Mendeleev Communications

Mendeleev Commun., 2025, **35**, 461–463

Asymmetric Friedel–Crafts alkylation of indoles with β-nitrostyrenes catalyzed by a chiral Ni^{II} complex based on (*S*)-(2-aminomethyl)pyrrolidine and 3,5-di-*tert*-butylsalicylaldehyde

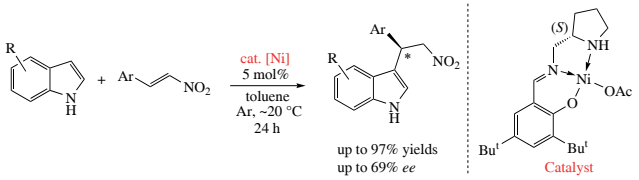
Evgeniy V. Rozhkov,[a,b] Nadezhda V. Stoletova,[a] Alexander V. Bachinskiy,[a] Mikhail M. Ilyin,[a] Victor I. Maleev[a] and Vladimir A. Larionov*[a]

[a] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 119334 Moscow, Russian Federation. E-mail: larionov@ineos.ac.ru*

[b] *Higher Chemical College of the Russian Academy of Sciences, D. I. Mendeleev University of Chemical Technology of Russia, 125047 Moscow, Russian Federation*

DOI: 10.71267/mencom.7701

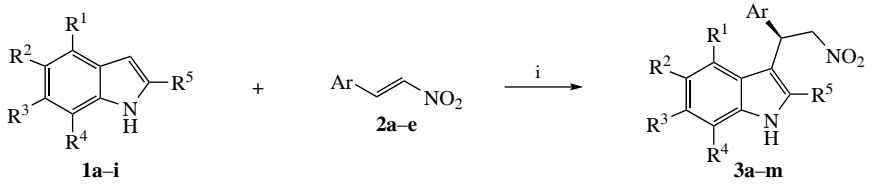
μ-(Acetato)nickel(II) complex with Schiff base of (*S*)-(2-aminomethyl)pyrrolidine and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde as the chiral ligand was tested in the asymmetric Friedel–Crafts alkylation of indoles with β-nitrostyrenes. The reactions catalyzed by 5 mol% of the complex provided the corresponding 3-(1-aryl-2-nitroethyl)indoles with up to 98% yields and up to 69% *ee* values.



Keywords: asymmetric Friedel–Crafts alkylation, indoles, β-nitrostyrenes, chiral nickel(II) complex, Lewis acids.

The synthesis of indole derivatives with stereogenic centers is a challenging process, mainly due to the diverse and complex structures of these compounds.[1] In recent years, there has been an increase in research on the direct alkylation of indoles with the goal of producing optically active derivatives for potential use in biological and medicinal chemistry.[2] Enantioselective Friedel–Crafts alkylation of indoles **1** with β-nitrostyrenes **2** is an efficient and straightforward synthesis of chiral indole derivatives **3** featuring nitro groups (for the structures, see Scheme 1).[2–6] Typically, the most effective catalysts for this reaction are chiral Lewis acids with sophisticated structures that require cumbersome steps for the synthesis of chiral ligands.[7–15] Among them, chiral Ni^{II} complexes have a great potential as catalysts.[16–18] However, the design of simple catalytic systems for the asymmetric Friedel–Crafts reaction is still desirable.

We have recently introduced novel chiral Cu^{II} and Ni^{II} complexes **4**, **5** based on commercially available (*S*)- or (*R*)-(2-aminomethyl)pyrrolidine and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde as simple catalysts for the asymmetric Henry reaction[19–21] and kinetic resolution of racemic epoxides with CO_2.[22] In this study, we aimed to expand the use of these chiral complexes for other valuable asymmetric reactions.[23] We present the results of our investigation of Ni^{II} complex **6** with basic



1a–i

2a–e

3a–m

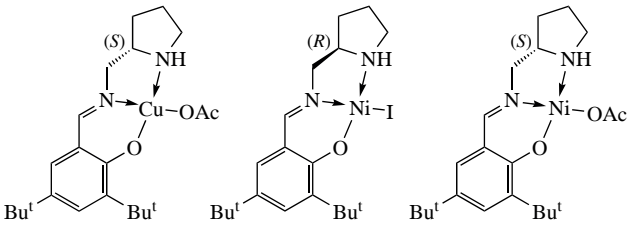
1a $R^1 = R^2 = R^3 = R^4 = R^5 = H$
1b $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$
1c $R^1 = R^2 = R^3 = R^5 = H$, $R^4 = Me$
1d $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Br$
1e $R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Cl$
1f $R^1 = OMe$, $R^2 = R^3 = R^4 = R^5 = H$
1g $R^1 = CO_2Me$, $R^2 = R^3 = R^4 = R^5 = H$
1h $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = CO_2Me$
1i $R^1 = R^3 = R^4 = H$, $R^2 = OMe$, $R^5 = Me$

