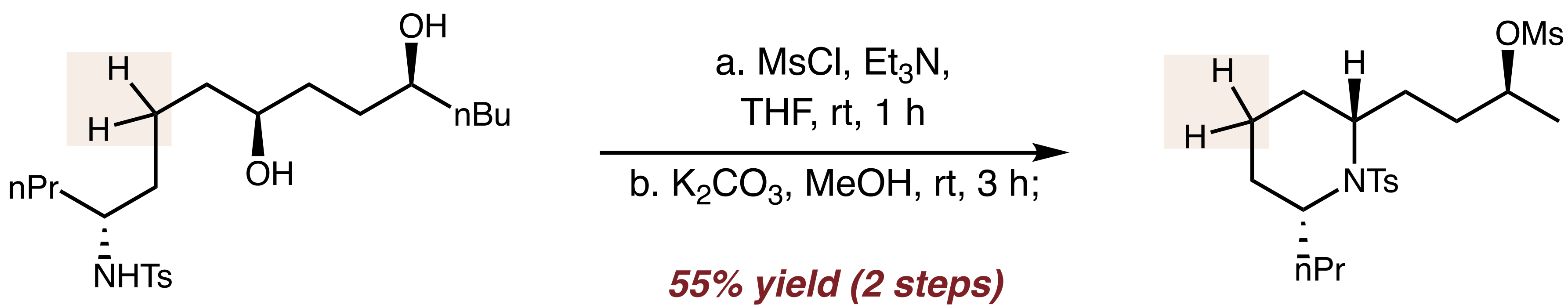
Conformational Effects of Fully Substituted Carbons

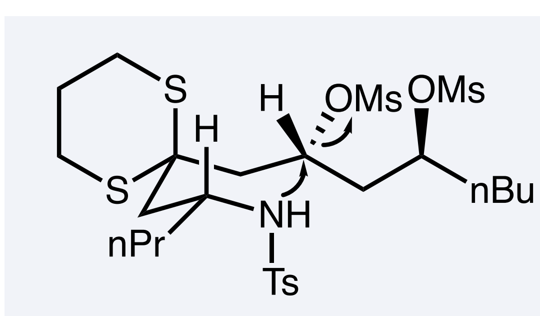
"Thorpe–Ingold" Effect in Complex Molecule Synthesis





(–) – Indolizidine 223AB



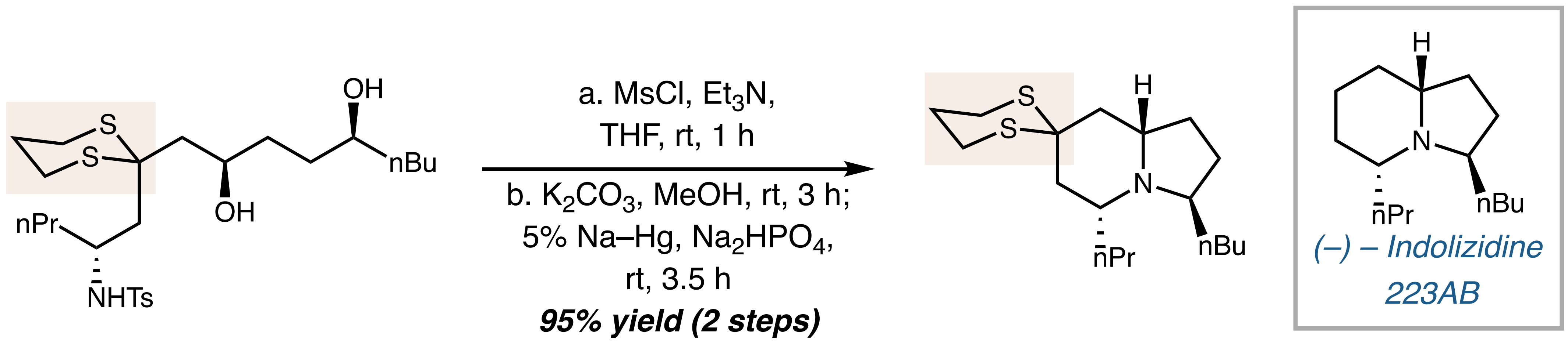


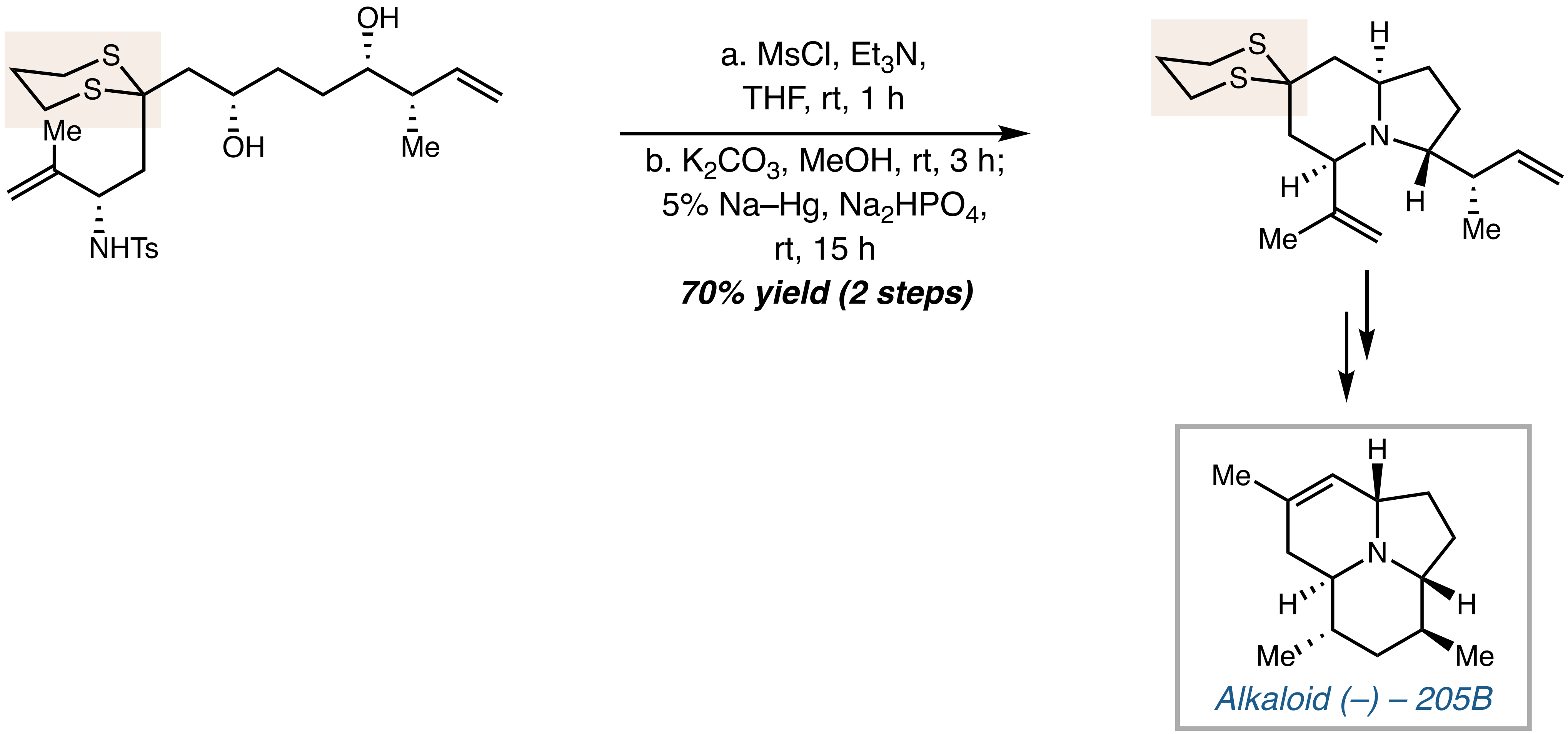
Dithiane stabilizes folded conformation and brings groups closer in proximity

Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547

Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in Complex Molecule Synthesis

