

Utilizing silicon chemistry: A greener approach for achieving regioselective Wittig rearrangements and [1,2]-Carbon to carbon silyl migration

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1 Abstract

- The Wittig rearrangements ([2,3], [1,2] and [1,4]) are a pivotal synthetic strategy for forming carbon-carbon bonds.
- Tin-lithium exchange provided regioselectivity in Wittig rearrangements, but tin's toxicity led to a search for other materials.

Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927-1928.

- Our prior research has demonstrated that directed carbanion generation through silicon-lithium exchange or α deprotonation to silicon significantly enhances regioselectivity in Wittig rearrangements. Therefore, it is a greener approach to Wittig rearrangements.

Mori-Quiroz, L. M.; Maleczka, R. E., Jr. *J. Org. Chem.* **2015**, *80*, 1163-1191

- An atom economical route for accessing α silyl alkanals has been developed using [1,2]-Carbon to carbon silyl migration chemistry.

For reviews on Wittig rearrangements see: Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885-902.; L. Rycek, L.; Hudlicky, T. *Angew. Chem., Int. Ed.*, **2017**, *56*, 6022-6066; and Wang, F.; Wang, J.; Zhang, Y.; Yang, J. *Tetrahedron* **2020**, *76*, 130857.

2 Possible Wittig rearrangement pathways of an allylic ether

3 Wittig rearrangement and its applications

- The Wittig rearrangement involves the isomerization of carbanionic ethers, resulting in products that predominantly feature alcohol or carbonyl functionalities.

Atom economy

- The Wittig rearrangement has gathered substantial interest within the scientific community owing to its mechanistic perspective and synthetic utility.
- Guo-Ming Ho and Yu-Jang Li developed a practical method in which after [1,2]-Wittig rearrangement/lactonization, γ -benzyl butenolides were applied in total synthesis.

Rautenstrauch, V. *Chem. Comm.* **1970**, 4.
 Ho, G.-M.; Li, Y.-J. *Asian J. Org. Chem.* **2018**, *7*, 145-149.

4 Control of regioselectivity during Wittig rearrangement using tin-lithium exchange chemistry

- For unsymmetrically substituted ethers, the generation of an anion capable of Wittig rearrangement can be controlled by installing an anion-generating group at either the α or α' .

[L] = anion generating group

- The tin-lithium exchange generates unstable carbanions, which can then be isomerized via Wittig rearrangements. The Wittig-Still rearrangement has been applied widely in the total synthesis of natural products.
- The major disadvantage of this method is the toxicity associated with tin, which led to a search for approaches involving non-toxic materials.

Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927-1928.
 Maleczka, R. E., Jr.; Geng, F. *Org. Lett.* **1999**, *1*, 1111-1118.

5 Regioselective Wittig rearrangement using silicon chemistry: a greener approach

- Our group developed regioselective Wittig rearrangements of α -alkoxy silanes via silicon-lithium exchange based on the previous idea.

- A milder approach utilizing fluoride deprotection of the silyl group also enables [2,3]-Wittig rearrangement.

- Another way of controlling the regioselectivity of unsymmetrically substituted ethers is by modifying the pKa of the protons at the α or α' position. For instance, placing a silyl group at α or α' position can act as an anion stabilizing group.
- Our research group has utilized this approach to provide selectively in [1,4]-Wittig rearrangement products.

Maleczka, R. E., Jr.; Geng, F. *Org. Lett.* **1999**, *1*, 1115-1118.
 Maleczka, R. E., Jr.; Geng, F. *Org. Lett.* **1999**, *1*, 1111-1113.
 Ornyozili, E. N.; Maleczka, R. E., Jr. *Chem. Commun.* **2006**, 23, 2466-2468

6 Stereoconvergent [1,2]- and [1,4]-Wittig rearrangements of 2-silyl dihydropyrans

- Wittig rearrangements of diastereomeric 2-silyl dihydropyrans result in regio-divergent ring contractions to α -silylcyclopentenols and/or (α -cyclopropyl)acylsilanes.

