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Asymmetric Friedel–Crafts Alkylation of α-Substituted β-Nitroacrylates: Access to $\beta^{2,2}$-Amino Acids Bearing Indolic All-Carbon Quaternary Stereocenters

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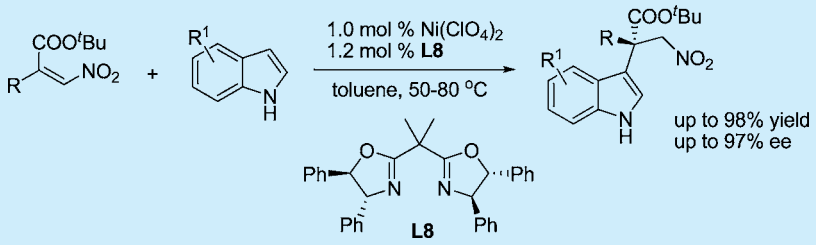
Supporting Information

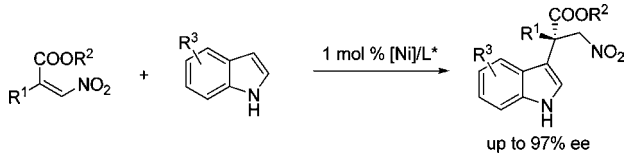


ABSTRACT: A highly enantioselective Friedel–Crafts alkylation reaction of indoles with acyclic α-substituted β-nitroacrylates is developed under the catalysis of Ni(ClO$_4$)$_2$–bisoxazoline complex at 1 mol % catalyst loading, affording chiral indolic β-nitroesters bearing all-carbon quaternary stereocenters in excellent yields and ees of up to 97%. Transformation of one of the products to $\beta^{2,2}$-amino ester and tetrahydro-β-carboline through nitro reduction and sequential Pictet–Spengler cyclization was exemplified.

β-Amino acids are important substructural motifs of β-peptides, β-lactams, and many other biologically active compounds.[1] As a result, extensive attention has been focused on the asymmetric synthesis of β-amino acids.[2] In the context of β^2-amino acid (α-substituted-β-amino acid) synthesis, a variety of catalytic asymmetric methods have been developed, and most of them appear to be for the construction of tertiary stereogenic center.[2e,f] In comparison, the synthesis of enantiomerically pure $\beta^{2,2}$-amino acids bearing all-carbon quaternary stereocenters is much less explored and has remained as a very challenging task.[3] Undoubtedly, asymmetric conjugate addition of a carbon-based nucleophile to α-substituted-β-nitroacrylate would be a reliable strategy for this purpose.[4] However, only a few examples were reported so far on the enantioselective additions of aldehydes,[5] thiols,[6] and oximes[7] to α-substituted-β-nitroacrylates.[8] Extension of carbon-based nucleophiles in this reaction would be highly valuable for the challenging $\beta^{2,2}$-amino acid synthesis.

Indole has become a popular nucleophile in the asymmetric Michael-type Friedel–Crafts reaction, which serves as an important carbon–carbon-forming reaction to access optically active aromatic compounds.[9] Various electron-deficient olefins have been used for indole alkylation. However, reaction with the β,β-disubstituted unsaturated system to generate an all-carbon quaternary stereocenter has met with very limited success, probably due to the steric repulsion of the two substituents in the substrates toward the nucleophilic attack of indole ring. Nevertheless, two pioneering examples have been documented,[10] and excellent enantioselectivities were recently achieved independently by Arai's and Zhang's groups in the reactions of indoles with isatin-derived cyclic electron-deficient olefins,[11] as well as our group in the reaction of trifluoromethylated β,β-disubstituted nitroalkenes.[12] However, the specific demand of the substrates and the high catalyst loading in these transformations still remained the major issue. Herein, we report a highly enantioselective alkylation reaction of indoles with acyclic α-substituted-β-nitroacrylates under the catalysis of 1 mol % of Ni–bisoxazoline complex,[13] providing reliable access to the potential biologically active β-tryptophan derivatives bearing all-carbon quaternary stereocenters (Scheme 1).[14] It is noteworthy that good results are also obtained at the lowest catalyst loading of 0.1 mol %, which represents a rare