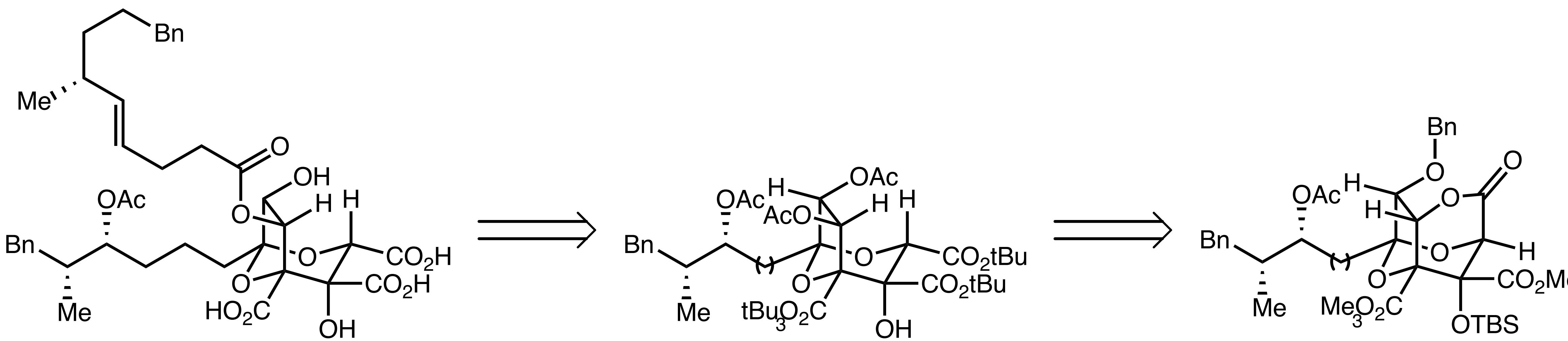




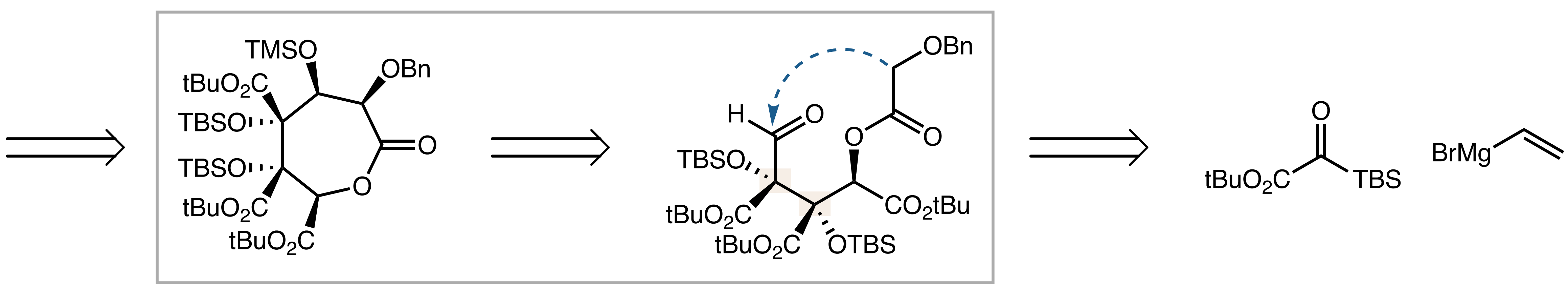
Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547

Conformational Effects of Fully Substituted Carbons

“Thorpe–Ingold” Effect in Complex Molecule Synthesis



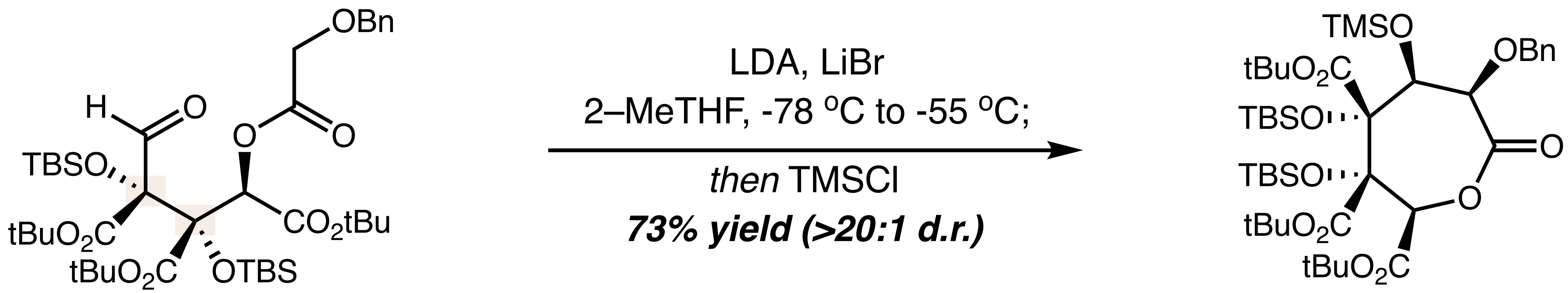
zaragozic acid C

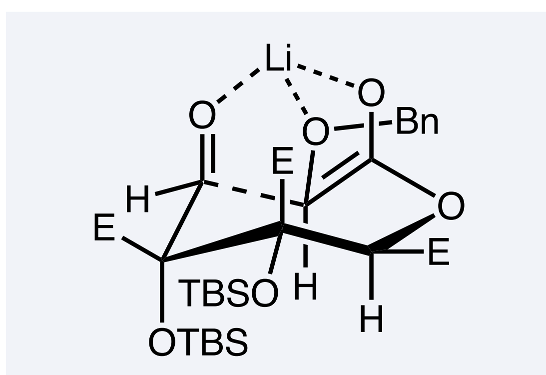


Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17281

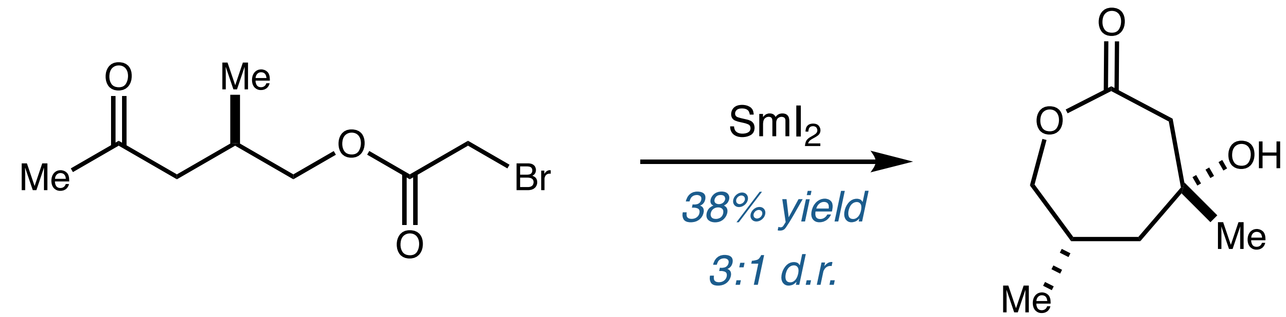
Conformational Effects of Fully Substituted Carbons

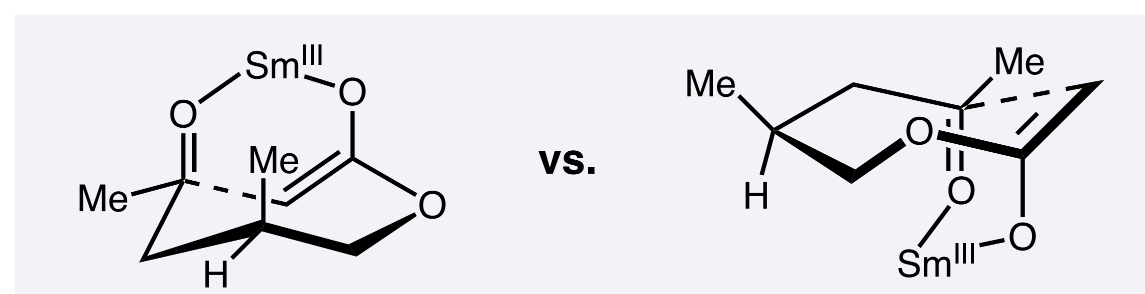
“Thorpe–Ingold” Effect in Complex Molecule Synthesis





Fully substituted carbons assist in stabilizing folded conformation necessary for selective cyclization



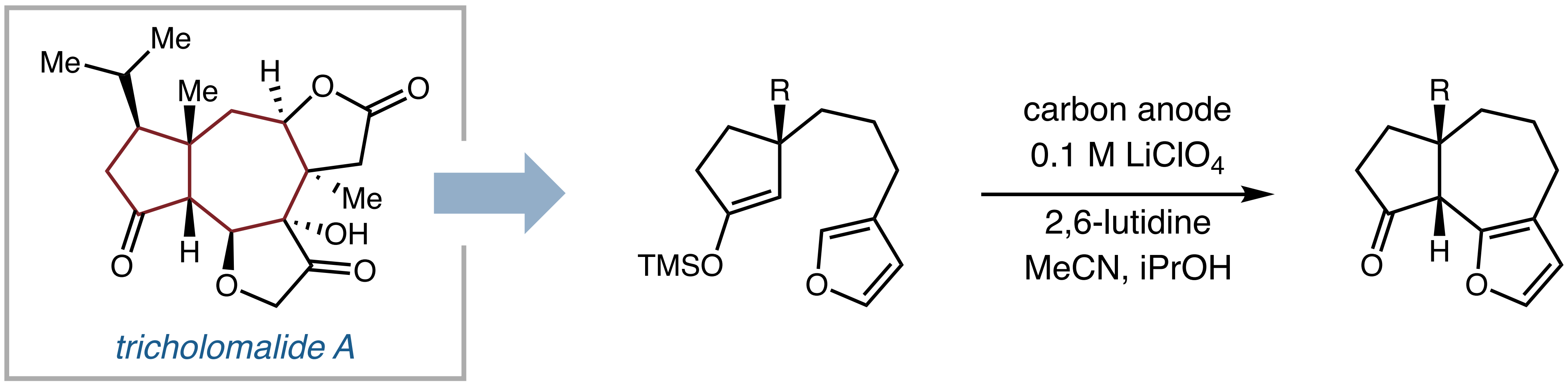


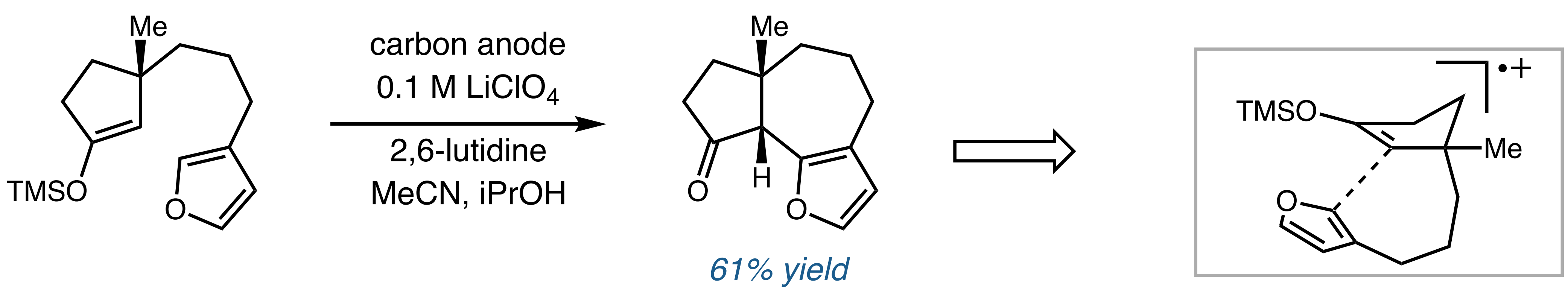
7 membered transition state often not “tight” enough for efficient diastereo–control

