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Thorpe-Ingold Effect Assisted Strained Ring Synthesis

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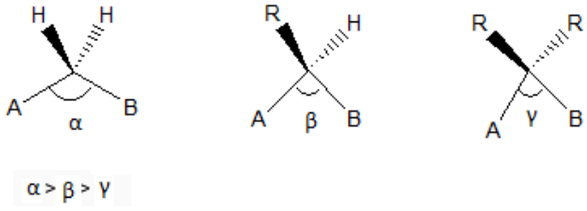
ABSTRACT

The Thorpe-Ingold effect (also known as the gem-dialkyl effect) is the term assigned to the acceleration of cyclization caused by the substitution of hydrogen atoms on the carbons anchoring the two reaction centres with alkyl groups. Because of the more favourable entropy shift that happens when the reaction reaches the transition state, intramolecular reactions often proceed faster than intermolecular reactions. The formation of five-and six-membered rings, among other things, benefits from these entropic effects. Alternatively, depending on the situation, increased ring strain can be countered and cyclization retarded in the formation of three-and four-membered rings. To overcome the unfavourable enthalpic parameters, alkyl substituents inserted onto the acyclic carbon chain that connects the two reacting junctions can be employed to improve the rate of cyclization. This article focuses on the application of the Thorpe-Ingold effect in the construction of strain three- and four-membered ring systems. To sum up, the Thorpe-Ingold effect can effectively speed up and increase the yield of both intramolecular and intermolecular cyclization.

Keywords: *Thorpe-Ingold Effect; Gem-Dialkyl Effect; Strained Molecules; Gem-Dimethyl Effect*

INTRODUCTION

The Thorpe-Ingold effect, also known as the gem-dimethyl effect or angle compression effect, refers to the promotion of cyclization through gem-di-substitution on the molecular chain (Jung & Piizzi, 2005). This effect was first proposed by Beesley, Ingold and Thorpe (1915), that is, when the hydrogen on the methylene group in the molecular chain is replaced by a bulky alkyl group, the internal angle (bond angle) is compressed (Ingold, 1921), and the two reactive groups at the end of the molecular chain are compressed close to each other for intramolecular cyclization (Ingold, Sako & Thorpe , 1922) (Figure 1).



α,β,γ are bond angles

Figure 1: Thorpe-Ingold effect

It was later found that the Thorpe-Ingold effect is very important in explaining the change in bond angle (Lightstone & Bruice, 1994). Small five- and six-membered rings with unchanged bond angles are not perfect(Von Ragué Schleyer, 1961), and it is difficult to explain the increase in bond angle changes problems with yield and rate of formation of macrocycles (Galli *et al.*, 1979).

Bruice and Pandit (1960a) proposed the reaction rotamer effect to explain the effects of dialkyl substitution (Figure 2) .When the base is present, the molecule mainly exists in the trans (anti) conformation; after the geminal dialkyl group is substituted, the higher energy ortho-crossing (gauche) is favourable for cyclization (Bruice & Pandit, 1960b). The conformation ratio is increased,

and the cyclization is easy. The Thorpe-Ingold effect is examined in this article for intramolecular and intermolecular cyclization to produce three- to six-membered ring products.

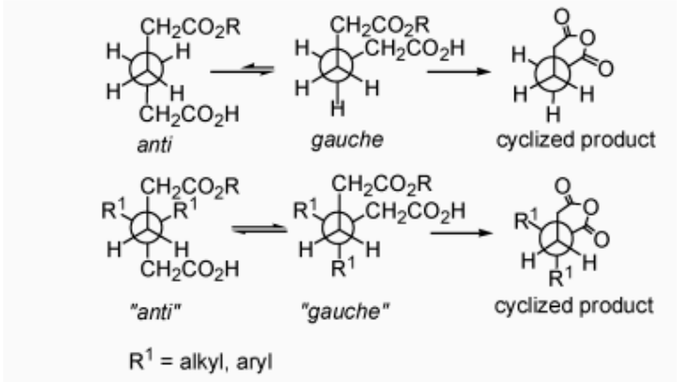


Figure 2: Reactive Rotamer Effect

Jung and Gervay (1991) studied the bond angle compression effect and the reaction rotamer effect in geminal dialkyl substitution by intramolecular D-A cycloaddition (Figure 3). Substrates 1d and 1e substituted with a spiro ring were designed, the internal angle β of the spiro ring substitution position was increased, and the cyclization would be dominated by the reaction rotamer effect.

