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Surprises in the Study of Ruthenium-catalyzed Stereo and Chemoselective Aldolizations

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ABSTRACT

A convenient and diastereoselective method was developed for the synthesis of aldol derivatives in the presence of a catalytic amount of $RuCl_3.nH_2O$ under solvent-free conditions. Aldol adducts were obtained in good yields and with high chemoselectivity in short reaction times. In this protocol, aromatic and heteroaromatic aldehydes readily participate as electrophilic cross-aldol partners with a range of cycloalkanones as ketone donors.

Key words: catalytic aldol reaction, diastereoselective aldolization, green synthesis

INTRODUCTION

Apart from the economic and environmental aspects, the use of catalysts has shown their attractiveness due to their activity and selectivity.[1-5] Metal-catalyzed reactions have made a great contribution to the recent growth of organic synthesis and a variety of synthetic methods have been reported using transition metal complexes in stoichiometric or catalytic amounts.[6,7] Among the transition metal Lewis acids, ruthenium salts and complexes display remarkable properties.[8,9]

During the last decade, molecular ruthenium catalysts have promoted tremendous developments in organic synthesis methodology and polymer science, and revealed novel activation processes. Ruthenium catalysis constitutes an emerging field for the selective preparation of fine chemicals. This is due to the availability of a large number of well-defined and stable ruthenium precatalysts offering several possible oxidation states. They usually tolerate functional groups and have revealed catalytic activities for a wide range of chemical transformations with atom economy.[10-15]

On the other hand, carbon-carbon bond formation is the essence of organic synthesis and its variants have been used extensively in many important syntheses.[16-19] The aldol reaction is a

powerful method for forming C-C bonds.[20-24] The reaction has proven to be a powerful and general method for the stereocontrolled construction of β-hydroxy ketone derivatives and has relevant application in the synthesis of carbohydrates, amino sugars, steroids, natural heteroatomic molecules, fine chemicals and pharmaceuticals. There are several methods to synthesized aldol products. However, only few reports described the use of catalyst to perform the aldol reactions in the simple conditions.

Over the last thirty years, seminal research from the laboratories of Evans,[25] Heathcock,[26,27] Masamune[28] and Mukaiyama[29] have established this venerable reaction as the principal chemical method for the stereoselective construction of complex polyol architecture. Also, many efforts have been addressed towards the synthesis of organocatalysts that have produced systems able to afford very good stereoselectivities. However, the achievement of a versatile organocatalyst, able to work with low catalyst loading remains a challenge.[30-34]

These observations prompted us to synthesize a series of aldol derivatives with complete diastereoselectivity using $RuCl_3.nH_2O$ as an efficient catalyst via a convenient one-pot reaction under solvent-free conditions. It is worth noting that only a little amount of ruthenium catalyst was used, which represents a significant improvement over the conventional aldol reaction.

MATERIAL AND METHODS

General

All solvents, organic and inorganic compounds were purchased from Merck and Fluka and used without further purification. All reactions were followed by TLC with detection by UV light. IR spectra were recorded on Shimadzu FTIR-8400S spectrometer. ^{1}H NMR spectra were obtained on a Bruker DRX-500 Avance spectrometer and ^{13}C NMR were obtained on a Bruker DRX-125 Avance spectrometer. Samples were analyzed in $CDCl_3$, and the chemical shift values are reported in ppm relative to TMS (tetramethylsilane) as the internal reference. Elemental analyses were made by a Carlo-Erba EA1110 CHNO-S analyzer and agreed with the calculated values. The isolation of pure products was carried out via preparative thin layer chromatography (silica gel 60 GF_{254}, Merck).

Typical procedure for ruthenium-catalyzed aldol reaction

A mixture of aldehyde (1 mmol), ketone (3 mmol), $RuCl_3.nH_2O$ (0.02 mmol) and KOH (28 mg, 0.5 mmol) was stirred at 15 °C and monitored by TLC. After the indicated reaction time, the reaction mixture was purified by thin layer chromatography (silica gel, EtOAc-petroleum ether, 4:12) providing the aldol adduct.