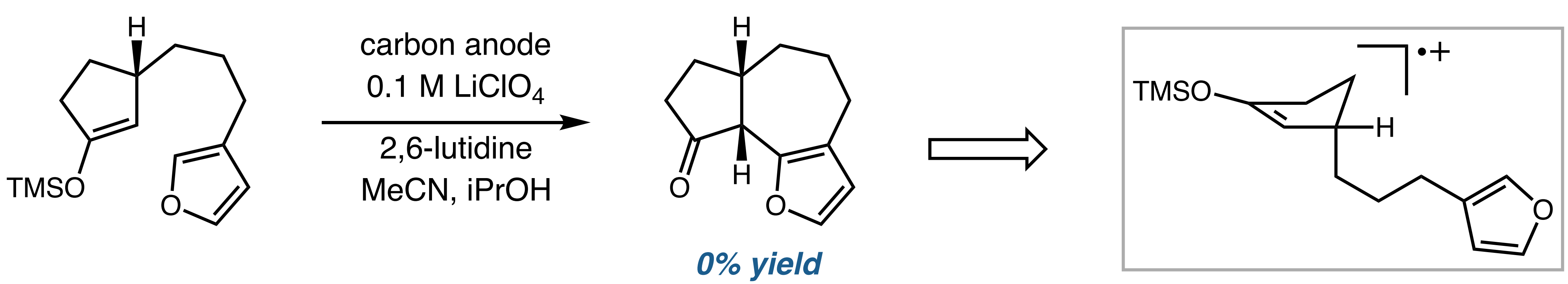
Molander, G. A.; Etter, J. B.; Harring, L.S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036
Nicewicz, D. A.; Satterfield, A. D.; Schmitt, D. C.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 17281

Conformational Effects of Fully Substituted Carbons

“Thorpe–Ingold” Effect in Complex Molecule Synthesis



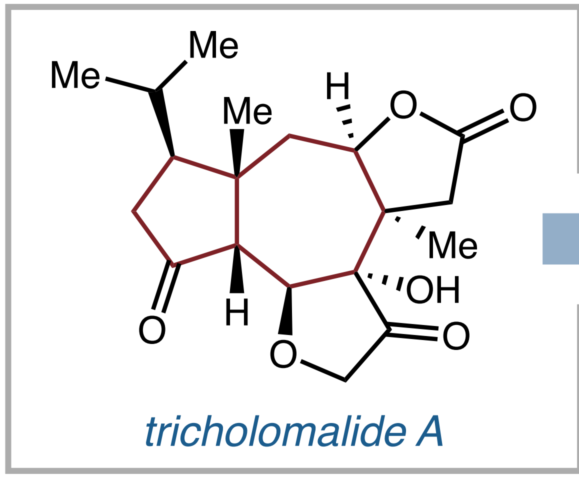


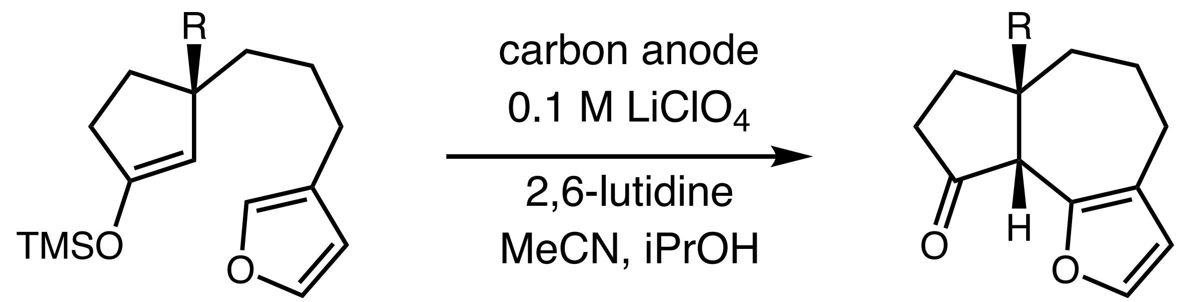


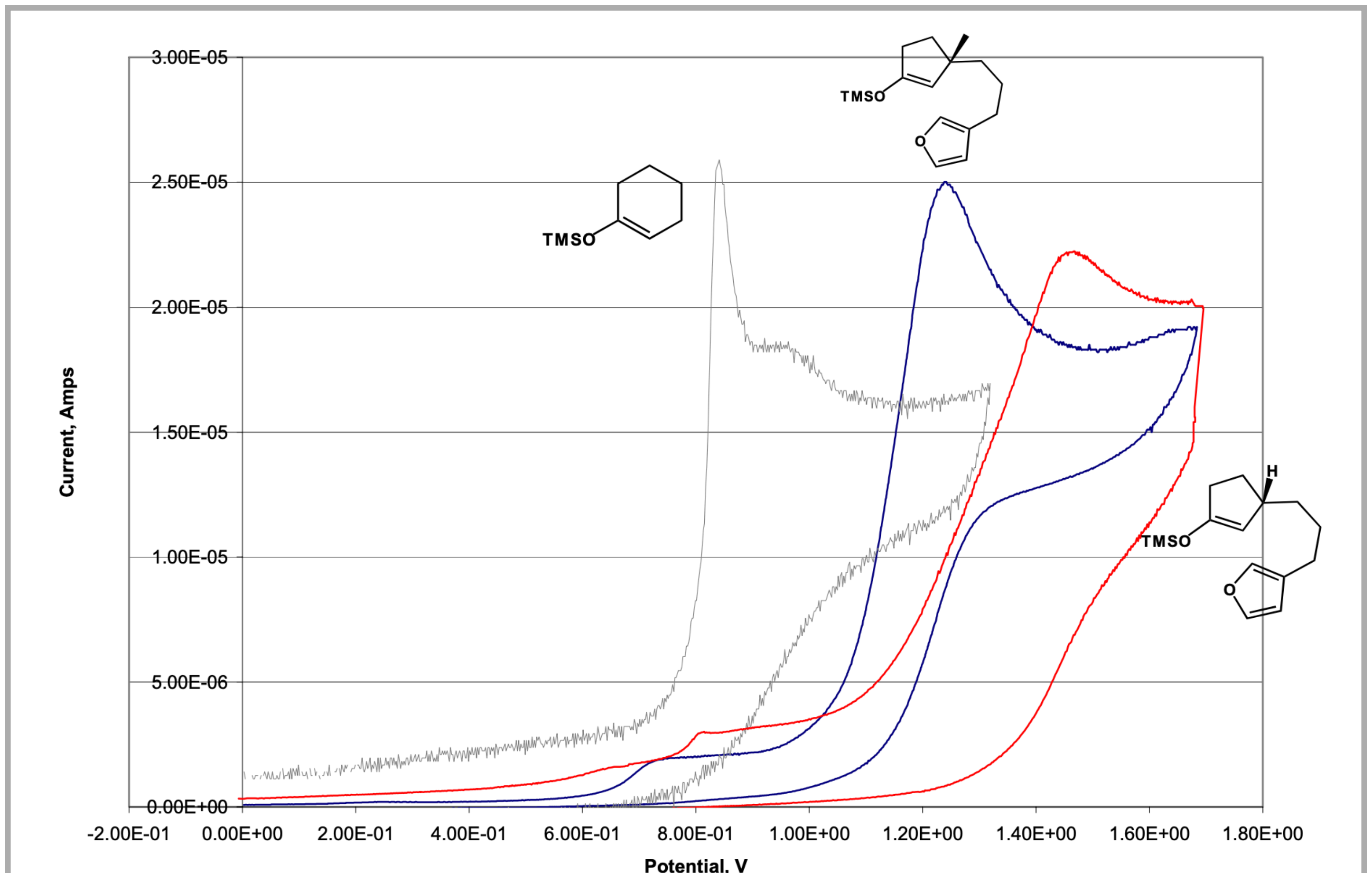
Sperry, J. B.; Wright, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 8034

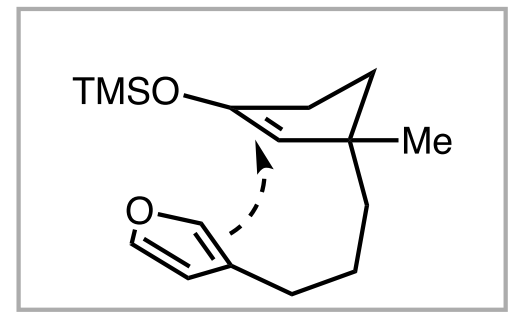
Conformational Effects of Fully Substituted Carbons

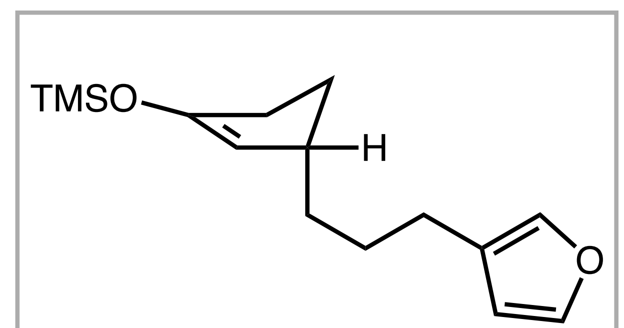
"Thorpe–Ingold" Effect in Complex Molecule Synthesis