Scheme 1. Ni-Catalyzed Enantioselective Friedel–Crafts Alkylation Reaction of Indoles with α-Substituted β-Nitroacrylates



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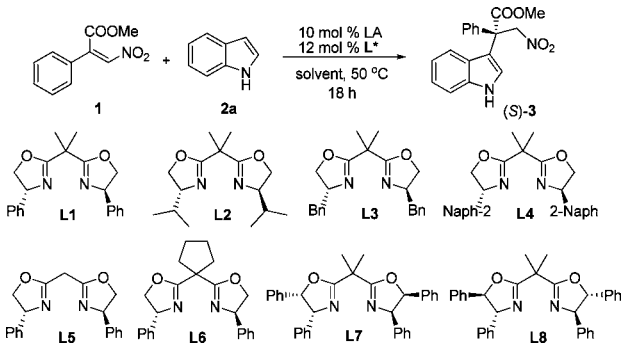
case of highly active Lewis acid catalyst in the asymmetric Friedel–Crafts reaction.[15]

Based on our previous result,[12] we identified the complex of $Ni(ClO_4)_2·6H_2O$[16] with chiral bisoxazoline as an efficient catalyst for the model reaction between (*Z*)-methyl 3-nitro-2-phenylacrylate (**1**) and indole (**2a**). Thus, the reaction in the presence of 10 mol % of $Ni(ClO_4)_2·6H_2O$ and 12 mol % of **L1** proceeded smoothly in toluene at 50 °C for 18 h to afford the product (*S*)-**3** in 81% ee with excellent yield (Table 1, entry 1).

Table 1. Reaction Condition Optimization[a]



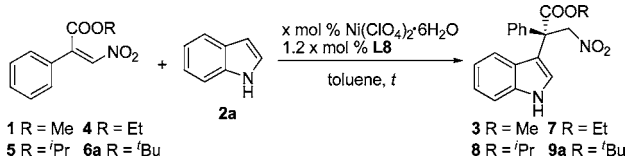
entry	LA	L*	solvent	yield[b] (%)	ee[c] (%)
1	$Ni(ClO_4)_2·6H_2O$	**L1**	toluene	96	81
2	$Zn(ClO_4)_2·6H_2O$	**L1**	toluene	91	70
3	$Ni(OTf)_2$	**L1**	toluene	96	78
4	$Zn(OTf)_2$	**L1**	toluene	94	75
5	$Cu(OTf)_2$	**L1**	toluene	34	79
6	$Ni(ClO_4)_2·6H_2O$	**L1**	Et_2O	90	50
7	$Ni(ClO_4)_2·6H_2O$	**L1**	CH_2Cl_2	89	53
8	$Ni(ClO_4)_2·6H_2O$	**L2**	toluene	82	<10
9	$Ni(ClO_4)_2·6H_2O$	**L3**	toluene	94	33
10	$Ni(ClO_4)_2·6H_2O$	**L4**	toluene	92	55
11	$Ni(ClO_4)_2·6H_2O$	**L5**	toluene	56	39
12	$Ni(ClO_4)_2·6H_2O$	**L6**	toluene	95	81
13	$Ni(ClO_4)_2·6H_2O$	**L7**	toluene	96	81
14	$Ni(ClO_4)_2·6H_2O$	**L8**	toluene	96	90

[a]The reaction of (*Z*)-methyl 3-nitro-2-phenylacrylate **1** (0.4 mmol) and indole **2a** (0.6 mmol) was performed in the presence of 10 mol % of Lewis acid and 12 mol % of chiral ligand in solvent (4.0 mL) at 50 °C for 18 h. [b]Isolated yield. [c]Determined by chiral HPLC.