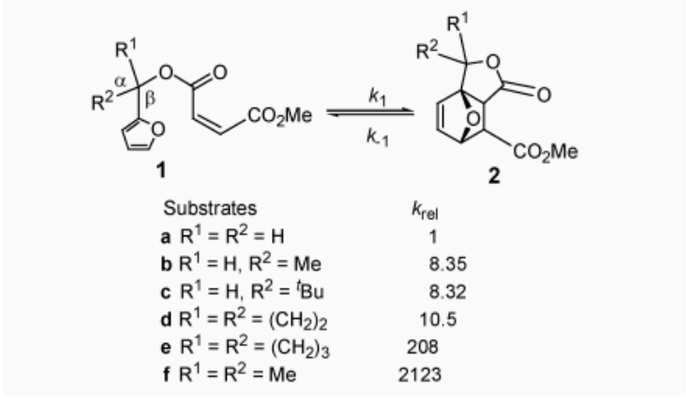


Figure 3: Bond angle compression effect and the reaction rotamer effect

As a result, the unsubstituted substrate 1a had the slowest cyclization rate, and the cyclization rates of monomethyl substituted 1b and mono-tert-butyl substituted 1c increased slightly but were largely unaffected by the volume change of the monosubstituent. The cyclization rate of geminal dimethyl substituted 1f is significantly increased, more than 2000-fold higher than that of 1a. The cyclization rates of 1d and 1e with enlarged internal angles of the substitution positions also increased, and the cyclization rate of 1e was approximately 208 and 25 times that of 1a and 1b, respectively. It is therefore believed that at least in cyclization to form a five-membered ring system, the effect of reaction rotamers should be fully considered.

The enthalpy and entropy changes of some reactions are also major contributors to the Thorpe-Ingold effect. Allinger and Zalkow (1960) calculated the thermodynamic properties of the geminal dimethyl effect in the cyclization of n-hexane to cyclohexane. When the hydrogen at the 2-position of n-hexane is replaced by a gem-dimethyl group, the cyclization rate can be increased by about 100 times, and when the hydrogen at the 3-position is replaced by a gem-dimethyl group, the cyclization rate is increased by about 1000 times. The authors believe that the enthalpy change or entropy change, or a combination of the two, caused by gem-dimethyl substitution results in a decrease in non-bonding interactions and rotational entropy, which increases the rate of intramolecular cyclization.

In 2009, Karaman studied the kinetic and thermodynamic properties of gem-disubstituted bromobutylamine by calculation and showed that the rate constant is only determined by the free energies of the ground and transition states (Figure 4). Although the initial studies were reported by Brown and Van Gulick in 1956, for the geminal alkyl effect on the rates of ring closure of bromobutylamines.