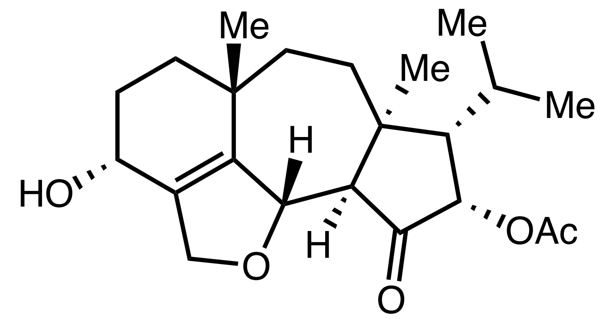




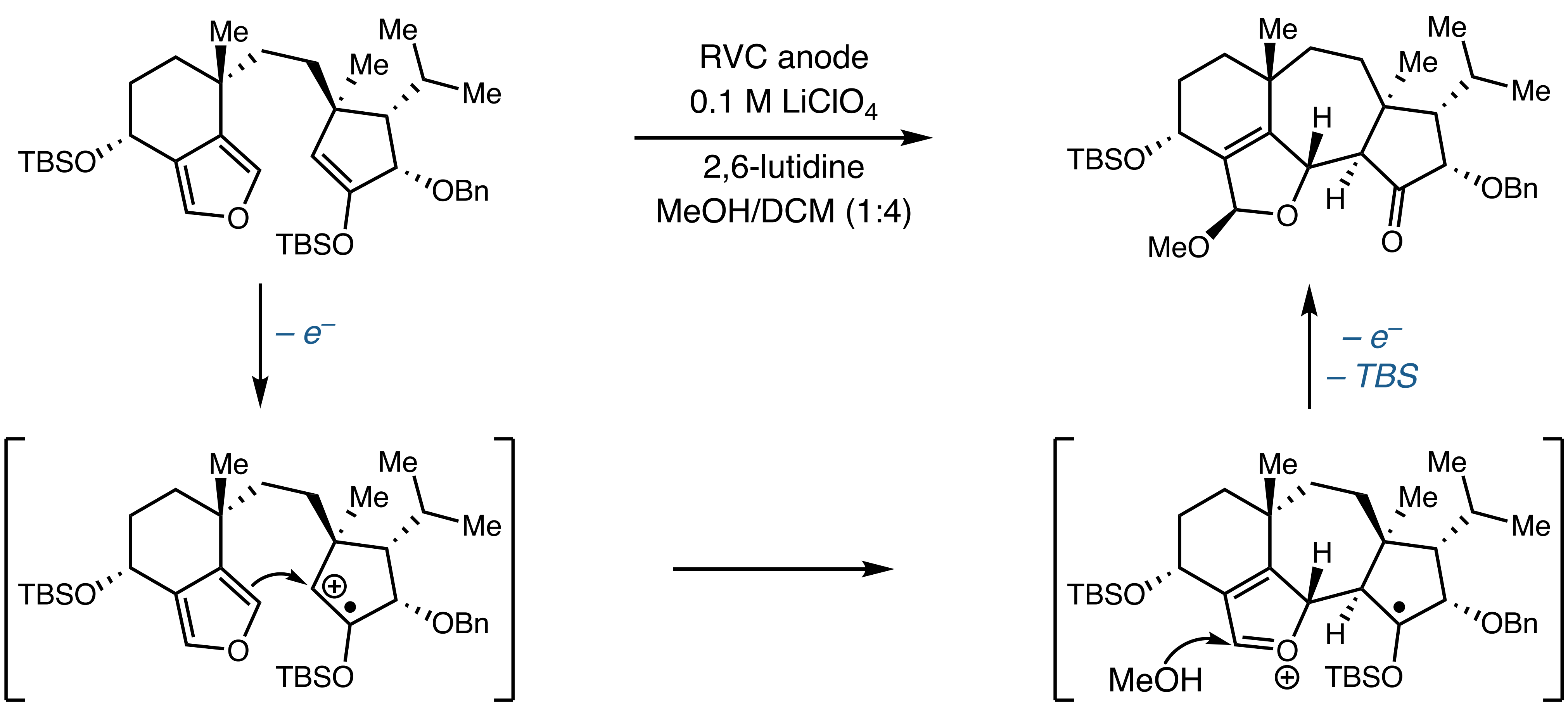
Sperry, J. B.; Wright, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 8034

Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in Complex Molecule Synthesis



(–)-guanacastepene



Miller, A. K.; Hughes, C. C.; Kennedy-Smith, J. J.; Gradl, S. N.; Trauner, D. *J. Am. Chem. Soc.* **2006**, *128*, 17057

Conformational Effects of Fully Substituted Carbons

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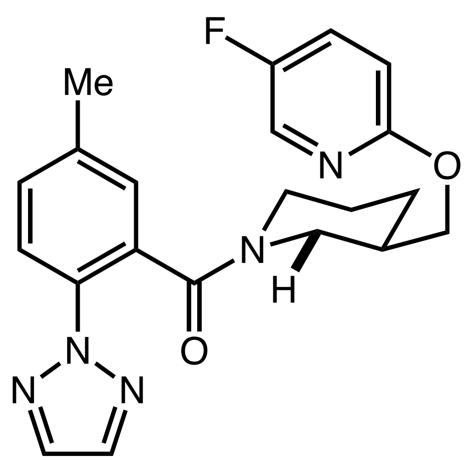
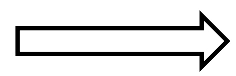
- Drug Discovery

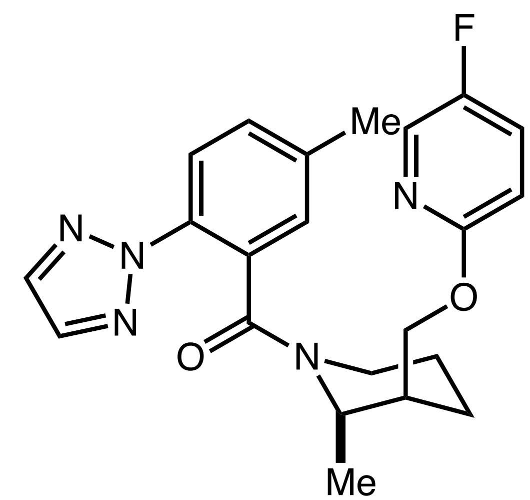
Conformational Effects of Fully Substituted Carbons

Conformational Effects in Medicinal Chemistry



96 nm





0.2 nm

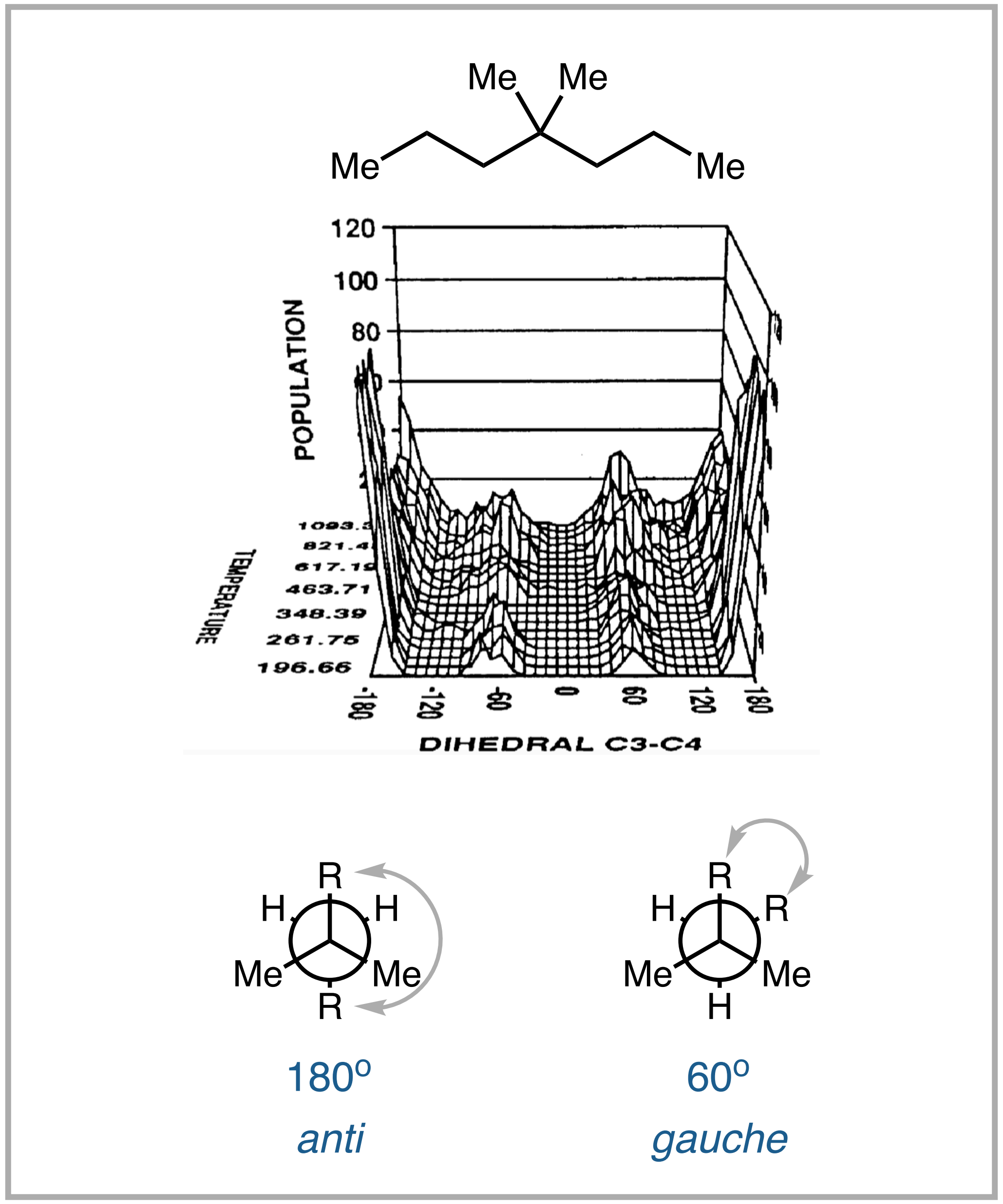
“Magic Methyl” effect forces the low energy conformer (unbound) to match the low energy binding conformer

Can we achieve similar levels of control in acyclic systems?