Selected Spectral Data of the Products

Product (3aa)

Yellow oil; FT-IR (neat) (υ_{max}/cm^{-1}): 1666, 3415. Only syn isomer was isolated. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H(ppm) 1.69-2.65 (m, 7H), 2.52 (s, 3H), 3.03 (d, *J* = 3.2 Hz, OH), 5.39 (m, 1H), 7.28 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C(ppm) 12.2, 14.0, 14.9, 41.1, 58.1, 72.2, 126.5, 128.5, 133.5, 135.2, 218.4. Anal Calcd for $C_{13}H_{16}O_2S$ (236): C, 66.10; H, 6.77; S, 13.55. Found: C, 66.10; H, 6.79; S, 13.56.

Product (3ba)

Yellow oil; FT-IR (neat) (υ_{max}/cm^{-1}): 1656, 3412. Only syn isomer was isolated. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H(ppm) 2.50-1.74 (m, 7H), 2.28 (s, 3H), 4.73 (s, OH), 5.61 (s, 1H), 6.81 (d, *J* = 5.0 Hz, 1H), 7.24 (d, *J* = 5.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C(ppm) 16.2, 23.4, 28.8, 44.0, 57.1, 58.2, 123.8, 125.5, 124.6, 138.3, 143.3, 217.1. Anal Calcd for $C_{11}H_{14}O_2S$ (210): C, 62.85; H, 6.66; S, 15.23. Found: C, 62.86; H, 6.66; S, 15.24.

Product (3bb)

Yellow oil; FT-IR (neat) (υ_{max}/cm^{-1}): 1667, 3345. Only syn isomer was isolated. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H(ppm) 2.71-1.59 (m, 9H), 2.27 (s, 3H), 4.08 (d, *J* = 1.6 Hz, OH), 5.52 (s, 1H), 7.24-7.19 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C(ppm) 16.4, 23.6, 28.8, 42.1, 44.5, 58.2, 124.8, 125.5, 125.8, 136.3, 143.1, 217.2. Anal Calcd for $C_{12}H_{16}O_2S$ (224): C, 64.28; H, 7.14; S, 14.28. Found: C, 64.31; H, 7.16; S, 14.28.

Product (3cc)

Yellow oil; FT-IR (neat) (υ_{max}/cm^{-1}): 1674, 3465. Only syn isomer was isolated. ^{1}H NMR (500

MHz, $CDCl_3$): δ_H(ppm) 2.92-1.54 (m, 11H), 2.44 (s, 3H), 3.37 (d, *J* = 3.9 Hz, OH), 5.25 (s, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 3.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C(ppm) 15.2, 23.6, 25.3, 28.4, 28.6, 44.0, 57.8, 71.5, 124.5, 124.6, 138.6, 143.3, 217.2. Anal Calcd for $C_{13}H_{18}O_2S$ (238): C, 65.54; H, 7.56; S, 13.44. Found: C, 65.53; H, 7.56; S, 13.44.

Product (3dc)

Yellow oil; FT-IR (neat) (υ_{max}/cm^{-1}): 1678, 3366. Only syn isomer was isolated. ^{1}H NMR (500 MHz, $CDCl_3$): δ_H(ppm) 2.91-1.50 (m, 11H), 3.35 (d, *J* = 3.5 Hz, OH), 5.35 (s, 1H), 6.63-6.86 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C(ppm) 23.1, 25.6, 28.4, 29.1, 44.3, 57.8, 71.6, 124.5, 124.5, 138.5, 141.3, 217.2. Anal Calcd for $C_{12}H_{16}O_2S$ (224): C, 64.28; H, 7.14; S, 14.28. Found: C, 64.29; H, 7.14; S, 14.28.

RESULTS AND DISCUSSION

Recently, we have examined an efficient protocol for the cross aldol reaction in the presence of $RuCl_3.nH_2O/PPh_3$. In this protocol, the reaction of 1-(thiophen-2-yl)ethanone with aldehydes resulted aldol adducts in good yields without the formation of any side product.[35] The study of the Ru^{III}/PPh_3-promoted aldol reaction urged us to investigate the aldolization of aryl alkyl ketones with aromatic and heteroaromatic aldehyds in the presence of $RuCl_2(PPh_3)_3$. Ru^{II}-catalyzed cross aldol reaction proceeded at 80°C, furnishing a wide variety of â-hydroxy ketones with moderate diastereos electivities.[36] This led us to discover unexpected effects of the nature of chiral ligand on the Ru^{III}-catalyzed aldolization of aromatic aldehyds with ketones. In this method, the aldol reaction proceeded smoothly, affording the corresponding product in good yields and complete diastereoselectivities.[37]

