

Cp₂TiCl₂–Catalyzed Synthesis of Tertiary Alcohols by the Reaction of AlCl₃ with Ketones and Arylolefins †

Liaisan K. Dilmukhametova ^{1,*}, Mariya G. Shaibakova ¹ and Ilfir R. Ramazanov ^{1,2}

¹ Institute of Petrochemistry and Catalysis of Russian Academy of Sciences, 141 Prospekt Oktyabrya, Ufa 450075, Russian Federation; shaibakovamg@mail.ru (M.G.S.); ilfir.ramazanov@gmail.com (I.R.R.)

² Ufa State Petroleum Technological University, 1, Kosmonavtov Str., Ufa, 450062, Russian Federation

* Correspondence: leisandil@inbox.ru

† Presented at the 26th International Electronic Conference on Synthetic Organic Chemistry, 15–30 Nov 2022.

Available online: <https://ecsoc-26.sciforum.net/>

Abstract: We have previously obtained significant results on the cycloalumination of olefins with EtAlCl₂ in the presence of magnesium and Cp₂ZrCl₂ or Cp₂TiCl₂ catalyst. Here we report the development of an efficient one-pot catalytic method for the synthesis of tertiary alcohols from AlCl₃, arylolefins and ketones under the action of Cp₂TiCl₂. The developed method for producing tertiary alcohols has a general character and allows to convert styrene and substituted styrenes (*ortho*-, *para*-methylstyrenes) into aryl-substituted tertiary alcohols with yields up to 76% in the reaction with acetone or methyl ethyl ketone. We assume that the reaction proceeds through the formation of titanacyclopropane intermediate.

Keywords: titanocene; catalysis; arylolefines; ketones; tertiary alcohols.

Citation: Dilmukhametova, L.K.; Shaibakova, M.G.; Ramazanov, I.R.

Cp₂TiCl₂–Catalyzed Synthesis of Tertiary Alcohols by the Reaction of AlCl₃ with Ketones and Arylolefins.

2022, 4, x.

<https://doi.org/10.3390/xxxxx>

Academic Editor(s):

Published: 15 November 2022

Publisher’s Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



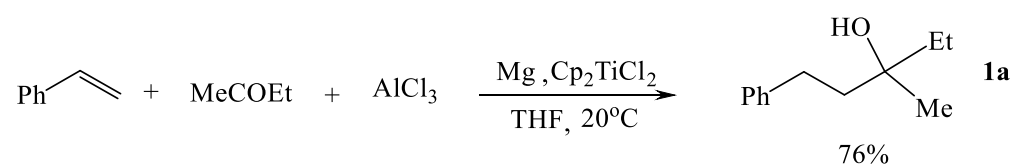
Copyright: © 2022 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Tertiary alcohols are widely used in medicine and industry [1,2]. One of the best methods for the preparation of tertiary alcohols is the reaction of ketones with organo-magnesium compounds [1,3,4]. We have previously obtained significant results on the cycloalumination of olefins with EtAlCl₂ in the presence of magnesium and Cp₂ZrCl₂ or Cp₂TiCl₂ catalyst [5–7]. Here we report the development of an efficient one-pot catalytic method for the synthesis of tertiary alcohols from AlCl₃, arylolefins and ketones under the action of Cp₂TiCl₂.

2. Results and Discussion

We found that the reaction of styrene with AlCl₃ and methyl ethyl ketone in the presence of metallic Mg as an acceptor of halide anions and Cp₂TiCl₂ catalyst (10 mol %) in THF solvent at 20 °C for 8 h leads to the formation of 3-methyl- 1-phenylpentan-3-ol **1a** in 76% yield (Scheme 1).

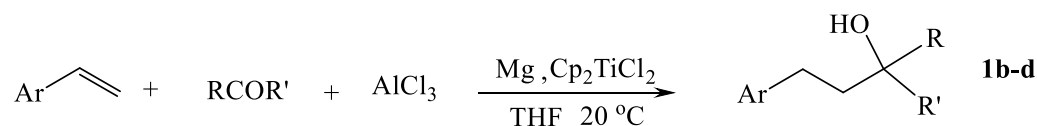


Scheme 1. The reaction of styrene with AlCl₃ and methyl ethyl ketone in the presence of metallic Mg.

In non-ether solvents (hexane, DMSO, DMF, methylene chloride), the yield of the reaction product **1a** is less than 11%. Carrying out the reaction at ~0 °C reduces its rate

and the conversion of the initial styrene, which does not exceed 20% for 15 h. With an increase in temperature to ~ 65 °C, the reaction is completed in almost 2 h, but it is less selective. The best results were obtained when the reaction was carried out in tetrahydrofuran in the presence of Ti-containing catalysts. The reaction does not proceed in the absence of a catalysts.