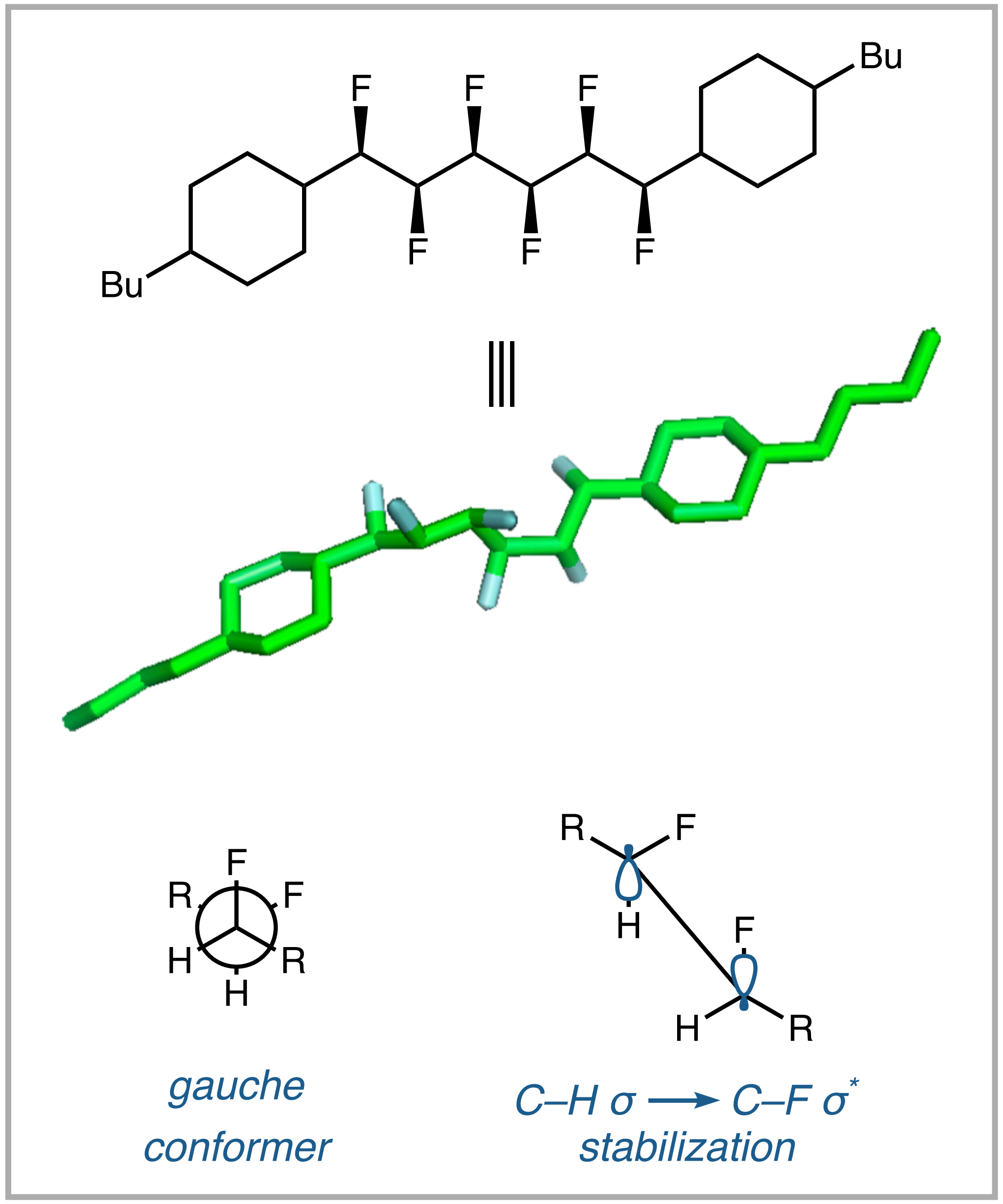
Schonherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256

Conformational Effects of Fully Substituted Carbons

Conformational Effects in Medicinal Chemistry



Gem–Disubstituent Effect

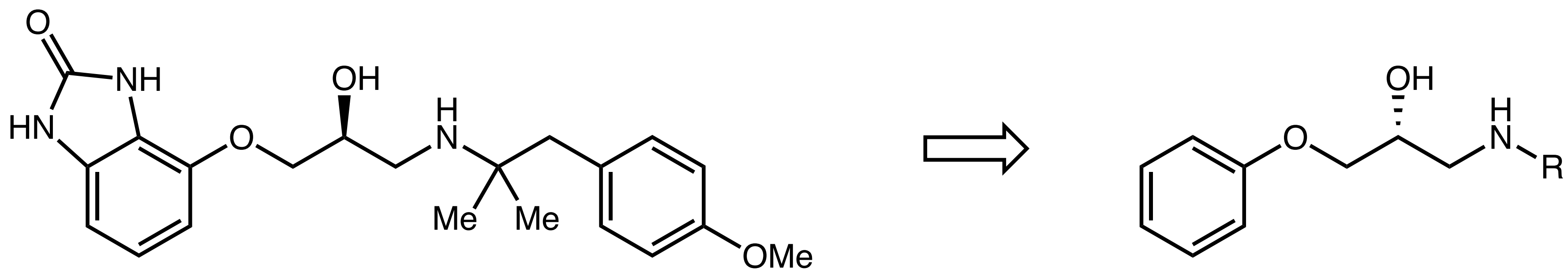


Fluorine Gauche Effect

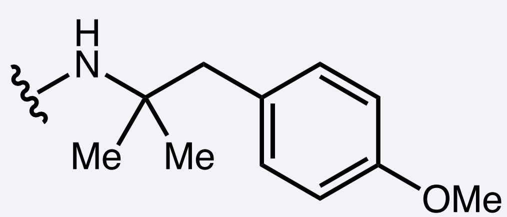
Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem.* **2015**, *58*, 8315
Wilson, S. R.; Cui, W.; Moskowitz, J. W.; Schmidt, K. E. *J. Comput. Chem.* **1991**, *12*, 342

Conformational Effects of Fully Substituted Carbons

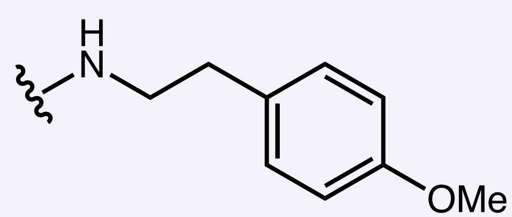
"Thorpe–Ingold" Effect in Medicinal Chemistry