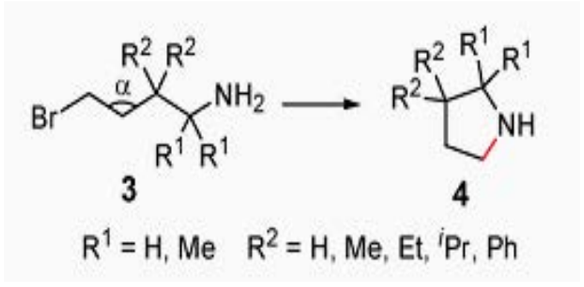


Figure 4: Cyclization of gem-disubstituted bromobutylamine

In 2010, Kostal and Jorgensen used quantum and statistical mechanics calculations to study the reactions of 2-chloroethanol, 1-chloro-2-propanol, and 2-methyl-1-chloro-2-propanol in the gas phase and liquid phase under base catalysis, respectively. Generate the corresponding epoxide. The results show that the C-C-C bond angle in the main chain does decrease with the increase of the substituted methyl groups. Gas-phase MP2 and CBS-Q calculations show that the energy changes in the reaction process of the three chloroethanol derivatives are very small; considering continuous hydration or MC/FEP calculations can accurately reproduce the reaction in the presence of water, thus It is speculated that the bond angle compression effect in the cyclization of chlorohydrin is mainly caused by the solvent effect.

In a nutshell, the Thorpe-Ingold effect may be affected by many factors, such as solvent, auxiliary agent, and substituent group. Therefore, these factors should be fully considered when considering the role of the Thorpe-Ingold effect in the reaction.

Although the essence of the Thorpe-Ingold effect has not yet been explained by a perfect theory, it is indeed a good method to apply the Thorpe-Ingold effect to effectively promote intramolecular cyclization. This article focuses on the study of the Thorpe-Ingold effect for intramolecular and intermolecular cyclization to form three-to six-membered ring products.

LITERATURE REVIEW

Synthesis of three-member ring products

Generally, intramolecular reactions go on more quickly than their intermolecular analogues due to the more favourable entropy change that occurs when the reaction enters the transition state. These entropic effects lead to rate enhancements in the production of five-and six-membered rings, among other things. As an alternative, enhanced ring strain may be counteracted and cyclization may be delayed in the development of three-and four-membered rings, depending on the situation. To get around the unfavourable enthalpic conditions, however, it is possible to use the faster rate of cyclization caused by adding alkyl substituents to the acyclic carbon chain that connects the two reacting junctions.

Synthesis of cyclopropane derivatives

Coscia and Lambert (2009) studied the palladium catalyzed intermolecular cyclopropanation reaction of gem-dialkyl substituted 3-oxo-7,9-decadienoate 5 to reveal the effect of the various gem-dialkyl groups. They have found that gem-dialkyl groups are necessary for the $Pd(OAc)_2$ catalyzed

propanation reaction to obtain the targeted bicyclic product 6 (Figure 5).

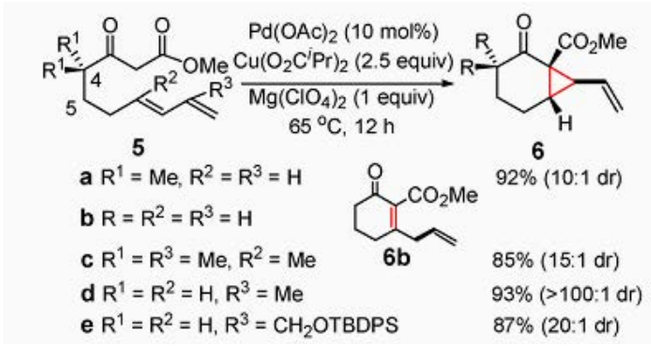


Figure 5: Thorpe-Ingold effect assisted cyclpropanation

If the substrate is an unsubstituted ketoester, it is prone to undergoing Saegusa-Ito type oxidation to give conjugated cyclohexenone (6b). Here, the Thorpe-Ingold effect not only promotes cyclization but also promotes the reaction in a specific direction. There are methyl groups (5c and 5d) and tert-butyldiphenylsiloxymethylene (5e) substitutions on the conjugated diene bonds, and the target products (85%-93%) can be obtained in high yields. When the geminal dimethyl group was at the fifth position, the yield decreased by 40%–59%. This shows that the position of the geminal disubstituted group on the molecular chain has some effect on the intramolecular cyclization, which may work through steric hindrance.