2a Ar = Ph
2b Ar = 2-$O_2NC_6H_4$
2c Ar = 3-$O_2NC_6H_4$
2d Ar = 4-$O_2NC_6H_4$
2e Ar = 2-naphthyl

Conversion of **2**/Yield (*ee*) of **3** (%)

3a	$R^1 = R^2 = R^3 = R^4 = R^5 = H$, Ar = Ph	99/99 (69)
3b	$R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Me$, Ar = Ph	99/84 (66)
3c	$R^1 = R^2 = R^3 = R^5 = H$, $R^4 = Me$, Ar = Ph	9/8 (15)
3d	$R^1 = R^3 = R^4 = R^5 = H$, $R^2 = Br$, Ar = Ph	78/73 (68)
3e	$R^1 = R^2 = R^4 = R^5 = H$, $R^3 = Cl$, Ar = Ph	99/91 (67)
3f	$R^1 = OMe$, $R^2 = R^3 = R^4 = R^5 = H$, Ar = Ph	90/76 (65)
3g	$R^1 = CO_2Me$, $R^2 = R^3 = R^4 = R^5 = H$, Ar = Ph	99/93 (59)
3h	$R^1 = R^3 = R^4 = R^5 = H$, $R^2 = CO_2Me$, Ar = Ph	99/98 (62)
3i	$R^1 = R^3 = R^4 = H$, $R^2 = OMe$, $R^5 = Me$, Ar = Ph	93/88 (22)
3j	$R^1 = R^2 = R^3 = R^4 = R^5 = H$, Ar = 2-$O_2NC_6H_4$	34/25 (15)
3k	$R^1 = R^2 = R^3 = R^4 = R^5 = H$, Ar = 3-$O_2NC_6H_4$	90/74 (69)
3l	$R^1 = R^2 = R^3 = R^4 = R^5 = H$, Ar = 4-$O_2NC_6H_4$	99/96 (69)
3m	$R^1 = R^2 = R^3 = R^4 = R^5 = H$, Ar = 2-naphthyl	90/83 (52)

Scheme 1 *Reagents and optimal conditions*: i, indole **1** (0.2 mmol, 2 equiv.), β-nitrostyrene **2** (0.1 mmol, 1 equiv.), Ni^{II} catalyst **6** (5 mol%), toluene (0.5 ml), Ar, room temperature (for **3g**,**h**, 40 °C), 24 h (for **3d**, 48 h). For optimization with **1a** and **2a** as model substrates, see Table 1. Conversions and yields were determined by ^{1}H NMR. Enantiomeric purity was determined by chiral HPLC analysis.



acetate anion as a catalyst for the enantioselective Friedel–Crafts alkylation of indoles with β-nitrostyrenes (see Scheme 1).

The study commenced with the conjugation of indole **1a** and β-nitrostyrene **2a**, which were selected as the model substrates. The coupling of two equivalents of **1a** with one equivalent of **2a**, conducted in CH_2Cl_2 at room temperature, in the presence of 5 mol% Cu^{II} complex **4** afforded the corresponding (*R*)-nitroalkylated indole **3a** with 47% enantioselectivity and 56% conversion (Table 1, entry 1). We then used the (*R*)-configured Ni^{II} complex **5** with iodide anion, which has previously shown high stereocontrol in kinetic resolution of epoxides.[22] This complex gave the desired (*S*)-product **3a** with higher *ee* (59%) and similar conversion (entry 2). Chiral Ni^{II} complex **6** with a basic acetate anion was found to be more effective providing full conversion (99%) and improved enantioselectivity of up to 68% (entry 3).

The solvent effect was then investigated (see Table 1, entries 4–11). Dichloromethane, EtOAc and methyl *tert*-butyl ether gave comparable results (entries 4, 5, 10) while acetonitrile, 1,4-dioxane, methanol and THF were less effective (entries 6–9). Toluene was the optimal solvent providing the formation of product **3a** with 69% *ee* (entry 11). The decrease (2 mol%) and increase (10 mol%) in catalyst loading did not improve the enantioselectivity of the reaction (entry 12). Further optimization of reaction conditions, including temperature, reaction time, solvent concentration, the ratio of indole **1a** to β-nitrostyrene **2a**, and the use of various additives, as demonstrated their positive effect on the enantioselectivity control in our previous work,[22] did not lead to an improvement in *ee* (see Online Supplementary Materials for more details). Expectedly, the reaction did not proceed without a catalyst (entry 13).