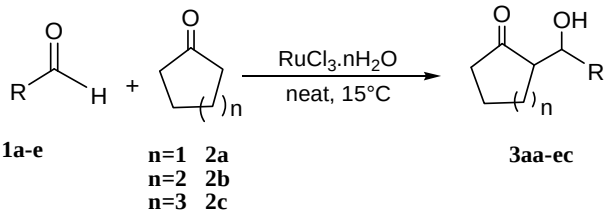
In the present protocol, due to the importance of development of new diastereoselective methodologies in the synthesis of organic compounds with high chemoselectivity, we performed Ru^{III}-catalyzed aldol reactions using various aldehydes and cycloalkanones without the use of chiral system in good yields with complete diastereoselectivity. In this method, all reactions were carried out by simply adding the ruthenium catalyst ($RuCl_3.nH_2O$) to a neat solution containing aldehyde and cycloalkanone at 15°C when the molar ratio of cycloalkanones and aldehydes was 3 (Scheme 1). The successful results of Ru^{III}-catalyzed aldol reactions are given in Table 1.

By comparing the entries, for the heteroaromatic aldehydes **1 b-d**, the reaction could complete within 1-3 h. For the aromatic aldehyde,

Table 1: Ruthenium-catalyzed cross aldol reactions of aldehydes with cycloalkanones 3aa-ec

Entry[a]	R	Aldol	Yield (%)[b]	Time (h)
1	1a 4-MeSC_6H_4	3aa	81	5
2	1b 3-Methylthiophen-2-yl	3ba	86	1.5
3	1c 5-Methylthiophen-2-yl	3ca	83	1
4	1d Thiophen-2-yl	3da	91	3
5	1a 4-MeSC_6H_4	3ab	79	4.5
6	1b 3-Methylthiophen-2-yl	3bb	76	2.5
7	1c 5-Methylthiophen-2-yl	3cb	77	3
8	1a 4-MeSC_6H_4	3ac	72	4.5
9	1b 3-Methylthiophen-2-yl	3bc	80	2.5
10	1c 5-Methylthiophen-2-yl	3cc	78	2.5
11	1d Thiophen-2-yl	3dc	73	2
12[c]	1e 4-$NO_2C_6H_4$	3ec	55	5

[a] All products were characterized by ^{1}H NMR, ^{13}C NMR and IR. [b] Yields after purification by chromatography. [c] Identified by comparison with authentic sample.[38]



1a-e **n=1 2a** **n=2 2b** **n=3 2c** **3aa-ec**

Scheme 1: Ru^{III}-catalyzed aldol reactions using various aldehydes and cycloalkanones

much longer reaction time was required. Although the activity of catalyst decreased when using aromatic aldehyde, it can be used at 2 mol% loading and only a slight excess of the ketone with respect to the aldehyde is required (3eq). This result provided a remarkable contrast to similar reactions, where a large excess of the donor carbonyl compound is mandatory to perform the reaction[37, 39-46]

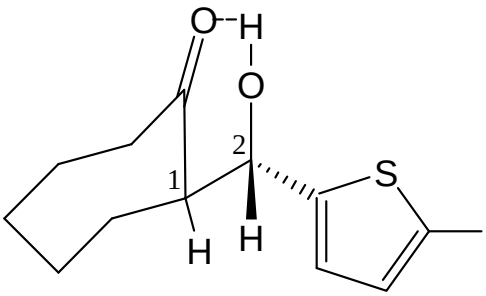


Fig. 1: Structure of proposed diastereomer 3cc

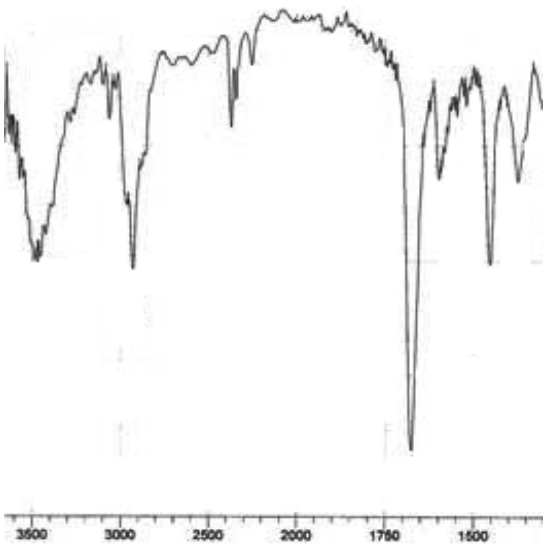


Fig. 2: IR spectrum of 3cc Wavenumber (cm^{-1})