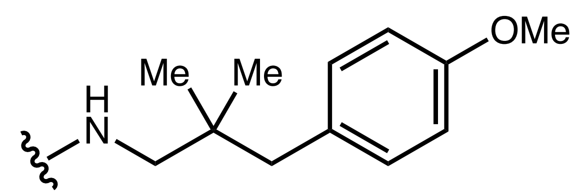
■ CaR IC_{50} = 11 μM



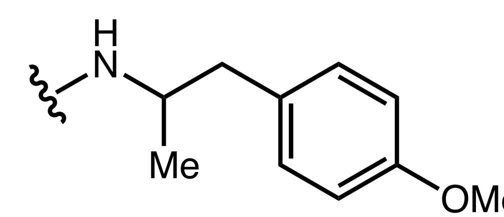
2.3 µM



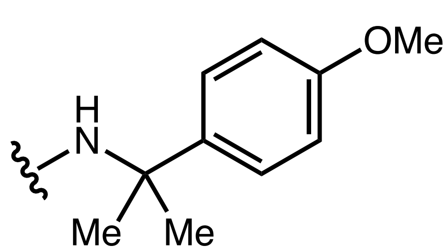
>100 µM



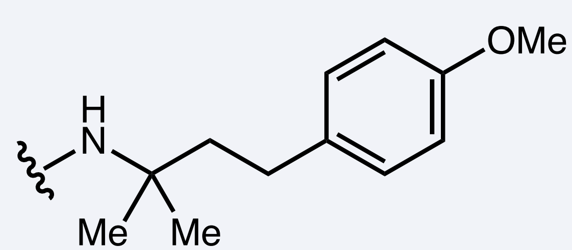
>100 µM



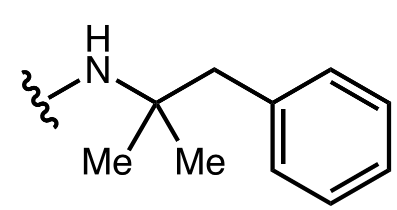
>100 µM



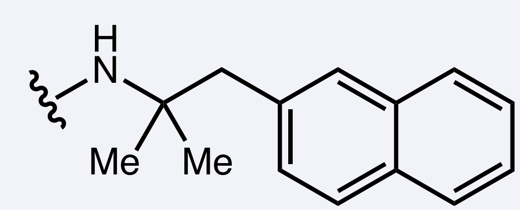
>100 µM



13 µM



2.3 µM

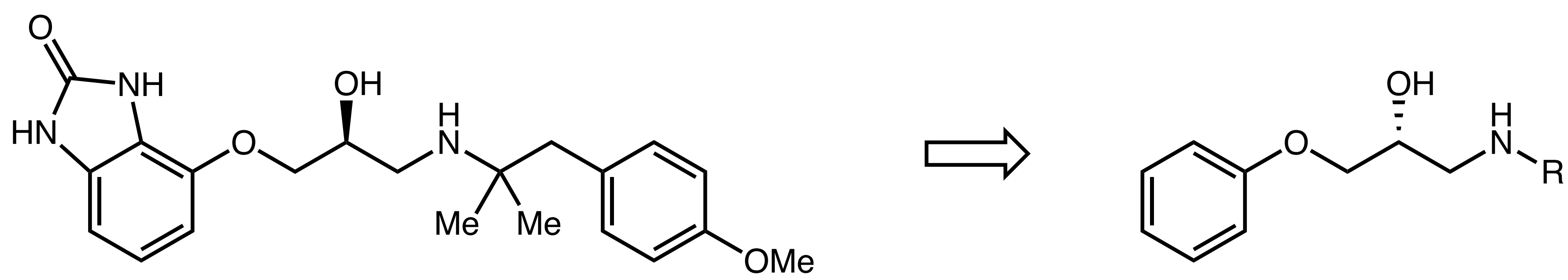


0.45 µM

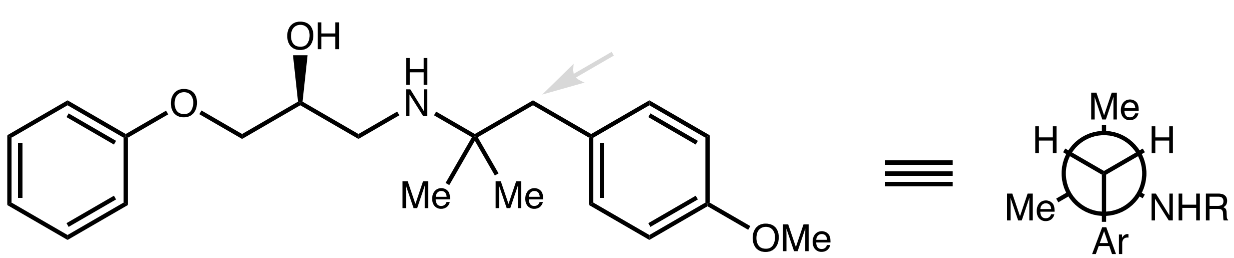
Marquis, R. W. et. al. *J. Med. Chem.* **2009**, *52*, 3982

Conformational Effects of Fully Substituted Carbons

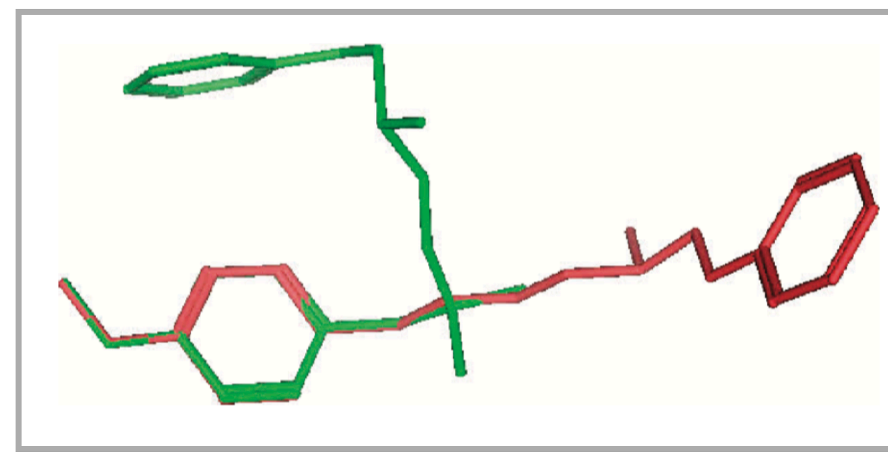
“Thorpe–Ingold” Effect in Medicinal Chemistry

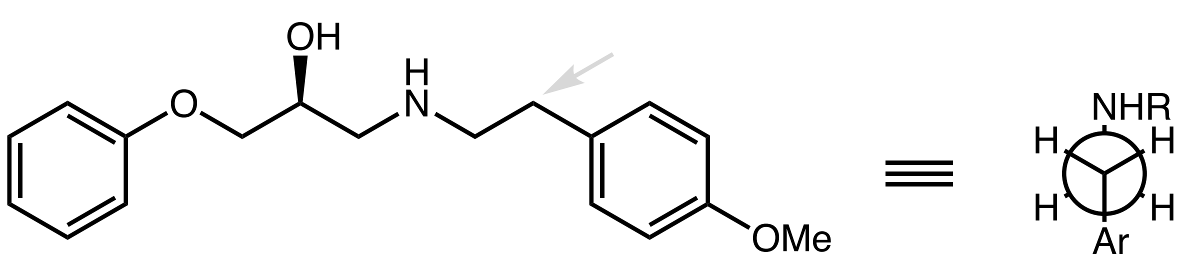


■ CaR IC_{50} = 11 μM



2.3 μM





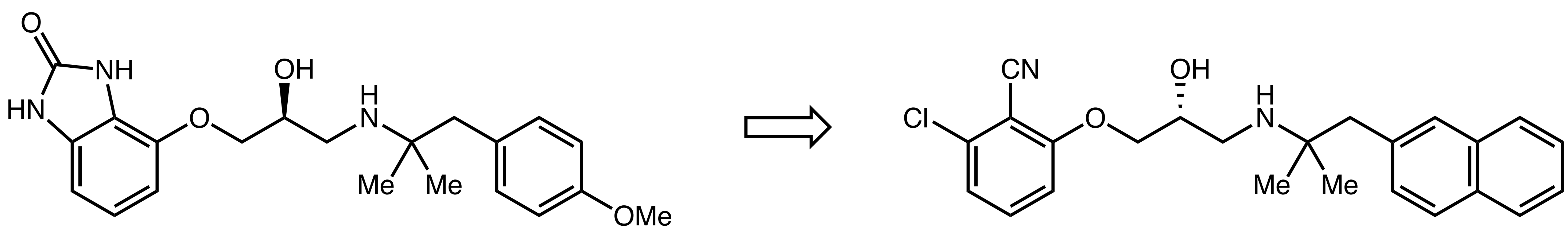
>100 μM

gem–dimethyl group stabilizes folded conformation

Marquis, R. W. et. al. *J. Med. Chem.* **2009**, *52*, 3982

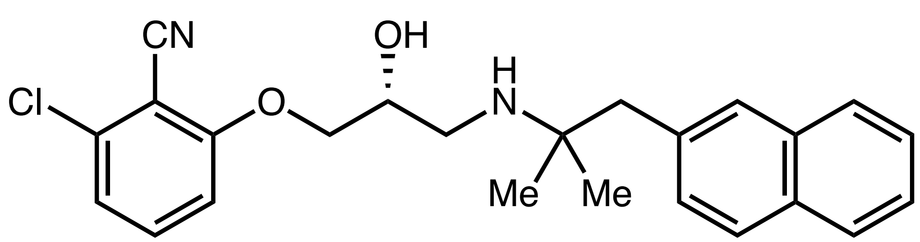
Conformational Effects of Fully Substituted Carbons

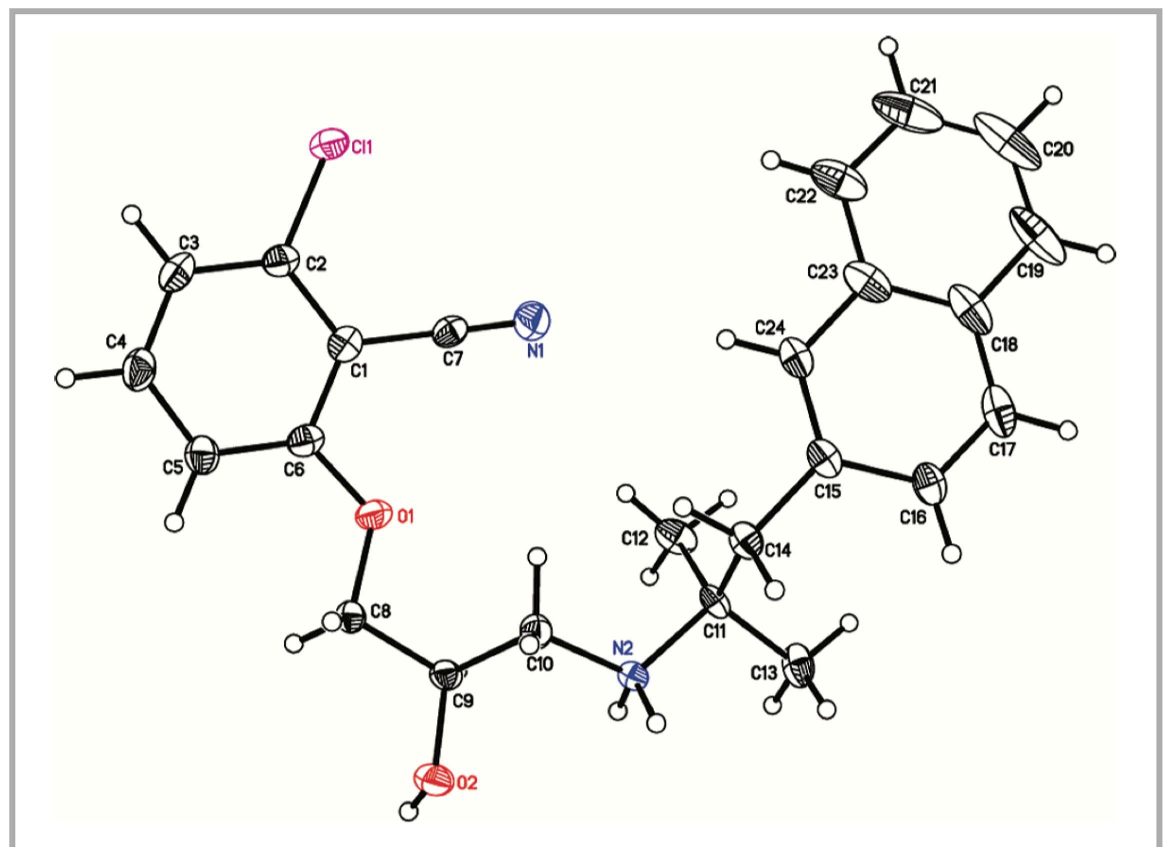
"Thorpe–Ingold" Effect in Medicinal Chemistry