Ethylene oxide derivatives

β-Halohydrin cyclization

In 1933, Nilsson and Smith studied the cyclization of o-chloroethanol 7 to form the corresponding epoxide 8, which was the first example of using the Thorpe-Ingold effect to explain the substitution-promoted intramolecular cyclization. The results show that the cyclization rate increases differently when different numbers of hydrogens are substituted in different methylene groups of o-chloroethanol (Figure 6). The cyclization rate was increased by about 250-fold when either the 1-or 2-carbon hydrogen was replaced by a geminal dimethyl group. When all four hydrogens in both methylene groups of o-chloroethanol were replaced by methyl groups, the cyclization rate increased more than 104-fold. The Thorpe-Ingold effect greatly accelerates the rate of intramolecular cyclization.

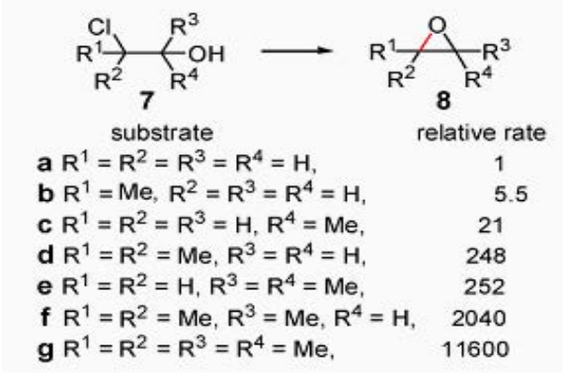


Figure 6: Thorpe-Ingold effect assisted epoxidation

Free radical reaction

The free radical reaction can easily form cyclopropane and cyclobutane, which are difficult to obtain by other methods, and the Thorpe-Ingold effect also greatly promotes the free radical cyclization reaction. In 1974, when Bloodworth *et al.* (1974) studied the rate constant of the formation of ethylene oxide from β-bromoperoxide by free radicals, they found that there was a geminal dialkyl effect in the process of homolytic cyclization (Figure 7). The corresponding ethylene oxide **10** was obtained by

reacting β-bromoperoxide **9** with hexamethylditin in a benzene solution at 25 °C using di-tert-butyl bis-nitric acid as an initiator. The results show that with the increase of substituted methyl groups, the cyclization rate increases significantly, and this study is the first to demonstrate that the Thorpe-Ingold effect also plays a role in the homolysis reaction.

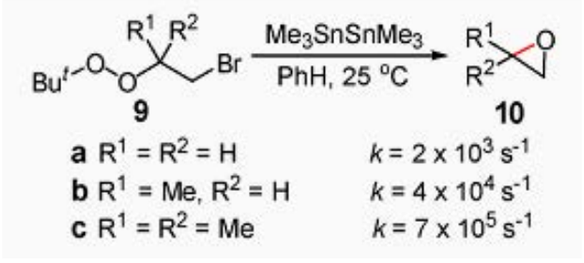


Figure 7: Thorpe-Ingold effect assisted epoxidation through radical reaction

The same research group also studied a system similar to the homolysis—that is, the cyclization of chloroethanol 11 to form ethylene oxide 10 (Figure 8), and the reaction rate ratio of compounds 11a-c is about 1:20:250. Due to the geminal substitution, on the one hand, the tension of forming the small ring is reduced, and on the other hand, it also plays the role of stabilizing the small ring. Thus, the presence of geminal disubstituents increases the rate of radical cyclization.

