Synthesis of 1,1′-diacetylferrocene imines via catalytic oxo/imido heterometathesis

Andrey V. Pichugov [a, b], Nikolai S. Bushkov [a, c], Liudmila V. Erkhova [c], Pavel A. Zhizhko [a, *],
Svetlana Ch. Gagieva [c], Dmitry N. Zarubin [a, **], Nikolai A. Ustynyuk [a],
Dmitry A. Lemenovskii [c], Haojie Yu [d], Li Wang [d]

[a] A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov str., 28, 119991, Moscow, Russia
[b] Higher Chemical College, D. Mendeleev University of Chemical Technology of Russia, Miusskaya sq., 9, 125047, Moscow, Russia
[c] Department of Chemistry, Moscow State University, Vorob'evy Gory 1, 119992, Moscow, Russia
[d] State Key Laboratory of Chemical Engineering, College of Chemical and Biological Engineering, Zhejiang University, 310027, Hangzhou, People's Republic of China

ARTICLE INFO

ABSTRACT

A novel C=N bond forming strategy based on oxo/imido heterometathesis between *N*-sulfinylamines and ketones, catalyzed by a well-defined silica-supported Ti imido complex, was applied to prepare a series of hardly accessible 1,1'-diacetylferrocene ketimines.

© 2019 Elsevier B.V. All rights reserved.

1. Introduction

During the sixty-year history, the chemistry of ferrocene and its derivatives developed extensively and in a broad-spectrum manner [1]. Complexes based on 1,1′-bis(diphenylphosphino)ferrocene are known to exhibit high activity in homogeneous catalysis and their chiral analogs have been used with success in enantioselective catalysis [1a]. For medical applications, of most interest are ferrocene derivatives which showed anticancer effect [2]. Materials with practically valuable properties have been synthesized based on ferrocene, among which are redox switchable molecular systems [3], molecular recognition and sensing materials [4], metallocene molecular gears [5], molecular machines [6] and other nanovehicles [7], and rod-like ferrocenylmesogenes [8]. Ferrocene chemistry is well-established and routes for binding heteroatoms (O, N, P, S etc.) either directly to the ring carbon atom or to the side-chain C_α atom have been developed. However certain derivatives remain difficult to access due to specific features of the ferrocene core. For instance, ferrocenyl-based amines [9] are not easily available because the standard route to aromatic amines (nitration followed by reduction) cannot be applied due to oxidation of the ferrocene core under

nitration conditions [10]. Nucleophilic addition to imines or their reduction is an alternative general strategy for amine preparation. This route seems particularly attractive in the ferrocene chemistry because acetyl (and other alkanoyl/arenoyl) derivatives are readily accessible. However, we were surprised to find that ferrocenyl-based ketimines are very difficult to obtain *via* classical condensation of ketone and amine [11]. Even with the simplest anilines the reactions require tedious multiday procedures and give only moderate yields (Scheme 1, a) [11c]. Significant improvement is achieved by the use of $TiCl_4$ as a homogeneous catalyst (Scheme 1, b) [12]. It should be also noted that ferrocenylketone hydrazones can be obtained via trialkylaluminum-assisted condensation [13].

We have recently elaborated an alternative X = N bond forming strategy based on the catalytic oxo/imido heterometathesis reactions [14]. In particular, we have previously shown that oxo and imido complexes of early transition metals catalyze imidation of carbonyl compounds with *N*-sulfinylamines according to the catalytic cycle shown in Scheme 2. This reaction represents a novel water-free method for preparation of imines and proved useful in preparation of ketimines that are difficult to access via classical acid-catalyzed condensation (e.g. employing poorly nucleophilic amines or acid-sensitive substrates). Herein we report that this approach is also very efficient in the case of acetyl derivatives of ferrocene (Scheme 1, c) and show that oxo/imido heterometathesis catalyzed by a well-defined silica-supported Ti imido complex ($\equiv$SiO)Ti(N*t*Bu)(Me$_2$-Pyr)(py)$_2$ (**Ti/SiO$_2$**, Me$_2$Pyr = 2,5-dimethylpyrrolyl, py = pyridine)