Next, with optimal conditions in hand, the scope of different indoles **1a**–**i** was examined (see Scheme 1). Nickel(II) catalyst **6** tolerates electron-acceptor- and electron-donor-substituted indoles **1b**,**d**–**h**, providing the desired products **3** with yields ranging from 73 to 98% and *ee* values between 59 and 68%. However, the indoles **1c** and **1i** with a methyl substituent on the C^2 and C^7 carbon atoms gave the alkylated products with low levels of enantiocontrol (15 and 22% *ee*, respectively). It is notable that the indole with a phenyl group at the C^2 position was inactive.

Table 1 Screening of reaction condition for the Friedel–Crafts alkylation reaction of indole **1a** with β-nitrostyrene **2a** catalyzed by complexes **4**–**6**.[a]

Entry	Catalyst	Solvent	Conversion of **2a**[b] (%)	*ee* of **3a**[c] (%)
1	**4**	CH_2Cl_2	56	47 (*R*)
2	**5**	PhCl	56	59 (*S*)
3	**6**	PhCl	99	68 (*R*)
4	**6**	CH_2Cl_2	99	60 (*R*)
5	**6**	EtOAc	90	62 (*R*)
6	**6**	MeCN	51	40 (*R*)
7	**6**	1,4-dioxane	45	34 (*R*)
8	**6**	MeOH	99	48 (*R*)
9	**6**	THF	23	17 (*R*)
10	**6**	MeOBu^t	99	55 (*R*)
11	**6**	**toluene**	**99**	**69** (*R*)
12	**6**	toluene	87[d]/99[e]	65[d]/62[e] (*R*)
13	–	toluene	NR[f]	–

[a]Reaction conditions: β-nitrostyrene **2a** (14.9 mg, 0.1 mmol, 1.0 equiv.), catalyst (5 mol%), indole **1a** (23.4 mg, 0.2 mmol, 2.0 equiv.), solvent (0.5 ml), argon, room temperature, 24 h. [b]Conversion was determined by ^{1}H NMR analysis. [c]Enantiomeric purity was determined by chiral HPLC analysis using the Chiralpak AS-H column. The configuration of the product was assigned by comparison of HPLC profiles with literature data. [d]With 2 mol% of the catalyst. [e]With 10 mol% of the catalyst. [f]No reaction.

As for other β-nitrostyrenes **2b**–**e**, *ortho*-nitro substituted β-nitrostyrene **2b** gave product **3j** with low conversion (34%), yield (25%) and *ee* value (15%). At the same time, the *meta*- and *para*-isomers **2c**,**d** led to the comparable results to β-nitrostyrene **2a**. 2-(2-Naphthyl)-1-nitroethene **2e** yielded product **3m** in 52% *ee*. Notably, bulky (*E*)-9-(2-nitrovinyl)anthracene and aliphatic (*E*)-3-methyl-1-nitrobut-1-ene did not react under our conditions.

In conclusion, we have presented the results of a study on a chiral Ni^{II} complex derived from (*S*)-(2-aminomethyl)pyrrolidine and 3,5-di-*tert*-butylsalicylaldehyde with basic acetate anion as a catalyst for the asymmetric Friedel–Crafts alkylation of indoles with β-nitrostyrenes. The enantioselectivity of the reaction varied from 14 to 69% *ee*, depending on the substituents present in the indole and phenyl rings of the nitroalkene.

This work was supported by the Russian Science Foundation (grant no. 20-13-00155); https://rscf.ru/project/23-13-45008/. NMR spectra were collected with support from the Ministry of Science and Higher Education of the Russian Federation.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7701.