Subsequent optimization of Lewis acid showed $Ni(ClO_4)_2·6H_2O$ was the best catalyst. Although $Zn(ClO_4)_2·6H_2O$, $Ni(OTf)_2$, and $Zn(OTf)_2$ could efficiently promote the reaction, the resulting enantioselectivities were below 80% (entries 2–4). Simple examination of solvent disclosed ether and dichloromethane were inferior to toluene (entries 6 and 7). We then turned our attention to ligand screening, and as shown in entries 8–10, chiral isopropyl, benzyl, and 2-naphthyl substituents on the oxazoline ring led to poor enantioselectivities. To our delight, ligand **L8** bearing *trans*-diphenyl substituents was revealed as the best choice, giving 90% ee of the product (entry 14). Modifications on the linker of **L1** and a *cis*-diphenyl ligand **L7** did not improve the enantiomeric excess (entries 11–13).

To further improve the enantioselectivity, we next investigated the effect of ester group on the reaction. Ethyl, isopropyl, and *tert*-butyl 2-phenylnitroacrylate were then synthesized and treated with indole under the conditions showed in entry 14 of Table 1. The reactions of ethyl and isopropyl esters (**4** and **5**) gave slightly lower enantioselectivities (Table 2, entries 2 and 3), while the ee value for *tert*-butyl ester **6a** was greatly improved to 96% and with a fast reaction rate (entry 4). This high reactivity inspired us to examine the reaction at a lower catalyst loading. As shown in entry 5, the same result could be obtained with 1 mol % of catalyst, albeit longer reaction time was needed. However, the catalyst activity could be enhanced after dehydration, and the reaction finished in 15 h (entry 6). Further lowering the catalyst loading to 0.1 mol % led to a sharp decrease of the yield, while a high level of enantioselectivity was retained (entry 7). Gratifyingly, the yield could be improved to 79% at 80 °C with slight loss of ee (entry 8).

Table 2. Optimization of the Ester Group and Catalyst Loading[a]



entry	*x*	R	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	10	Me	50	18	96	90
2	10	Et	50	18	95	89
3	10	^{i}Pr	50	18	95	86
4	10	^{t}Bu	50	4	97	96
5	1	^{t}Bu	50	24	96	96
6[d]	1	^{t}Bu	50	15	98	96
7[d]	0.1[e]	^{t}Bu	50	36	52	96
8[d]	0.1[e]	^{t}Bu	80	20	79	93

[a]Reaction conditions: nitroacrylate (0.4 mmol), indole **2a** (0.6 mmol), toluene (4.0 mL). [b]Isolated yield. [c]Determined by chiral HPLC. [d]$Ni(ClO_4)_2·6H_2O$ was dried under vacuum at 160 °C for 2 h before complex with ligand. [e]For operation, see the Supporting Information.

The optimal reaction conditions were then applied to the reactions of a variety of nitroacrylates (**6a–n**). As shown in Table 3, the yields and enantioselectivities are generally excellent for *α*-aryl-*β*-nitroacrylates (**6a–i**) bearing either electron-donating groups or electron-withdrawing groups on the phenyl ring (entries 1–11). But no reaction occurred for *o*-methyl-substituted substrate, implying a negative steric effect on the reactivity. Heteroaryl (**6j**, **6k**) and 2-naphthyl (**6l**) substrates also react well with indole to furnish the corresponding products in similarly excellent yields and ees (entries 12–14). To our delight, alkylated substrates **6m** and **6n** are suitable for this transformation to afford the products in slightly lower yield and enantioselectivity with 5 mol % of catalyst (entries 15 and 16). It should be noted that in the presence of 0.1 mol % catalyst the reactions of substrates **6e** and **6g** occurred smoothly to afford the corresponding products in modest yields and good enantioselectivities (entries 6 and 9).