■ CaR IC_{50} = 11 μM

■ CaR IC_{50} = 43 nM

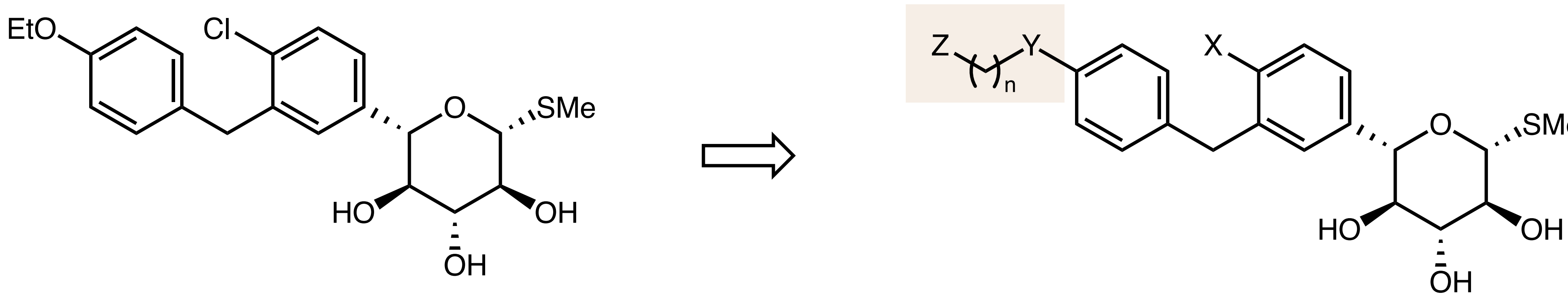




Marquis, R. W. et. al. *J. Med. Chem.* **2009**, *52*, 3982

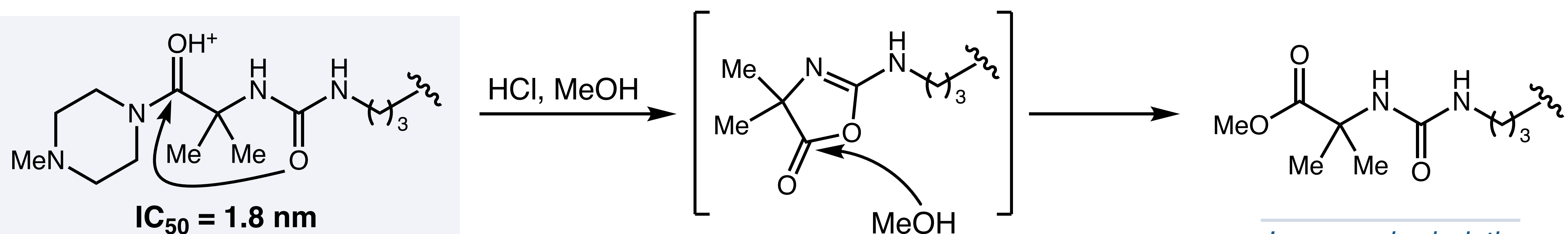
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in Medicinal Chemistry



■ hSGLT1 IC_{50} = 36 nm

Improve potency, reduce F%



IC_{50} = 1.8 nm
F = < 1%

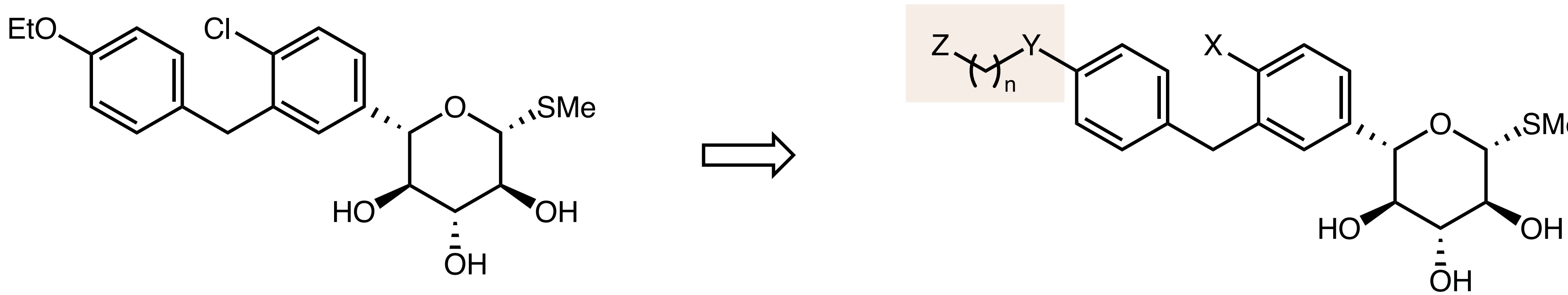
Increase hydrolytic stability

Accelerated by Thorpe–Ingold Effect?

Goodwin, N. C. et. al. *J. Med. Chem.* **2017**, *60*, 710

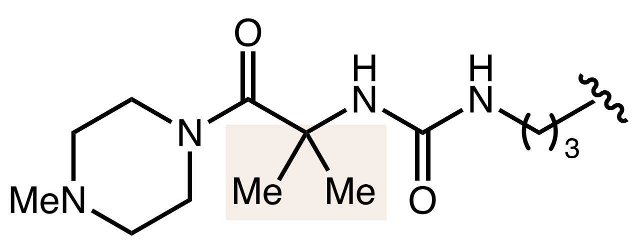
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in Medicinal Chemistry