(a) Classical Condensation:
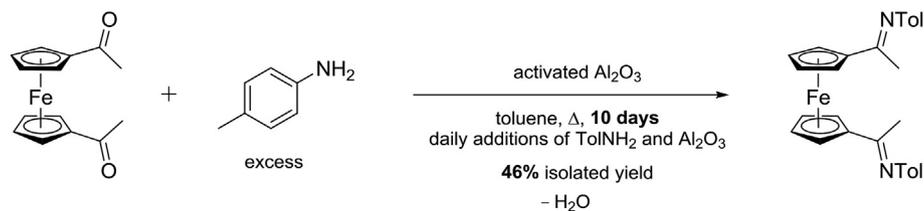
(b) TiCl₄-Catalyzed Condensation:
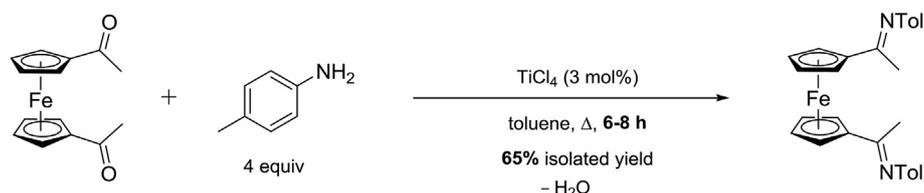
(c) Oxo/Imido Heterometathesis:
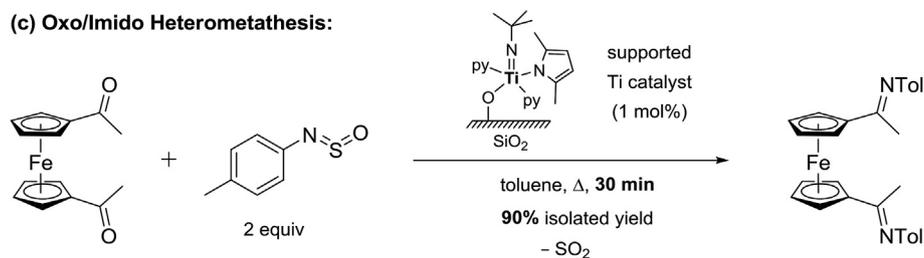
Scheme 1. Comparison of different methods for the preparation of 1,1'-diacetylferrocene imines.
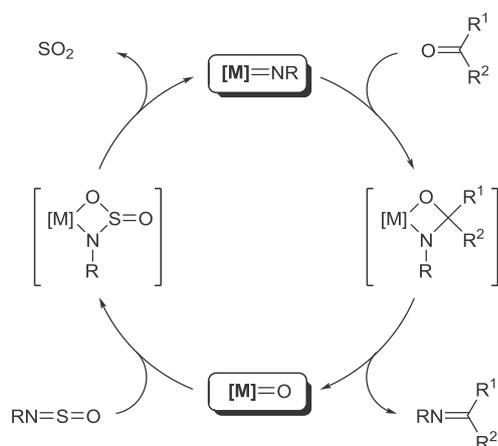
Scheme 2. Catalytic cycle of oxo/imido heterometathesis between *N*-sulfinylamines and ketones.

provides a straightforward access to a wide range of imines of 1,1'-diacetylferrocene.

2. Results and discussion

Ti/SiO₂ heterogeneous catalyst was designed using the Surface Organometallic Chemistry approach [15]. Its preparation was described previously and includes grafting of the imido complex Ti(N*t*Bu)(Me₂Pyr)₂(py)₂ onto a surface of silica partially dehydroxylated at 700 °C (SiO₂₋₇₀₀) to give a well-defined silica-supported Ti imido complex (≡SiO)Ti(N*t*Bu)(Me₂Pyr)(py)₂ (Scheme 3),

that was fully characterized by IR and solid-state NMR spectroscopy, as well as by elemental and mass balance analyses [14a]. This catalyst was found to be significantly more active towards imidation of carbonyl compounds with *N*-sulfinylamines as compared to the other previously reported systems based on V, Mo, and Ta. This observation is in agreement with the general reactivity trend recognized in transition metal imido chemistry, where the most reactive imides are found when going to the left across the d-block of the Periodic table [16]. Immobilization of the catalyst on the surface of the support plays an essential role, since it prevents the deactivation of the active species *via* the formation of catalytically inert μ-oxo bridged oligomers at the step of the formation of Ti=O intermediate (Scheme 2).

