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This Week's Citation Classic®

Prelog V. Untersuchungen über asymmetrische Synthesen I. Über den sterischen Verlauf der Reaktion von α-Ketosäure-estern optisch aktiver Alkohole mit *Grignard*'schen Verbindungen (Asymmetric syntheses. I. The steric reaction of α-keto acid esters of optically active alcohols with Grignard reagents). *Helv. Chim. Acta* 36:308-19. 1953.
[Organisch-chemisches Laboratorium. Eidgenössische Technische Hochschule. Zürich. Switzerland]

A scheme was proposed that correlated the configurations of the α-hydroxy acids formed by addition of Grignard reagents to α-keto acid esters of chiral alcohols with the configuration of these alcohols. It was an early successful attempt to rationalize stereoselectivity. [The *SCI*® indicates that this paper has been cited in over 250 publications.]

Making Sense of Stereoselectivity

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I became aware of the extensive work of Alexander McKenzie and coworkers only in 1948 by reading a review article of P.D. Ritchie about asymmetric synthesis.[1] Since 1904 they had studied optical activity of α-hydroxy acids obtained by treatment of α-keto acid esters of chiral alcohols with Grignard reagents and saponification of the resulting esters.

On the basis of the assumption that in acyclic cases the stereoselectivity is sterically controlled by conformation, a simple scheme was proposed to predict the steric course of these asymmetric reactions. It gave me great satisfaction that several previous experimental results, which were not in agreement with these predictions, turned out to be erroneous. By repeating McKenzie's experimental work we could show that those results, which contradicted the scheme, were due to partial asymmetric saponification of the α-hydroxy acid esters of the chiral alcohols. When saponification was complete, the results were in agreement with our predictions.

By this discovery I became so confident about the predictive power of the scheme that I started to use, successfully as it turned out, the asymmetric synthesis of atrolactic acid, from phenylglyoxylic acid esters of chiral natural alcohols, to determine the unknown absolute configuration of these alcohols.[2,3] Applying the same ideas to the steric control of "asymmetric syntheses," we also designed and prepared auxiliary alcohols, leading to increased optical yields of α-hydroxy acids.[4,5]

I lectured about this work in the summer of 1951 to the XIIth International Congress of Pure and Applied Chemistry in New York City.[6] On a trip after the congress I met Don Cram for the first time. He told me that he developed ideas similar to ours to explain the stereoselectivity of reactions studied by his group. His seminal paper about this topic appeared in 1952.[7] Our common early efforts to predict and control stereoselectivity, which today plays such an enormous role in organic chemistry [see, for example, reference 8], stimulated experimental work as well as criticism from many chemists. This is probably the reason my paper is also often cited.

1. **Ritchie P D.** Recent views on asymmetric synthesis and related processes. *Advan. Enzymol.* 7:65-110. 1947. (Cited 15 times.)
2. **Dauben W G, Dickel D F, Jeger O & Prelog V.** Untersuchungen über asymmetrische Synthesen III. Über die Anwendung der asymmetrischen Synthese zur Konfigurationsbestimmung bei Triterpenen und Steroiden (Asymmetric syntheses. III. The application of asymmetric synthesis for determining the configuration of triterpenes and steroids). *Helv. Chim. Acta* 36:325-35. 1953. (Cited 65 times.)
3. **Fiaud J C.** Prelog's method. (Kagan H B, ed.) *Stereochemistry*. Stuttgart, FRG: Thieme. 1977. Vol. 3. p. 11-49. (Cited 5 times.)
4. **Prelog V, Ceder O & Wilhelm M.** Untersuchungen über asymmetrische Synthesen VII. Über optisch aktive Hilfsalkohole für asymmetrische Synthese von α-Oxysauren aus α-Ketosäure-estern und *Grignard*'schen Verbindungen (Asymmetric syntheses. VII. Optically active auxiliary alcohols for asymmetric synthesis of α-hydroxy acids from α-keto acid esters and Grignard reagents). *Helv. Chim. Acta* 38:303-12. 1955. (Cited 20 times.)
5. **Prelog V, Philbin E, Watanabe E & Wilhelm M.** Untersuchungen über asymmetrische Synthesen VIII. Optisch aktive Hilfsalkohole mit einem asymmetrischen Kohlenstoffatom (Asymmetric syntheses. VIII. Optically active auxiliary alcohols with an asymmetric carbon atom). *Helv. Chim. Acta* 39:1086-95. 1956. (Cited 50 times.)
6. **Prelog V & Dauben W.** *Abstracts of papers of the XIIth International Congress of Pure and Applied Chemistry*. September 1951. p. 401. (Cited 5 times.)
7. **Cram D J & Abd Elhafez F A.** Studies in stereochemistry. X. The rule of "steric control of asymmetric induction" in the synthesis of acyclic systems. *J. Amer. Chem. Soc.* 74:5828-35. 1952. (Cited 615 times.) [See also: **Cram D J.** Citation Classic. (Barrett J T, ed.) *Contemporary classics in the life sciences. Volume 2: the molecules of life*. Philadelphia: ISI Press. 1986. p. 248.]
8. **Harada K.** Asymmetric heterogeneous catalytic hydrogenation. (Morisson J D, ed.) *Asymmetric syntheses*. New York: Academic Press. 1985. Vol. 5. p. 381. (Cited 5 times.)

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