Highly diastereoselective Friedel–Crafts reaction of indoles with an *N-tert*-butanesulfinylimino ester: an efficient and practical approach to enantiomerically enriched α-(3-indolyl)glycines†

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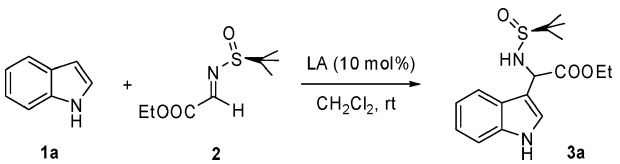
An efficient, mild and general method for the preparation of highly enantiomerically enriched α-(3-indolyl)glycines by the transition-metal-based Lewis acid-catalyzed diastereoselective Friedel–Crafts reaction of indoles with an *N-tert*-butanesulfinylimino ester has been developed.

Optically active non-proteinogenic amino acids are currently of great interest due to their significant biological activities, and extensive applications in organic synthesis and new drug discovery.[1] Among those valuable amino acids, α-(3-indolyl)-glycine and its derivatives that exist in many biologically natural and unnatural products have attracted much attention.[2] Accordingly, considerable efforts have been devoted to the development of stereoselective approaches for their synthesis.[3,4] In general, asymmetric Friedel–Crafts reaction of indoles with glyoxylate imines represents the most direct and convenient approach in terms of reagent availability. However, despite the fact that the strategies of asymmetric catalysis,[3a–d] enzymatic resolution[3e] and chiral auxiliary-mediated induction[3f–j] have been employed, far fewer methods capable of the efficient synthesis of highly enantioenriched α-(3-indolyl)glycines have been documented. The issues of unprotected indole substrate usage, reaction stereoselectivity control, and amine *N*-substituent removal remain to be addressed and are the subject of intense investigation. In this communication, we report a highly practical asymmetric Friedel–Crafts reaction of indoles with an *N-tert*-butanesulfinylimino ester under Lewis acid-catalyzed conditions, leading to enantioenriched α-(3-indolyl)glycines directly at room temperature.

Given our recent involvement[5] in the asymmetric synthesis of vicinal diamines,[5b,c] β-amino alcohols,[5d,e] and homoallylic amines[5f,g] using chiral *N-tert*-butanesulfinyl imine chemistry,[6] we sought to further extend this protocol for optically active non-proteinogenic amino acid preparation. To access chiral α-(3-indolyl)glycines, we envisaged the possibility of asymmetric Friedel–Crafts alkylation of indoles with an *N-tert*-butanesulfinyl glyoxylate imine promoted by a proper transition-metal-based Lewis acid catalyst.[7] Since much prior research has shown the success of metal coordination to *N*-sulfinyl imines,[5,6] a stereospecific addition of indoles *via* a chelation controlled configurationally rigid transition state to afford diastereomerically enriched α-(3-indolyl)glycines is anticipated.

Table 1 Screening of Lewis acids for diastereoselective Friedel–Crafts reaction of indole with an *N-tert*-butanesulfinylimino ester[a]



Entry	Catalyst	Time/h	Yield (%)[b]	de (%)[c]
1	$Cu(OTf)_2$	0.5	79	98
2	CuOTf	16	57	91
3	$Zn(OTf)_2$	16	55	92
4	$ZnCl_2$	53	18	54
5	$In(OTf)_3$	0.6	72	97
6	$InBr_3$	25	40	69
7	$AgNO_3$	19	55	41
8	AgOTf	30	59	85
9	$Yb(OTf)_3$	0.5	80	97

[a] Reactions were performed with 10 mol% of catalyst, 0.1 mmol of glyoxylate imine and 0.2 mmol of indole in dry CH_2Cl_2 at room temperature. [b] Yields of isolated and purified products. [c] de was measured as enantiomeric excess for the acetate derivative of **3a** after the removal of the sulfinyl group; determined by HPLC analysis, see ESI for details.