The catalyst was tested in the imidation of 1,1'-diacetylferrocene with different *N*-sulfinylamines (Table 1). The reactions were carried out in boiling toluene and monitored by IR spectroscopy to ensure the disappearance of the carbonyl C=O band at 1676 cm⁻¹ and the appearance of the C=N band in 1640–1620 cm⁻¹ region. Evolution of SO₂ serves as a driving force for shifting the equilibrium, quantitative conversions being reached in most reactions. In certain cases, separation of the heterogeneous catalyst and crystallization from toluene/heptane straightforwardly gave the analytically pure product; however, in some cases additional recrystallization was required, which lowered the final yield. It should be noted that *N*-sulfinylamines, used as a source of the imido group, are readily available compounds that can be prepared from the corresponding anilines in nearly quantitative yields by treatment with SOCl₂ [17].
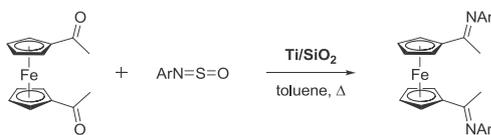
While the influence of electronic effects in *N*-sulfinylaniline is not obvious from this data, steric factor clearly plays a key role in the reaction. While *ortho*-non-substituted *N*-sulfinylanilines
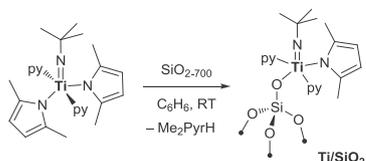
Scheme 3. Preparation of **Ti/SiO₂** catalyst.

Table 1
Preparation of 1,1'-diacetylferrocene imines by oxo/imido heterometathesis.

#	ArNSO	Ti, mol%[a]	Time	Yield[b]
1	4-Me-C₆H₄	1	30 min	90%
2	4-MeO-C₆H₄	1	1 h	93%
3	4-Br-C₆H₄	1	1.5 h	77%
4	4-I-C₆H₄	1	3 h	72%
5	4-O₂N-C₆H₄	1	4 h	43%[c]
6	2-OMe-C₆H₄	1	3 h	76%
7	2-CN-C₆H₄	2	30 min	71%
8	2-SMe-C₆H₄	2	2.5 h	81%
9	2-CF₃-C₆H₄	3	2 h	65%
10	C₆F₄ (tetrafluoro)	3	2 h	64%[c]
11	2,4,6-Cl₃-C₆H₂	3	1.5 h	46%[c]
12	2,4,6-Br₃-C₆H₂	5	4 h	55%[c]

[a] Per carbonyl group (based on the total Ti content in the catalyst as determined by elemental analysis, 0.23 mmol/g).
[b] Isolated yield.
[c] Additional recrystallization was required.

reacted smoothly at 1 mol% catalyst loading, *ortho*-substituted *N*-sulfinylanilines typically required higher catalyst loadings to reach quantitative conversions, up to 5 mol% in the case of very bulky tribromophenylaniline derivative (entry 12). It should be noted that the imines of extremely poorly nucleophilic polyhalogenated anilines (entries 10–12) are often challenging to obtain even in the case of ordinary ketones. Thus, the isolation of the corresponding acetylferrocene derivatives demonstrates the remarkable potential of oxo/imido heterometathesis reactions in preparation of difficult imines, even though lower yields were observed in these cases (possibly due to higher propensity of these compounds to hydrolysis which complicated their crystallization).

We have shown that oxo/imido heterometathesis catalyzed by silica-supported Ti imido complex and employing *N*-sulfinylamines as imidating agents serves as a powerful imidation methodology and allows for the efficient and high-yielding preparation of ketimines of 1,1'-diacetylferrocene that are difficult to access via classical methods.