As far as the diastereomeric ratios are concerned, complete selectivities in favor of the *syn* products were observed in all the cases 3aa-ec. Configurational assignment of diastereoisomers was attributed by NOESY, ^{1}H NMR and IR.

It is a well understood phenomenon that the lower values of the ^{1}H NMR coupling constants of the carbinol protons than 1 Hz, for example **3cc**, along with very weak correlation between the 1-H and 2-H (Figure 1) in the NOESY spectrum clearly indicate the relative stereochemistry of the aldol adduct in favor of the syn geometry. Also, in the IR spectrum of 3cc, the broad band of OH was observed with a maximum at 3500 cm^{-1}, which indicates the existence of hydrogen bonding of aldol adduct **(**Figure 2**).** In fact, the structure has been fixed in a special stereochemistry which dominated by hydrogen bonding observed in IR spectra and the tendency to minimize the steric crowding between the 5-Methylthiophen-2-yl and cycloheptanone rings. These results illuminate that 1-C, 2-C, 1-H and 2-H has the same chemical environment, that is to say **3cc** is exclusively of *syn* stereochemistry.

The fact that all of the products shared almost the same NMR and IR patterns suggests the stereochemistry of these compounds to be identical.

CONCLUSION

In brief, the direct aldol reaction of various cycloalkanones with heteroaromatic and aromatic aldehydes using catalytic amount of $RuCl_3.nH_2O$ without the use of chiral ligand proceeded smoothly under extremely mild conditions to give the corresponding aldol adducts in moderate to good yields with complete diastereoselectivity. The reaction can efficiently proceed at 15 °C with a small excess of ketone. From a practical and economic point of view this reaction condition is convenient

with respect to most of other protocols where a large excess of ketone is used. Also, the chemoselective aldolization has shown good generality and enough activity without using any organic solvent. Further investigations focusing on the mechanism and full scope of related systems are currently underway and

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REFERENCES

1. Masters, C. Homogeneous Transition Metal Catalysis-A Gentle Art, Chapman and Hall Ltd. (1981).
2. Meijere, A. D.; Diederich, F. Metal-Catalyzed Cross-Coupling Reactions, Vol. 2, 2nd edn. Wiely-VCH, New York, (2004).
3. Dou, X.-Y.; Wang, J. Q.; Du, Y.; Wang, E.; He, L.-N. *Synlett* **2007**, 3058-3062.
4. Hossein Nia, R.; Mamaghani, M.; Tabatabaeian, K.; Shirini, F.; Rassa, M. *Acta Chim. Slov*. **2013**, *60*, 889-895.
5. Qian, S.-S.; Cheng, X.-S.; You, Z.-L.; Zhu, H.-L. *Acta Chim. Slov.* **2013**, *60*, 870–874.
6. Madern, N.; Talbi, B.; Salmain, M. *Appl. Organomet. Chem*. **2013**, *27*, 6-12.
7. Kidwai, M.; Jain, A. *Appl. Organomet. Chem*. **2012**, *26*, 528-535.
8. Murahashi, S.-I. Ruthenium in Organic Synthesis, Wiely-VCH, New York, (2004).
9. Murai, S. Activation of Unreactive Bonds and Organic Synthesis, Springer, (1999).
10. Tabatabaeian, K.; Heidari, H.; Mamaghani, M.; Mahmoodi, N. O. *Appl. Organomet. Chem*. **2012**, *26*, 56-61.
11. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *Tetrahedron Lett.* **2008**, *49*,1450-1454.
12. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *Catal. Commun.* **2008**, *9*,416-420.
13. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *J. Mol. Catal.* A. **2007**, *270*, 112-116.
14. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Khorshidi, A. *Can. J. Chem*. **2006**, *84*,1541-1545.
15. Tabatabaeian, K.; Keshavarz, E.; Mamaghani, M.; Mahmoodi, N. O. *Org. Chem. Int.* **2011**, ID *325291*, 5 pages.
16. Stodulski, M.; Mamiñska, A.; Mlynarski,J. *Tetrahedron: Asymmetry*, **2011**, *22*, 464-467.
17. Gotoh, R.; Yamanaka,M. *Molecules* **2012**, *17*, 9010-9022.
18. El-Sepelgy, O.; Schwarzer, D.; Oskwarek, P.; Mlynarski, J. *Eur. J. Org. Chem.* **2012**, 2724-2727.
19. Woyciechowska, M.; Forcher, G.; Buda, S.; Mlynarski, J. *Chem. Commun.* **2012**, *48*, 11029-11031.
20. Nicolas, C.; Pluta, R.; Pasternak-Suder, M.; Martin, Q. R.; Mlynarski, J. *Eur. J. Org. Chem.* **2013**, 1296-1305.
21. Kawato, Y.; Iwata, M.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Tetrahedron*, **2011**, *67,* 6539-6546.
22. El-Sepelgy, O.; Mlynarski, J. *Adv. Synth. Catal.* **2013**, *355*, 281-286.
23. Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131-173.
24. Yamanaka, M.; Hoshino, M.; Katoh, T.; Mori, K.; Akiyama, T. *Eur. J. Org. Chem.* **2012**, 4508-4514.
25. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127-2129.
26. Danda, H.; Hansen, M. M.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 173-181.
27. Heathcock, C. H. *Science* **1981**, *214*, 395-400.
28. Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566-1568.
29. Mukaiyama, T.; Banno, K. Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509.
30. Chandrasekhar, S.; Johny, K.; Reddy, C. R.