The developed method for producing tertiary alcohols has a general character and allows to convert styrene and substituted styrenes (*ortho*-, *para*-methylstyrenes) into aryl-substituted tertiary alcohols with 66-73 % yields in the reaction with acetone or methyl ethyl ketone (Scheme 2).



b: Ar = Ph, R, R' = Me

d: Ar = *p*-methylphenyl, R = Me, R' = Et

c: Ar = *o*-methylphenyl, R = Me, R' = Et

Scheme 2. Cp₂TiCl₂-Catalyzed synthesis of tertiary alcohols by the reaction of AlCl₃ with ketones and arylolefins.

The structures of compounds 1a-d were identified using one-dimensional (¹H, ¹³C, DEPT135) and two-dimensional (HSQC, HMBC, HHCOSY) NMR spectroscopy, HRMS.

3. Conclusion

Thus, we have developed a new one-pot method for the production of substituted tertiary alcohols from arylolefins and ketones in the presence of AlCl₃ and catalytic amounts of Cp₂TiCl₂.

4. Experimental Part

General. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance-II 400 Ascend (400 MHz for ¹H and 100 MHz for ¹³C) and Bruker Avance II 500 HD Ascend (500,17 MHz for ¹H and 125,78 MHz for ¹³C) instruments in CDCl₃. Mass spectra were obtained on a Finnigan 4021 instrument. Chromatographic analysis was performed on a Shimadzu GC-9A instrument using a 2000×2 mm column, the SE-30 (5 %) stationary phase on Chromaton N-AW-HMDS (0.125-0.160 mm), helium carrier gas (30 mL/min), temperature programming from 50 to 300 °C at a 8 °C/min rate. IR spectra were recorded on Bruker VE Vertex 70v spectrometr as liquid films and are reported in wavenumbers (cm⁻¹). Elemental analysis was performed using a Carlo-Erba CHN 1106 elemental analyser. For column chromatography, Acros silica gel (0.060–0.200 mm) was used. Reactions with organometallic compounds were performed in a dry argon flow. Commercially available styrenes, ketones, Cp₂TiCl₂, Mg and EtAlCl₂ (Aldrich) were used. The solvents were dried and distilled immediately prior to use.

Experimental Procedures. A 50 mL glass reactor equipped with a magnetic stirrer under a dry argon atmosphere at 0 °C, was charged under stirring with 5 mL of THF, 2 mmol of aryl olefin, 4 mmol of AlCl₃, 2 mmol of ketone, 4 mmol of Mg (powder), and 0.2 mmol of Cp₂TiCl₂. The temperature was brought to room temperature (20–21 °C) and the reaction mixture was stirred for 8 h. The reaction mixture was treated with a 7–10% HCl aqueous solution, the reaction products were extracted with diethyl ether, dried over calcined MgSO₄, the solvent was evaporated on a rotary evaporator. The products were isolated by column chromatography (silica gel L, 180/250 μ, eluent–hexane:ethyl acetate (1:1)).

Compound 1a was isolated by column chromatography provided 3-methyl-1-phenylpentan-3-ol as a yellow oil (73 %). R_f 0.61. IR (film): 3375; 3027; 2930;

2873; 1454; 1379; 1137; 1026; 752 cm⁻¹. ¹H NMR (500.1 MHz, CDCl₃), δ: 0.97 (t 3H, J 7.0 Hz), 1.26 (s 3H), 1.55–1.62 (m 2H), 1.77–1.81 (m 2H), 2.68–2.72 (m 2H), 7.27–7.30 (m 5H). ¹³C NMR (500.1 MHz, CDCl₃), δ: 8.30, 26.34, 30.35, 34.42, 43.28, 72.85, 125.75, 128.36, 128.43, 142.73. HRMS, m/z: 201.0618 [M + Na]⁺. Found (%): C, 80.82; H, 10.06. Calc. for C₁₂H₁₈O (%): C, 80.85; H, 10.18.

Compound 1b was isolated by column chromatography provided 2-methyl-4-phenylbutan-2-ol as a yellow oil (69 %). R_f 0.61. IR (film): 3376; 3011; 2916; 2902; 1466; 1359; 1131; 828; 744 cm⁻¹. ¹H NMR (500.1 MHz, CDCl₃), δ: 1.32 (s 6H), 1.80–1.84 (m 2H), 2.71–2.75 (m 2H), 7.19–7.33 (m 5H). ¹³C NMR (500.1 MHz, CDCl₃), δ: 29.35, 30.76, 45.75, 70.92, 125.76, 128.32, 128.42, 142.53. HRMS, m/z: 187.0274 [M + Na]⁺. Found (%): C, 80.40; H, 9.70. Calc. for C₁₁H₁₆O (%): C, 80.44; H, 9.82.