3. Experimental section

The catalyst **Ti/SiO₂** was prepared as described before [14a]. Catalytic runs were performed under argon atmosphere using standard Schlenk techniques. Toluene was distilled from Na/benzophenone and stored over activated 3 Å MS. Importantly, CDCl₃ should be distilled from CaH₂ in order to remove the acidic impurities that facilitate decomposition of ferrocene derivatives in chloroform (poor quality NMR spectra were sometimes obtained if CDCl₃ was only distilled from usually recommended P₂O₅). 1,1'-diacetylferrocene was synthesized according to a standard procedure. *N*-sulfinylanilines were prepared according to standard procedures using Merck SOCl₂ ("for synthesis" grade) and freshly distilled or recrystallized anilines [17]. ^{1}H, ^{13}C, ^{19}F NMR spectra were recorded using Bruker Avance 400 and Agilent 400-MR spectrometers. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hz. ^{1}H chemical shifts were referenced relative to the residual solvent peak: 7.26 (CHCl₃ in CDCl₃). ^{13}C chemical shifts were referenced relative to the solvent peak: 77.00 (CDCl₃). ^{19}F spectra were referenced externally to CFCl₃. Monitoring of the reactions by IR spectroscopy was performed using Specord M82 spectrometer. IR spectra of isolated products were recorded in KBr pellets on a Bruker Tensor 37 FTIR spectrometer. Wavenumbers are given in cm^{-1}. Elemental analysis was performed at the Laboratory of Microanalysis of the INEOS RAS.

3.1. General procedure for the preparation of imines

A double-neck Schlenk flask was charged under argon with **Ti/SiO₂**, dry toluene, 1,1'-diacetylferrocene and *N*-sulfinylamine, and the mixture was stirred under reflux. The reaction was monitored by IR spectroscopy by taking aliquots of the reaction mixture until complete disappearance of the carbonyl C=O band at 1676 cm^{-1}. The catalyst was filtered off in air using a glass filter and the product was isolated by crystallization from the appropriate solvent and dried in vacuum. Crystallization was typically performed under argon, however most of the products do not show evidence of decomposition upon short exposure to air.

Acknowledgements

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jorganchem.2019.01.018.

References

[1] (a) A. Togni, T. Hayashi (Eds.), Ferrocenes: Homogeneous Catalysis, Organic Synthesis, Materials Science, VCH, 1995;
(b) L. Wang, H. Yu, Synthesis, Properties and Applications of Ferrocene-Based

Derivatives, Polymers and Hydrogels, Springer, 2018.

[2] (a) C.G. Hartinger, N. Metzler-Nolte, P.J. Dyson, Organometallics 31 (2012) 5677–5685;
(b) J. Spencer, J. Amin, M. Wang, G. Packham, S.S.S. Alwi, G.J. Tizzard, S.J. Coles, R.M. Paranal, J.E. Bradner, T.D. Heightman, ACS Med. Chem. Lett. 2 (2011) 358–362;
(c) V.N. Babin, Y.A. Belousov, V.I. Borisov, V.V. Gumenyuk, Y.S. Nekrasov, L.A. Ostrovskaya, I.K. Sviridova, N.S. Sergeeva, A.A. Simenel, L.V. Snegur, Russ. Chem. Bull. 63 (2014) 2405–2422.

[3] (a) G. Grelaud, G. Argouarch, M.P. Cifuentes, M.G. Humphrey, F. Paul, Tetrahedron 69 (2013) 3316–3322;
(b) E.M. Broderick, N. Guo, C.S. Vogel, C. Xu, J. Sutter, J.T. Miller, K. Meyer, P. Mehrkhodavandi, P.L. Diaconescu, J. Am. Chem. Soc. 133 (2011) 9278–9281.

[4] R. Sun, L. Wang, H. Yu, Z.-u. Abdin, Y. Chen, J. Huang, R. Tong, Organometallics 33 (2014) 4560–4573.

[5] A.M. Stevens, C.J. Richards, Tetrahedron Lett. 38 (1997) 7805–7808.

[6] G. Rapenne, G. Jimenez-Bueno, Tetrahedron 63 (2007) 7018–7026.

[7] Y. Shirai, J.-F. Morin, T. Sasaki, J.M. Guerrero, J.M. Tour, Chem. Soc. Rev. 35 (2006) 1043–1055.

[8] (a) C. Imrie, P. Engelbrecht, C. Loubser, C.W. McCleland, Appl. Organomet. Chem. 15 (2001) 1–15;
(b) T. Chen, D. Wang, L.-H. Gan, Y. Matsuo, J.-Y. Gu, H.-J. Yan, E. Nakamura, L.-J. Wan, J. Am. Chem. Soc. 136 (2014) 3184–3191;
(c) O.N. Kadkin, E.H. Kim, S.Y. Kim, M.-G. Choi, Polyhedron 28 (2009) 1301–1307;
(d) M.V. Makarov, D.A. Lemenovskii, A.E. Bruce, M.R.M. Bruce, V.P. Dyadchenko, Liq. Cryst. 33 (2006) 485–494.