Initially, the Friedel–Crafts reaction of simple indole (**1**) with the *N-tert*-butanesulfinylimino ester of ethyl glyoxylate (**2**) was carefully carried out in the presence of various transition-metal Lewis acids in CH_2Cl_2 at ambient temperature.[8] As indicated in Table 1, the desired optically active α-(3-indolyl)-glycine **3a** can be successfully afforded as the main product under the catalysis of a number of Cu-, Zn-, In-, Ag-, and Yb-based Lewis acids. In all cases, minor formation of the bisindolylacetate was observed.[9] According to the results, the use of triflate salts as catalysts for the reaction seems superior to others such as chloride, bromide and nitrate. $Cu(OTf)_2$, $In(OTf)_3$ and $Yb(OTf)_3$ were proven to be effective catalysts in terms of reaction rate, yield and diastereoselectivity (entries 1, 5 and 9). With 10 mol% of $Cu(OTf)_2$,[10] the reaction completed in 30 min and gave **3a** in 79% yield with the best de of 98% (entry 1), along with 9% of bisindolylacetate.

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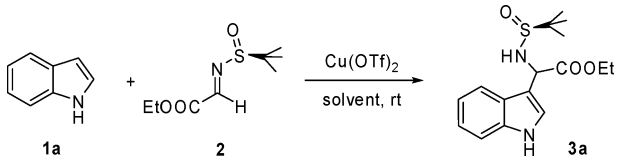
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data of all obtained α-(3-indolyl)-glycine products, and copies of ^1H and ^{13}C NMR spectra. CCDC 740797 and 740822. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b914687c

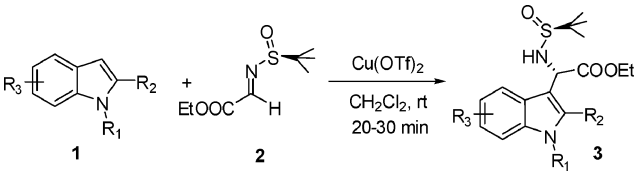
Table 2 Optimization of the reaction conditions using $Cu(OTf)_2$ as a catalyst[a]



Entry	mol (%)	Indole (equiv.)	Solvent	Time/h	Yield (%)[b]	de (%)[c]
1	10	2	CH_2Cl_2	0.5	79	98
2	10	2	$ClCH_2CH_2Cl$	0.6	75	96
3	10	2	Toluene	16	65	91
4	10	1.5	CH_2Cl_2	0.5	77	98
5	10	1.5	$CHCl_3$	24	51	92
6	10	1.5	THF	42	35	79
7	10	1.1	CH_2Cl_2	2.5	72	98
8	5	1.5	CH_2Cl_2	9	66	95
9	15	1.5	CH_2Cl_2	0.5	87	98
10	20	1.5	CH_2Cl_2	0.5	81	98

[a] Reactions were performed with 0.1 mmol of glyoxylate imine in dry CH_2Cl_2 at room temperature. [b] Yields of isolated and purified products. [c] de was measured as enantiomeric excess for the acetate derivative of **3a** after the removal of the sulfinyl group; determined by chiral HPLC analysis, see ESI for details.

Table 3 Diastereoselective Friedel–Crafts reaction of indoles with an *N-tert*-butanesulfinylimino ester[a]



Entry	1	R_1	R_2	R_3	3	Yield (%)[b]	de (%)[c]
1	**1a**	H	H	H	**3a**	87	98
2	**1b**	CH_3	H	H	**3b**	81	95
3[d]	**1c**	H	CH_3	H	**3c**	90	95
4	**1d**	H	Ph	H	**3d**	86	97
5	**1e**	H	2-BrPh	H	**3e**	87	98
6	**1f**	H	PhC≡C	H	**3f**	77	98
7	**1g**	H	H	4-Br	**3g**	81	98
8	**1h**	H	H	5-CH_3	**3h**	88	97
9	**1i**	H	H	5-CH_3O	**3i**	86	96
10	**1j**	H	H	5-F	**3j**	88	97
11	**1k**	H	H	5-Cl	**3k**	84	97
12	**1l**	H	H	5-Br	**3l**	76	97
13	**1m**	H	H	6-F	**3m**	90	98