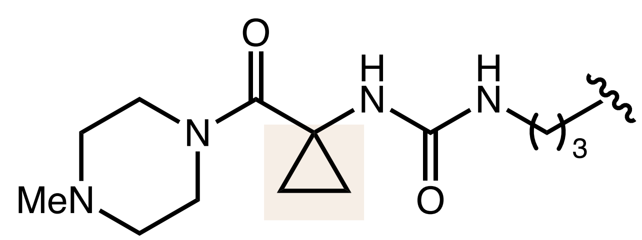


hSGLT1 IC_{50} = 36 nm

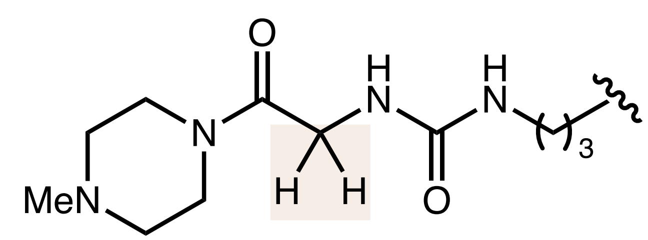
Improve potency, reduce F%



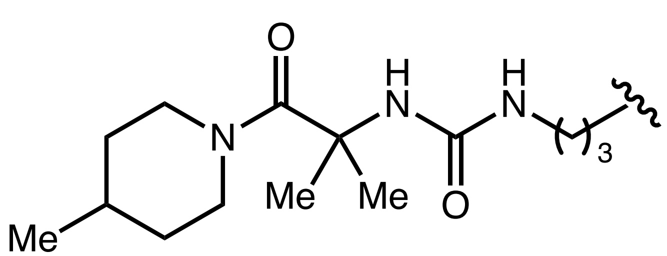
IC_{50} = 1.8 nm
stable? = No



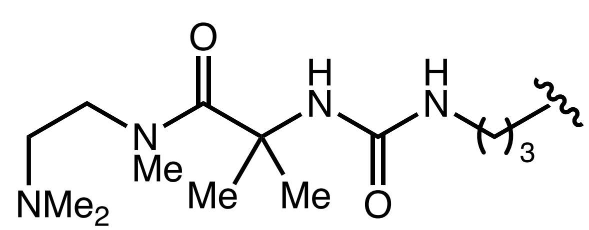
IC_{50} = 1.1 nm
*stable? = No**



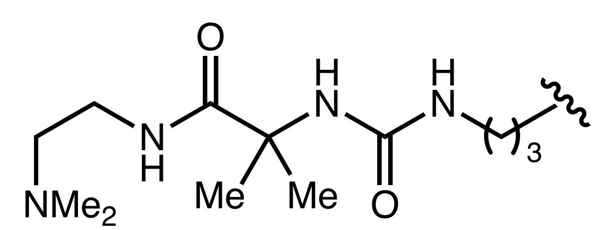
IC_{50} = 8.4 nm
*stable? = No**



IC_{50} = 1.6 nm
stable? = No



IC_{50} = 1.7 nm
*stable? = **Yes***



IC_{50} = 2.2 nm
*stable? = **Yes***

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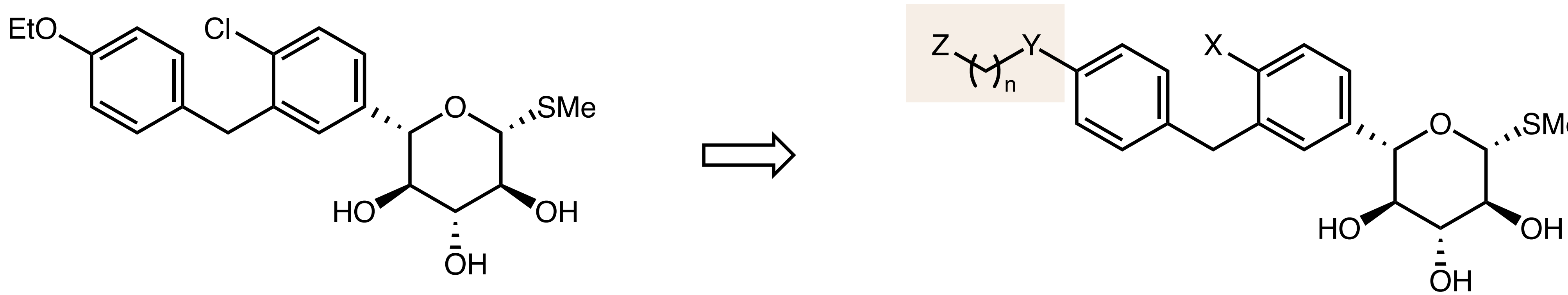
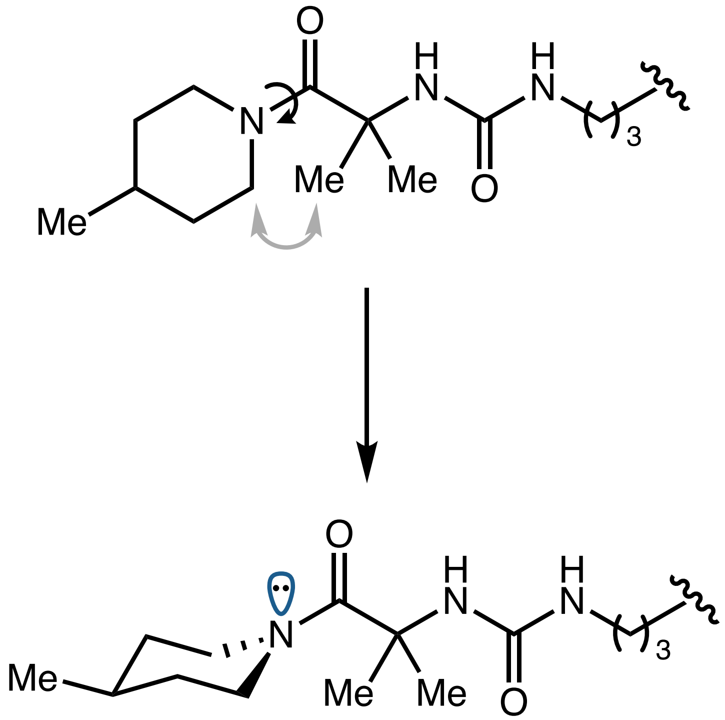
Conformational Effects of Fully Substituted Carbons

"Thorpe–Ingold" Effect in Medicinal Chemistry

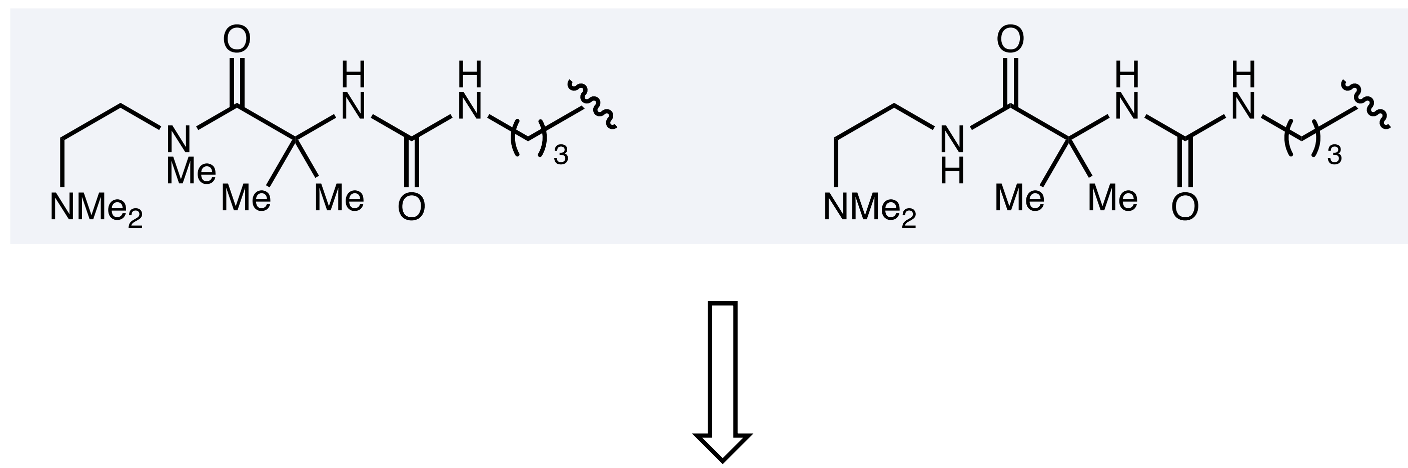


■ hSGLT1 IC_{50} = 36 nm

Improve potency, reduce F%



lone pair orthogonal to π system increases reactivity



Flexible amides aleviate this A 1,3 strain and increase stability while maintaining potency

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Questions?

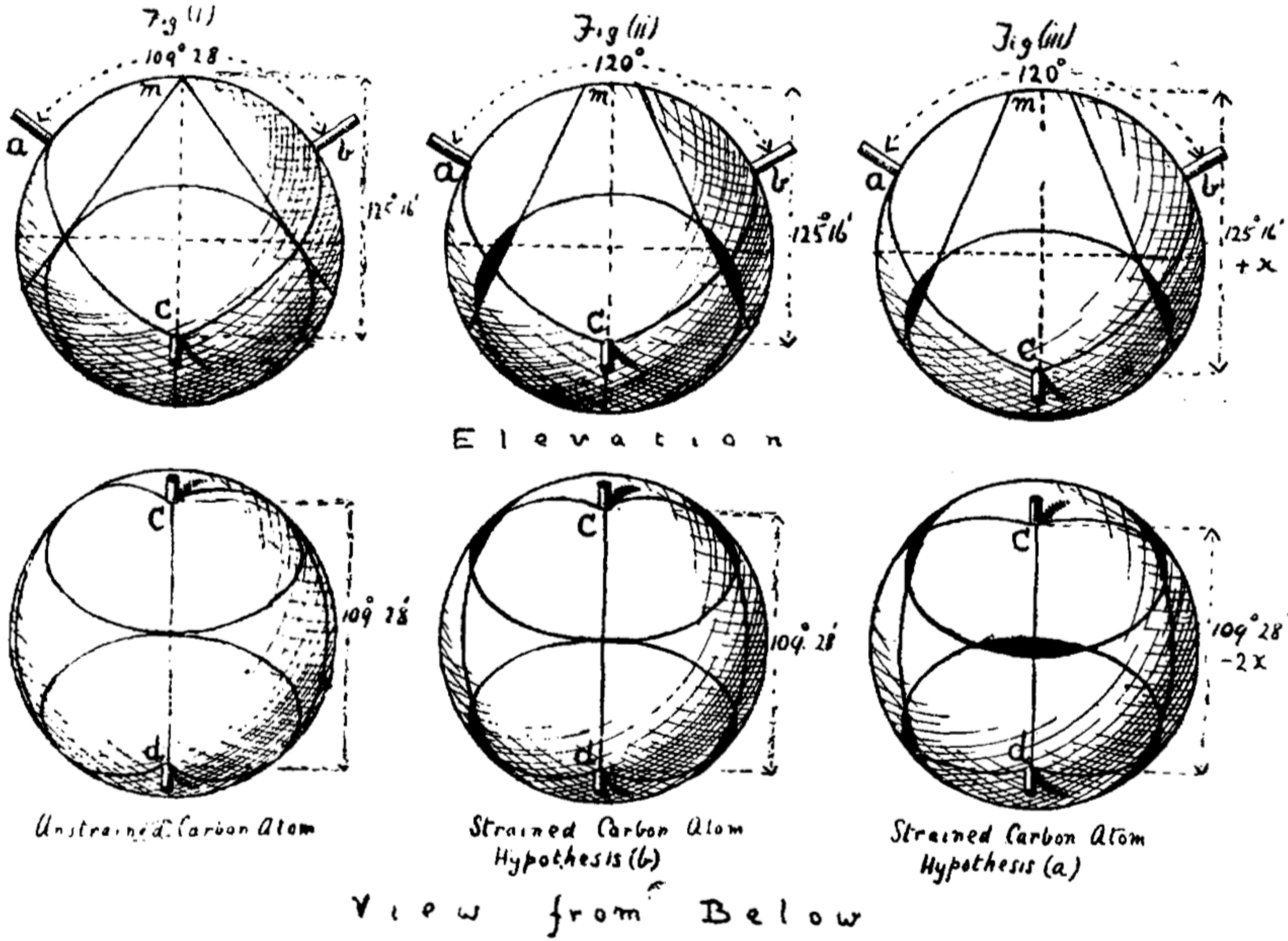

Fig (I)
109° 28
Fig (II)
120°
Fig (III)
120°
m
a
b
c
125° 16'
+ x
Elevation
c
d
109° 28'
-2 x
Unstrained Carbon Atom
Strained Carbon Atom
Hypothesis (b)
Strained Carbon Atom
Hypothesis (a)
View from Below