References

1 M. M. Heravi, Z. Amiri, K. Kafshdarzadeh and V. Zadsirjan, *RSC Adv.*, 2021, **11**, 33540; https://doi.org/10.1039/D1RA05972F.
2 T. Ahmad, S. Khan and N. Ullah, *ACS Omega*, 2022, **7**, 35446; https://doi.org/10.1021/acsomega.2c05022.
3 M. Bandini, A. Melloni, S. Tommasi and A. Umani-Ronchi, *Synlett*, 2005, 1199; https://doi.org/10.1055/s-2005-865210.
4 M. Zeng and S.-L. You, *Synlett*, 2010, 1289; https://doi.org/10.1055/s-0029-1219929.
5 M. M. Heravi, V. Zadsirjan, M. Heydari and B. Masoumi, *Chem. Rec.*, 2019, **19**, 2236; https://doi.org/10.1002/tcr.201800190.
6 J. Ohata, *Org. Biomol. Chem.*, 2024, **22**, 3544; https://doi.org/10.1039/D4OB00406J.
7 R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 6576; https://doi.org/10.1002/anie.200500227.
8 Y.-X. Jia, S.-F. Zhu, Y. Yang and Q.-L. Zhou, *J. Org. Chem.*, 2006, **71**, 75; https://doi.org/10.1021/jo0516537.
9 S.-F. Lu, D.-M. Du and J. Xu, *Org. Lett.*, 2006, **8**, 2115; https://doi.org/10.1021/ol060586f.
10 J. Itoh, K. Fuchibe and T. Akiyama, *Angew. Chem., Int. Ed.*, 2008, **47**, 4016; https://doi.org/10.1002/anie.200800770.
11 L.-A. Chen, X. Tang, J. Xi, W. Xu, L. Gong and E. Meggers, *Angew. Chem., Int. Ed.*, 2013, **52**, 14021; https://doi.org/10.1002/anie.201306997.
12 J. Liu, L. Gong and E. Meggers, *Tetrahedron Lett.*, 2015, **56**, 4653; https://doi.org/10.1016/j.tetlet.2015.06.046.
13 K. Huang, Q. Ma, X. Shen, L. Gong and E. Meggers, *Asian J. Org. Chem.*, 2016, **5**, 1198; https://doi.org/10.1002/ajoc.201600288.
14 I. Ibáñez, M. Kaneko, Y. Kamei, R. Tsutsumi, M. Yamanaka and T. Akiyama, *ACS Catal.*, 2019, **9**, 6903; https://doi.org/10.1021/acscatal.9b01811.
15 B. Karimi, E. Jafari, F. Mansouri and M. Tavakolian, *Sci. Rep.*, 2023, **13**, 14736; https://doi.org/10.1038/s41598-023-41921-9.
16 H. Wu, W.-J. Sheng, B. Chen, R.-R. Liu, J.-R. Gao and Y.-X. Jia, *Synlett*, 2015, **26**, 2817; https://doi.org/10.1055/s-0035-1560538.
17 R. Sato, T. Tosaka, H. Masu and T. Arai, *J. Org. Chem.*, 2019, **84**, 14248; https://doi.org/10.1021/acs.joc.9b02006.
18 W.-J. Zhu, J.-F. Gong and M.-P. Song, *J. Org. Chem.*, 2020, **85**, 9525; https://doi.org/10.1021/acs.joc.0c00336.

19 V. A. Larionov, L. V. Yashkina, A. F. Smol'yakov, Y. V. Zubavichus, K. K. Babievsky, N. V. Akat'yev, A. A. Titov, Y. N. Belokon and V. I. Maleev, *ChemistrySelect*, 2018, **3**, 653; https://doi.org/10.1002/slct.201702689.
20 V. A. Larionov, L. V. Yashkina, M. G. Medvedev, A. F. Smol'yakov, A. S. Peregudov, A. A. Pavlov, D. B. Eremin, T. F. Savel'yeva, V. I. Maleev and Y. N. Belokon, *Inorg. Chem.*, 2019, **58**, 11051; https://doi.org/10.1021/acs.inorgchem.9b01574.
21 O. V. Khromova, L. V. Yashkina, N. V. Stoletova, V. I. Maleev, Y. N. Belokon and V. A. Larionov, *Molecules*, 2024, **29**, 5207; https://doi.org/10.3390/molecules29215207.
22 M. A. Emelyanov, A. V. Bachinskiy, Y. Derkach, V. A. Chaliy, A. F. Smol'yakov, M. G. Medvedev, A. A. Titov, V. I. Maleev and V. A. Larionov, *Tetrahedron Chem*, 2024, **12**, 100115; https://doi.org/10.1016/j.tchem.2024.100115.
23 T. F. Savel'yeva, Z. T. Gugkaeva, Yu. V. Nelyubina, A. F. Smol'yakov, M. A. Moskalenko, V. A. Larionov and V. I. Maleev, *Mendeleev Commun.*, 2024, **34**, 496; https://doi.org/10.1016/j.mencom.2024.06.008.

Received: 2nd December 2024; Com. 24/7701