- The [1,4]-Wittig predominates when the starting pyrans bear *ortho* and *para*-directing groups on the aromatic appendage and/or by sterically demanding silyl groups.
- The [1,2]-pathway dominates with *meta*-directing or electron-poor aromatic moieties and/or smaller silyl groups.

Substrate	Yield (%)	
	[1,4]-Wittig	[1,2]-Wittig
SiMe ₃ , 4-MeC ₆ H ₄	86	7
SiMe ₃ , 4-CF ₃ C ₆ H ₄	trace	80
SiMe ₃ , C ₆ H ₅	58	24
SiEt ₃ , C ₆ H ₅	93	5

- Cis* and *trans* diastereomers exhibit different reactivities but converge to a single [1,2]- or [1,4]-Wittig product with high diastereoselectivity and yield.

Mori-Quiroz, L. M.; Maleczka, R. E., Jr. *J. Org. Chem.* **2015**, *80*, 1163-1191.

7 Silylcyclopropanes by selective [1,4]-Wittig rearrangement of 4-silyl dihydropyrans

- Relocating the silyl group to the 4-position of the dihydropyran scaffold led to a highly selective [1,4]-Wittig rearrangement, which afforded silyl cyclopropyl acetaldehydes.

2a^a, dr = 3.3:1; 2b^b, dr = 11:1; 2c, dr = 2.5:1; 2d, dr = 2:1; 2e, dr = 8.3:1; 2f, dr = 1.1:1; 2g, dr = 1.6:1; 2h^a, dr = 2:1; 2i, dr = 1:1; 2j, dr = 1:1; 2k^c, dr = 4.3:1; 2l^d, dr = 9.4:1

^a Diastereoselectivity determined by ¹H NMR of the crude reaction mixture.
^b Reaction run on a 2 mmol scale.
^c A small amount (<5%) of the presumed [1,2]-Wittig product within a complex mixture was observed but not fully characterized.
^d 15% of unreacted dihydropyran 1h was recovered.
^e 2.2 equiv of sec-BuLi was used.

Mori-Quiroz, L. M.; Maloba, E. W.; Maleczka, R. E., Jr. *Org. Lett.* **2021**, *23*, 5724-5728.

8 General scheme towards the synthesis of [1,2]- and [1,4]-Wittig starting materials (2-silyl-6-aryl-5,6-dihydropyrans)

Mori-Quiroz, L. M.; Maleczka, R. E., Jr. *J. Org. Chem.* **2015**, *80*, 1163-1191.

9 Serendipitous [1,2]-Carbon to carbon silyl migration

Atom economy

Singh, D.; Maloba, E. W.; Maleczka, R. E., Jr. *manuscript in preparation*

10 Multicomponent reaction for the synthesis of spiro oxindole (Master's thesis)

- Atom economy
- Greener solvent
- Visible light as an energy source

Department of Chemistry, Indian Institute of Technology Patna (Unpublished work)

11 Conclusions / Future Work

- Wittig rearrangements of diastereomeric 2-silyl-dihydropyrans result in regio-divergent ring contractions to α -silylcyclopentenols and/or (α -cyclopropyl)acylsilanes.
- Under acidic conditions, α -hydroxy allyl silanes undergo [1,2]-carbon to carbon silyl migration, leading to the formation of α -silyl aldehydes.
- A one-pot multicomponent reaction for the synthesis of spiro oxindole was developed. This method has the advantages of high yields, low temperatures, visible light as an energy source, and ethanol/water as a solvent.
- Efforts are being made towards a more sustainable method for Wittig rearrangement by integrating photochemistry into the Wittig rearrangement.

12 Acknowledgements and funding

Maleczka Group Members

NIH National Institutes of Health
 Turning Discovery Into Health

MICHIGAN STATE UNIVERSITY

- Dr. Dan Holmes
- Tony Schillmiller
- Casey Johnny