[a] Reactions were performed with 0.1 mmol of glyoxylate imine in dry CH_2Cl_2 at room temperature. [b] Yields of isolated and purified products. [c] de was measured as enantiomeric excess for the acetate or benzoate derivative of product **3** after the removal of the sulfinyl group; determined by chiral HPLC analysis, see ESI for details. [d] 5 mol% of $Yb(OTf)_3$ was used.

To optimize the reaction conditions, we chose $Cu(OTf)_2$ as catalyst and further examined the influence of solvent, catalyst loading, and molar ratio of indole to imine. A similar result was attained (75% yield and 96% de) when the reaction was run in $ClCH_2CH_2Cl$ (Table 2, entry 2). With toluene and $CHCl_3$, a 6–7% drop of diastereoselectivity was observed (entries 3 and 5). Surprisingly, only 79% de was realized, and the conversion was very sluggish when THF was used as reaction solvent (entry 6). In addition, reducing the amount of indole from 2 to 1.5 equiv. did not affect the yield (entry 4). Further reducing the catalyst loading to 5 mol% resulted in a significant decrease of reaction rate and yield (entry 8). Gratifyingly, in the presence of 15 mol% of $Cu(OTf)_2$, α-(3-indolyl)glycine **3a** could be obtained in 87% yield without any loss in diastereoselectivity (entry 9). Notably, with these reaction conditions, the same level of both yield (93%) and diastereoselectivity (>98%) could be obtained on a gram scale (5 mmol of glyoxylate imine).

With the optimal reaction conditions identified, we then turned our attention to the evaluation of substrate generality. A wide range of indoles bearing different substituents were investigated using the conditions in entry 9 of Table 2. To our delight, the reaction was found to be general (Table 3). In all cases, it proceeded smoothly to completion in 20–30 min, indoles containing either electron-donating or electron-withdrawing groups could be successfully applied, affording α-(3-indolyl)glycine products **3** in good yields and with excellent diastereoselectivities (95–98% de). It is noteworthy that both the reaction yield and diastereoselectivity were not even affected by substitution close to the reaction site at the indole 2-position, regardless of the size or nature of the group (entries 3–6). Unlike other *N*-substituents on amine functionality, the removal of the sulfinyl group[11] can be easily accomplished under mild acidic conditions[5b,c] with complete retention of stereochemical configuration. To better understand the stereochemical outcome of the reaction, single-crystal growth of product **3** with/without an R_2 substituent was performed. By X-ray crystallography, the stereochemistry of the newly formed carbon center of both α-(3-indolyl)glycine **3e** and **3l** was determined to be *S* (Fig. 1).[12] Assuming an analogous reaction mechanism, the same absolute configuration of the obtained α-(3-indolyl)-glycines could be readily assigned.

Encouraged by the above success, we also examined pyrroles **4a** and **4b** as substrates (Scheme 1). It is likely due

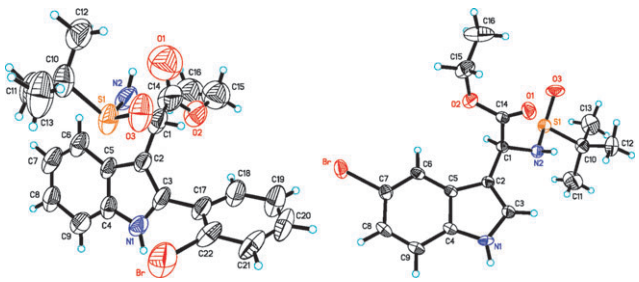
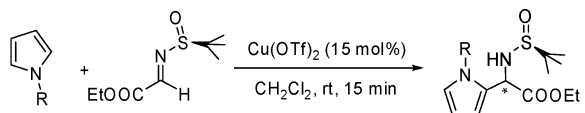


Fig. 1 X-Ray structure of **3e** (left) and **3l** (right).