We have also investigated the substituent effect of indole. Excellent enantioselectivities were achieved for indoles bearing substituents at the C5–C7 positions (Table 4, entries 2–6), while an electron-withdrawing substituent (Br) resulted in a lower yield. The yield could be improved to 95% at 80 °C with slight erosion of the enantioselectivity (entry 4). Furthermore, the reactions were unfavorably influenced by the steric effect. Poor to modest yields and enantioselectivities were obtained for **2b** and **2g** bearing substituents at the C2 or C4 position of

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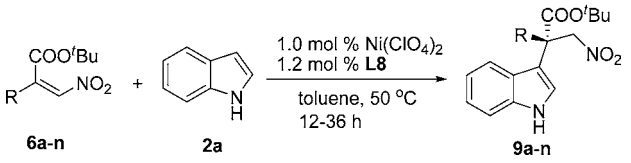
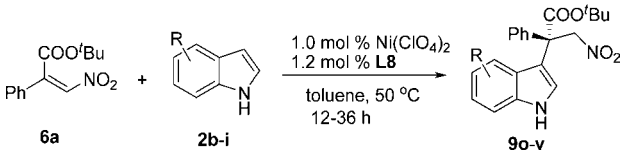
Table 3. Substrate Scope of Nitroacrylate[a]



entry	R	product	yield[b] (%)	ee[c] (%)
1	C_6H_5 (**6a**)	**9a**	98	96
2	3-MeC_6H_4 (**6b**)	**9b**	98	95
3	3-MeOC_6H_4 (**6c**)	**9c**	98	97
4	3-FC_6H_4 (**6d**)	**9d**	97	97
5	4-MeOC_6H_4 (**6e**)	**9e**	97	93
6[d]	4-MeOC_6H_4 (**6e**)	**9e**	63	86
7	4-ClC_6H_4 (**6f**)	**9f**	93	93
8	4-$CF_3C_6H_4$ (**6g**)	**9g**	98	93
9[d]	4-$CF_3C_6H_4$ (**6g**)	**9g**	70	87
10	3,4-$MeO_2C_6H_3$ (**6h**)	**9h**	98	95
11	3,5-$Me_2C_6H_3$ (**6i**)	**9i**	98	97
12	2-thienyl (**6j**)	**9j**	97	96
13	2-furyl (**6k**)	**9k**	97	95
14	2-naphthyl (**6l**)	**9l**	98	95
15[e]	2-phenylethyl (**6m**)	**9m**	89	88
16[e]	benzyl (**6n**)	**9n**	87	88

[a]Reaction conditions: nitroacrylate **6a**−**n** (0.4 mmol), indole **2a** (0.6 mmol), 1 mol % of Ni$(ClO_4)_2$ (dried from Ni$(ClO_4)_2$·6H_2O under vacuum at 160 °C for 2 h) toluene (4.0 mL), and 1.2 mol % **L8** in toluene (4.0 mL) at 50 °C for 12−36 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]0.1 mol % catalyst loading at 80 °C for 24 h. [e]With 5 mol % of catalyst.

Table 4. Substrate Scope of Indole[a]



entry	R	product	yield[b] (%)	ee[c] (%)
1	4-MeO (**2b**)	**9o**	61	77
2	5-MeO (**2c**)	**9p**	97	97
3	5-Br (**2d**)	**9q**	75	95
4[d]	5-Br (**2d**)	**9q**	95	93
5[d]	6-Cl (**2e**)	**9r**	95	93
6	7-Me (**2f**)	**9s**	98	96
7	2-Me (**2g**)	**9t**	43	54
8[e]	1-Me (**2h**)	**9u**	62	64
9[e]	1-allyl (**2i**)	**9v**	57	76

[a]Reaction conditions: nitroacrylate **6a** (0.4 mmol), indole **2b**−**i** (0.6 mmol), 1 mol % of Ni$(ClO_4)_2$ (dried from Ni$(ClO_4)_2$·6H_2O under vacuum at 160 °C for 2 h), toluene (4.0 mL), and 1.2 mol % of **L8** in toluene (4.0 mL) at 50 °C for 12−36 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]At 80 °C for 12 h. [e]At 80 °C for 36 h.

indole (entries 1 and 7). Also, modest ee's were observed in the reaction of *N*-methylindole **2h** and *N*-allylindole **2i** at 80 °C (entries 8 and 9).