Compound 1c was isolated by column chromatography provided 3-methyl-1-(2-methylphenyl)pentan-3-ol as a yellow oil (66 %). R_f 0.61. IR (film) 3301; 3037; 2902; 1647; 1359; 1016; 746 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ: 0.98 (t 3H, J 7.0 Hz), 1.28 (s 3H), 1.61–1.64 (m 2H), 1.70–1.74 (m 2H), 2.35 (s 3H), 2.67–2.71 (m 2H), 7.14–7.17, 7.28 (m 4H). ¹³C NMR (400 MHz, CDCl₃) δ: 8.28, 19.23, 26.28, 27.67, 34.37, 41.98, 72.90, 125.92, 126.09, 128.75, 130.23, 135.81, 140.79. HRMS, m/z: 215.0726 [M + Na]⁺. Found (%): C, 81.17; H, 10.35. Calc. for C₁₃H₂₀O (%): C, 81.20; H, 10.48.

Compound 1d was isolated by column chromatography provided 3-methyl-1-(4-methylphenyl)pentan-3-ol as a yellow oil (70 %). R_f 0.61. IR (film) 3309; 3063; 2935; 1674; 1386; 1081; 751 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ: 0.97 (t 3H, J 7.0 Hz), 1.21 (s 3H), 1.58–1.61 (m 2H), 1.67–1.71 (m 2H), 2.21 (s 3H), 2.62–2.67 (m 2H), 7.12–7.16 (m 4H). ¹³C NMR (400 MHz, CDCl₃) δ: 8.26, 21.00, 26.26, 30.01, 34.37, 41.68, 72.90, 126.99, 128.05, 136.11, 139.60. HRMS, m/z: 215.0735 [M + Na]⁺. Found (%): C, 81.18; H, 10.35. Calc. for C₁₃H₂₀O (%): C, 81.20; H, 10.48.

Author Contributions: Conceptualization, L.D. and M.Sh.; methodology, M.Sh.; software, L.D.; validation, L.D.; formal analysis, L.D.; investigation, L.D.; resources, I.R.; data curation, L.D.; writing—original draft preparation, L.D.; writing—review and editing, I.R.; visualization, L.D.; supervision, M.Sh.; project administration, I.R.; funding acquisition, I.R.

Funding: This research was funded by Russian Science Foundation, grant number 19-73-20128. The analytical part of the study was carried out within the framework of the state assignment of the Ministry of Education and Science (No. FMRS-2022-0076).

Acknowledgments: The results were obtained on unique equipment at the “Agidel” Collective Usage Center (Ufa Federal Research Center, Russian Academy of Sciences).

Institutional Review Board Statement:

Informed Consent Statement:

Data Availability Statement:

Conflicts of Interest: The authors declare no conflict of interest.

References

1. H. G. Richey, *Grignard Reagents: New Developments*, Wiley, New York, **1999**.
2. J. G. de Vries in *Quaternary stereocenters, challenges and solutions for organic synthesis* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**, chap. 2, 25–50.
3. V. Grignard, *C.R. Hebd. Seances Acad. Sci.* **1900**, *130*, 1322.
4. D. Seyferth, *The Grignard Reagents. Organometallics* **2009**, *28*, 1598–1605, doi:10.1021/om900088z.
5. L.O. Khafizova, R.R. Gubaidullin, M.G. Shaibakova, U.M. Dzhemilev, *Synthesis of substituted cyclopropanes from vinylarenes and esters in the presence of Cl_nAlEt_{3-n} and Cp₂ZrCl₂ as catalyst. Rus. J. of Organic Chemistry* **2013**, *49*, 815–821, doi:10.1134/S107042801306002X.
6. L.O. Khafizova, M.G. Shaibakova, U.M. Dzhemilev *A new one-pot synthesis of tetrasubstituted pyrazines by the Ti-catalyzed reaction of aromatic and benzyl-substituted nitriles with EtAlCl₂. Chemistry Select* **2018**, *3*, 11451–11453, doi:10.1002/slct.201802787.

-
7. M.G. Shaibakova, L.O. Khafizova, N.M. Chobanov, R.R. Gubaidullin, N.R. Popod'ko, U.M. Dzhemilev. The efficient one-pot synthesis of tetraalkyl substituted furans from symmetrical acetylenes, EtAlCl₂ and carboxylic esters catalyzed by Cp₂TiCl₂. *Tetrahedron Letters* **2014**, *55*, 1326–1328, doi:10.1016/j.tetlet.2014.01.015.

1
2
3
4