Tetrahedron: Asymmetry **2009**, *20*, 1742-1745.
31. Rani, R.; Peddinti, R. K. *Tetrahedron:Asymmetry* **2010**, *21*, 775-779.
32. Chen, F.; Huang, S.; Zhang, H.; Liu, F.; Peng, Y. *Tetrahedron* **2008**, *64*, 9585-9591.
33. Siyutkin, D. E.; Kucherenko, A. S.; Zlotin, S. G. *Tetrahedron* **2009**, *65*, 1366-1372.
34. Tzeng, Z.-H.; Chen, H.-Y.; Reddy, R. J.; Huang, C. T.; Chen, K. *Tetrahedron* **2009**, *65*, 2879-2888.
35. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Keshavarz, E. *Int. J. Inorg. Chem.* **2010**, ID *621376*, 4 pages.
36. Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O.; Keshavarz, E. *Arkivoc* **2009**, *II*, 68-75.
37. Tabatabaeian, K.; Keshavarz, E.; Mamaghani, M.; Mahmoodi, N. O. *Arkivoc* **2010**, *IX*,155-162.
38. Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Tetrahedron* **2007**, *63*, 1923-1930.
39. Jia, Y.-N.; Wu, F.-C.; Ma, X.; Zhu, G.-J.; Da, C.-S. *Tetrahedron Lett.* **2009**, *50*, 3059-3062.
40. Miura, T.; Yasaku, Y.; Koyata, N.; Murakami, Y.; Imai, N. *Tetrahedron Lett.* **2009**, *50*, 2632-2635.
41. Kan, S.-S.; Li, J.-Z.; Ni, C.-Y.; Liu, Q.-Z.; Kang, T. R. *Molecules* **2011**, *16*, 3778-3786.
42. Keshavarz, E.; Tabatabaeian, K.; Mamaghani, M.; Mahmoodi, N. O. *Curr. Chem. Lett.* **2012**, *1*,91-94.
43. Shanmuganathan, S.; Greiner, L.; Domínguez de María, P. *Tetrahedron Lett.* **2010**, *51*, 6670-6672.
44. Inoue, H.; Kikuchi, M.; Ito, J.-I.; Nishiyama, H. *Tetrahedron* **2008**, *64*, 493-499.
45. Chen, Y.-L.; Li, W.; Liu, Y.; Guan, Z.; He, Y.-H. *J. Mol. Catal. B.* **2013**, *87*, 83-87.
46. Shen, C.; Lia, H.; Shen, F.; Zhang, P. Catal. Commun. **2013**, *41*, 106-109.