The absolute configuration of product **9q** was determined to be *S* on the basis of its single-crystal X-ray structure. Proposed asymmetric induction model was then depicted in Figure 1. As observed in our previous result,[12] nitroacrylate interacts with Ni(II) through a 1,3-coordinate fashion and is hence activated, followed by the nucleophilic attack of indole ring. The *Re*-attack

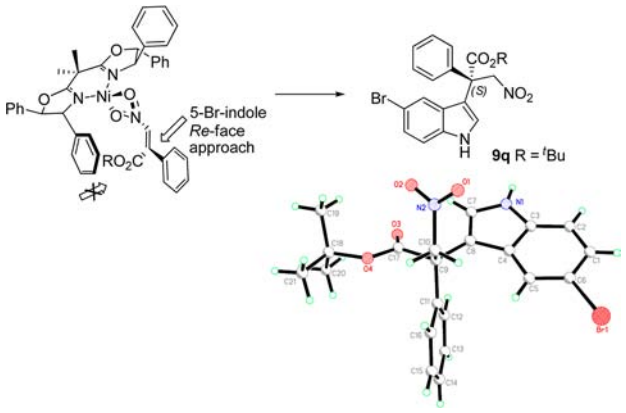
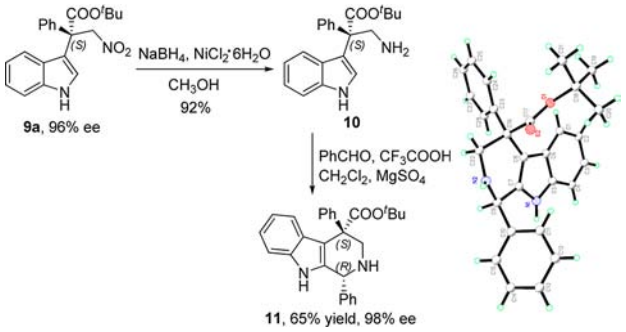


Figure 1. Proposed asymmetric induction model.

at the α-position of β-nitroacrylate is favored to furnish the product in the observed *S* configuration.

We next investigated the synthetic transformations of product **9a** to the corresponding potential biologically active compounds $\beta^{2,2}$-amino ester and tetrahydro-β-carboline. As shown in Scheme 2, chiral $\beta^{2,2}$-amino ester **10** was readily

Scheme 2. Synthetic Transformations of Product 9a



obtained in 92% yield by the reduction of nitro group with $NaBH_4/NiCl_2·6H_2O$ in methanol at room temperature. Through a CF_3CO_2H-mediated Pictet−Spengler cyclization with benzaldehyde, $\beta^{2,2}$-amino ester **10** was further converted to tetrahydro-β-carboline **11** bearing an all-carbon quaternary stereocenter, isolated as a single isomer in 65% yield and with 98% ee.

In summary, we have developed a highly enantioselective Michael-type Friedel−Crafts alkylation reaction of indoles with acyclic α-substituted-β-nitroacrylates as a reliable approach to $\beta^{2,2}$-amino acids bearing all-carbon quaternary stereocenters. One of the products was readily converted to chiral tryptophan-type $\beta^{2,2}$-amino ester and tetrahydro-β-carboline as important potential biologically active compounds. High activity of the Ni catalyst was observed, and the catalyst loading could be lowered to 0.1 mol %. Further extension of this methodology in organic synthesis is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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