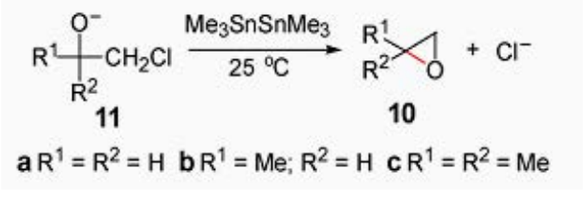


Figure 8: Thorpe-Ingold effect assisted epoxidation of chloroethanol

Synthesis of four-member ring products

Cyclobutane derivatives

Radical reaction

When studying the formation of cyclobutane by free radical reaction, Jung *et al*. found that geminal disubstitution can improve the cyclization efficiency (Figure 9) (Jung, Trifunovich & Lensen, 1992; Jung & Kiankarimi, 1995,1998; Jung & Marquez, 1997; Jung, Marquez & Houk, 1999). When R is ethoxy and ethoxycarbonyl, cyclobutane product **14** is mainly obtained; when R is methyl, only 25% of cyclobutane product **14** is obtained; and when R is hydrogen, only reduction product **13** is obtained. When the two Rs are $O(CH_2)_3O$ and $O(CH_2)_2O$, as the internal angle of the substitution position increases, it is not conducive to cyclization, and the product changes from cyclobutane 14 as the main product to the reduction product **13** as the main product. Electronic effects and steric hindrance together affect the selectivity of the reaction (Jung, 1999).

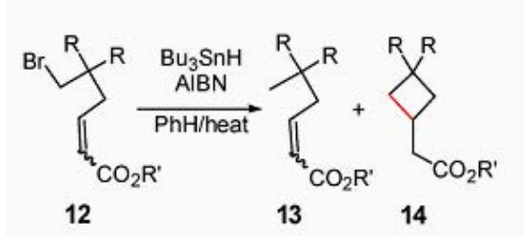


Figure 9: Thorpe-Ingold effect assisted cyclobutane formation via radical reaction

Metal-catalyzed cyclization

Chaumontet *et al*. (2008) studied the palladium catalyst system to activate CH on methyl to

synthesize benzocyclobutene (BCB) **16** (Figure 10).

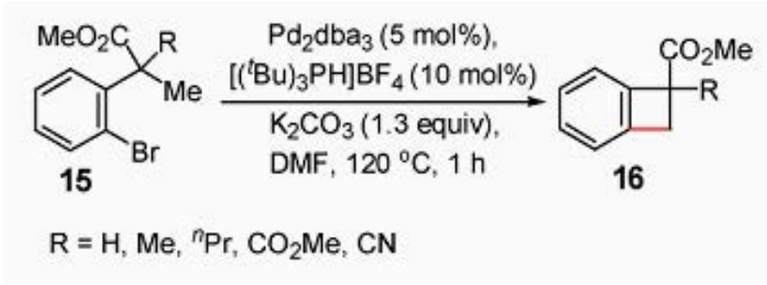


Figure 10: Thorpe-Ingold effect assisted formation benzocyclobutanes

When R = H, no target product was formed even if the reaction time was extended to 4 h. Substituted BCB,**16** can be obtained in higher yields when R is an alkyl group, an alkoxycarbonyl group, or a nitrile group. When R = Me, the corresponding BCB can be obtained regardless of whether there are electron-withdrawing or electron-donating groups on the benzene ring, with yields ranging from 44% to 92%. The results show that after geminal di-substitution at the benzylic position, the dominant conformation for ring formation is dominant. After palladium is added to the C–Br bond in an oxidative way, the C–H bond on the methyl group can be activated to make benzocyclobutene (BCB).

Oxetane derivatives

Shiina *et al*. (2012) studied 2-methyl-6-nitrobenzoic anhydride (MNBA) to assist in the total synthesis of orlistat and found that there is no substituent on the molecular chain of β-hydroxycarboxylic acid, the yield is very low, and only a small amount can be obtained by increasing the temperature of Cyclobutyrolactone (Figure 11).