[9] (a) F.S. Arimoto, A.C. Haven, J. Am. Chem. Soc. 77 (1955) 6295–6297;
(b) E.M. Acton, R.M. Silverstein, J. Org. Chem. 24 (1959) 1487–1490;
(c) G.R. Knox, P.L. Pauson, J. Chem. Soc. (1961) 4615–4618;
(d) A. Shafir, M.P. Power, G.D. Whitener, J. Arnold, Organometallics 19 (2000) 3978–3982.

[10] H. Grubert, K.L. Rinehart, Tetrahedron Lett. 1 (1959) 16–17.

[11] (a) C. López, J. Sales, X. Solans, R. Zquiak, J. Chem. Soc., Dalton Trans. (1992) 2321–2328;
(b) R. Bosque, C. López, J. Sales, X. Solans, M. Font-Bardía, J. Chem. Soc., Dalton Trans. (1994) 735–745;
(c) R. Bosque, C. López, X. Solans, M. Font-Bardia, Organometallics 18 (1999) 1267–1274;
(d) T.-Y. Lee, P.-R. Chiang, M.-C. Tsai, C.-Y. Lin, J.-H. Huang, J. Mol. Struct. 935 (2009) 102–109.

[12] H.-X. Wang, R.-Q. Gao, X.-L. Yang, L. Wan, H.-F. Wu, F.-Y. Geng, R. Jin, Polyhedron 26 (2007) 1037–1044.

[13] B. Bildstein, P. Denifl, Synthesis (1994) 158–160.

[14] (a) P.A. Zhizhko, A.V. Pichugov, N.S. Bushkov, F. Allouche, A.A. Zhizhin, D.N. Zarubin, N.A. Ustynyuk, Angew. Chem. Int. Ed. 57 (2018) 10879–10882;
(b) P.A. Zhizhko, A.A. Zhizhin, O.A. Belyakova, Y.V. Zubavichus, Y.G. Kolyagin, D.N. Zarubin, N.A. Ustynyuk, Organometallics 32 (2013) 3611–3617;
(c) P.A. Zhizhko, A.A. Zhizhin, D.N. Zarubin, N.A. Ustynyuk, Mendeleev Commun. 22 (2012) 64–66;
(d) P.A. Zhizhko, A.A. Zhizhin, D.N. Zarubin, N.A. Ustynyuk, D.A. Lemenovskii, B.N. Shelimov, L.M. Kustov, O.P. Tkachenko, G.A. Kirakosyan, J. Catal. 283 (2011) 108–118;
(e) A.A. Zhizhin, D.N. Zarubin, N.A. Ustynyuk, Mendeleev Commun. 19 (2009) 165–166;
(f) A.A. Zhizhin, D.N. Zarubin, N.A. Ustynyuk, Tetrahedron Lett. 49 (2008) 699–702.

[15] C. Copéret, A. Comas-Vives, M.P. Conley, D.P. Estes, A. Fedorov, V. Mougel, H. Nagae, F. Núñez-Zarur, P.A. Zhizhko, Chem. Rev. 116 (2016) 323–421.

[16] (a) W.A. Nugent, R.J. McKinney, R.V. Kasowski, F.A. Van-Catledge, Inorg. Chim. Acta. 65 (1982) L91–L93;
(b) W.A. Nugent, J.M. Mayer, Metal–Ligand Multiple Bonds, Wiley, New York, 1988;
(c) D.E. Wigley, Prog. Inorg. Chem. 42 (1994) 239–482.

[17] (a) A. Michaelis, Justus Liebigs Ann. Chem. 274 (1893) 200–266;
(b) G. Kresze, A. Maschke, R. Albrecht, K. Bederke, H.P. Patzschke, H. Smalla, A. Trede, Angew. Chem. Int. Ed. 1 (1962) 89–98;
(c) A. Meller, W. Maringgele, H. Fetzer, Chem. Ber. 113 (1980) 1950–1961.