Scheme 1 Diastereoselective Friedel–Crafts alkylation of pyrroles.

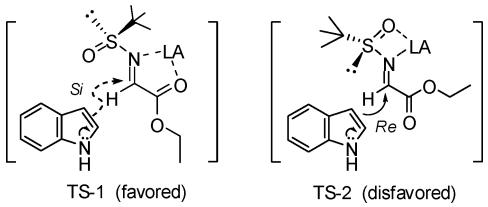


Fig. 2 Mechanistic proposals for stereocontrol.

to the higher reactivity of pyrroles that the reactions took place rapidly and went to completion in several minutes to give the desired α-(2-pyrrolyl)glycines **5a** and **5b** in 48% and 67% yield, along with 2,5-dialkylation products in 51% and 22% yield, respectively. The diastereomeric excesses of **5a** and **5b** proved to be high (88% and 97% de).

On the basis of the observed diastereofacial selectivity, a plausible transition state model for this asymmetric Friedel–Crafts alkylation is illustrated in Fig. 2. In comparison with the chelation of Lewis acid with the imine nitrogen and sulfinyl oxygen (TS-2), activation of the imino ester by the coordination of the Lewis acidic metal to the imine nitrogen and carbonyl oxygen is more favorable (TS-1), in which the uncoordinated *N*-sulfinyl group adopts an approximately synperiplanar configuration.[13] With the (*S*)-*N*-*tert*-butanesulfinyl substrate, to avoid the steric repulsion with the bulky *tert*-butyl group, indole attacks preferentially from the sterically non-blocked bottom face (*Si*-face) of the C=N bond to give the corresponding (*S*)-product.

In summary, we have developed a highly diastereoselective Friedel–Crafts alkylation of unprotected indoles with an *N*-*tert*-butanesulfinylimino ester. The reaction could be accomplished with ease in the presence of a catalytic amount of $Cu(OTf)_2$ at room temperature. It enables fast, efficient and general access to various enantiomerically enriched α-(3-indolyl)glycines. Moreover, the method provides opportunities for extensive future applications of optically active α-(3-indolyl)glycines in medicinal chemistry and organic synthesis. Further exploration of this methodology is currently under study in our laboratory.

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8 Reaction conducted in the absence of Lewis acid catalysts gave no results in 24 h.

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12 Crystal data for **3e** ($C_{22}H_{25}BrN_2O_3S$): T = 293(2) K; wavelength: 0.71073 Å; crystal system: orthorhombic, $P2_12_12_1$; unit cell dimensions: a = 10.7973(14) Å, b = 14.2880(18) Å, c = 15.311(2) Å, α = 90°, β = 90°, γ = 90°; V = 2362.0(5) Å^3; Z = 4; ρ_c = 1.343 Mg m^{-3}; $F(000)$ = 984; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0710, wR_2 = 0.1940; R indices (all data), R_1 = 0.1533, wR_2 = 0.2290; 12 471 reflections measured, 4407 were unique ($R_{(int)}$ = 0.0569). CCDC 740797. Crystal data for **3l** ($C_{16}H_{21}BrN_2O_3S$): T = 293(2) K; wavelength: 0.71073 Å; crystal system: monoclinic, $P2_1$; unit cell dimensions: a = 9.3558(14) Å, b = 9.4206(14) Å, c = 10.6930(16) Å, α = 90°, β = 99.473(3)°, γ = 90°; V = 929.6(2) Å^3; Z = 2; ρ_c = 1.434 Mg m^{-3}; $F(000)$ = 412; final R indices [$I > 2\sigma(I)$]: R_1 = 0.0478, wR_2 = 0.1071; R indices (all data), R_1 = 0.0595, wR_2 = 0.1110; 5119 reflections measured, 3425 were unique ($R_{(int)}$ = 0.0425). CCDC 740822.

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