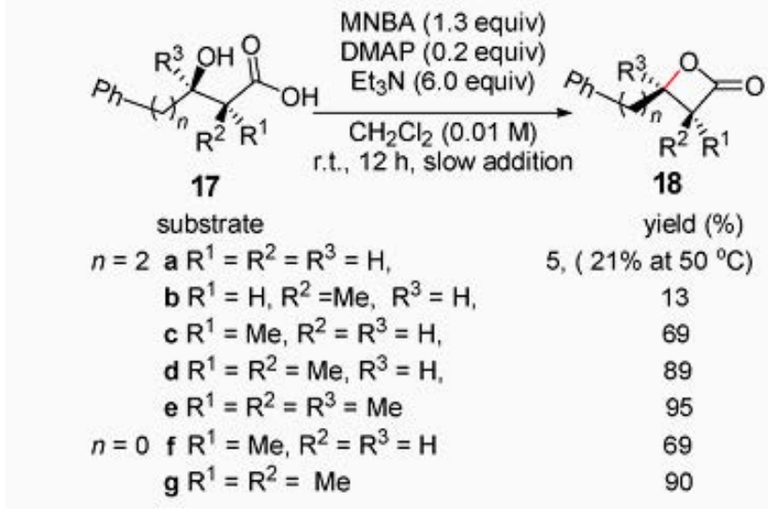


Figure 11: Thorpe-Ingold effect assisted esterification of β-hydroxyacids

The introduction of substituents at the α and β positions of the carboxylic acid can improve the yield. Compared to 17b and 17c, it is more favourable for cyclization when the methyl group at the α-position of the carboxylic acid and the hydroxyl group at the β-position are in trans, because when the α-position of the carboxylic acid is substituted by a methyl group, the internal angle decreases, which is favourable for the cyclization reaction. The methyl group of the formula structure has a large steric hindrance with the hydroxyl group, which is not conducive to cyclization. The benzene ring (17f) connected to the same carbon as the hydroxyl group has no effect on the esterification yield. The α-position of the carboxylic acid was substituted with a geminal dimethyl group (17d, 17e, 17g), the internal angle was further reduced, the energy required for the reaction was reduced, and high yields of β-lactones were obtained.

The methyl substitution (17e) on the hydroxyl carbon is also helpful because it lowers the energy needed for the reaction, which helps improve the yield even more.

DISCUSSION

The Thorph-Ingold effect is not only limited in the reactivity of the substrate molecules but also effective for ligand binding with metal salts. The Thorpe-Ingold effect caused by gem-dialkyl substitution of the ligand framework led to a chelation effect that produced excellent yields and selectivities for maintaining the nucleophile configuration. While working on optimising the ligand to increase the branched product ratio, an intriguing gem-dialkyl effect was found in the ligand backbone. Traditionally, the Thorpe-Ingold effect has been used to describe how gem-dialkyl substitution causes a conformational restriction that speeds up the process by bringing the two active hemispheres of the molecules into proximity (O'Neill, Riesebeck & Cornella, 2018). The Thorpe-Ingold effect caused by gem-Dialkyl replacement of the ligand backbone led to a chelation effect that produced excellent yields and selectivities for maintaining the nucleophile configuration. Recent developments in using the Thorpe-Ingold effect concept to explain certain synthetic chemistry, including organosilicon compounds, were addressed by Luh and co-workers, with a focus on the photophysical characteristics of some dialkylsilylene spaced conjugated chromophores (Luh & Hu, 2010). In these silicon-containing copolymers, the silicon moieties are regarded as insulating tetrahedral spacers. The silicon substituents are easily adjustable, and their steric environment may determine the orientation (or helicity) of the copolymers and, consequently, their photophysical characteristics. The Thorpe-Ingold effect may be used to understand this substituent impact on silicon.

CONCLUSION

In conclusion, the Thorpe-Ingold effect can effectively promote intramolecular and intermolecular cyclization and improve the reaction rate and yield. Moreover, this effect is applicable to various systems and reaction types, and the effect is obvious. Therefore, the Thorpe-Ingold effect can be utilized in the cyclization reaction to improve the synthesis efficiency. It is believed that there will be more theoretical and experimental studies on this effect in the future, and improving the understanding of the essence of this effect will be beneficial to its application in synthesis.

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