Preparation of *N*-2-Nitrophenylsulfenyl Imino Peptides and Their Catalyst-Controlled Diastereoselective Indolylation

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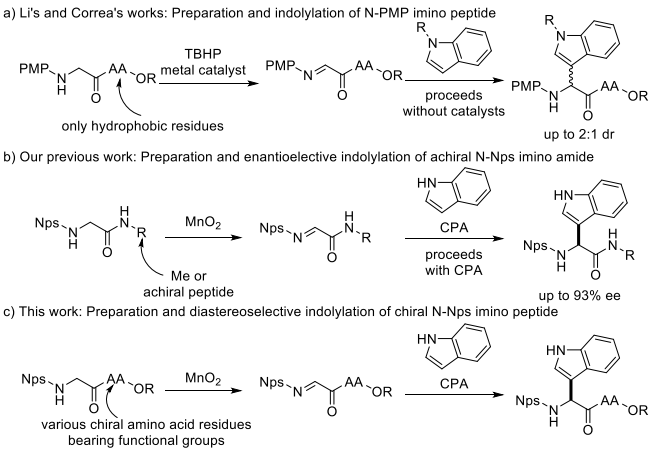
Abstract: *N*-2-Nitrophenylsulfenyl (Nps) imino dipeptides bearing various functional groups were successfully prepared via MnO_2-mediated oxidation and then subjected to diastereoselective indolylation. Each diastereomer of the adduct was selectively obtained from the same substrates using the appropriate chiral phosphoric acid catalysts. These transformations would be useful for synthesizing non-canonical amino acid-containing peptides as novel drug candidates.

Introduction

Peptides have attracted considerable attention in the field of drug discovery. The installation of a non-canonical amino acid unit enhances the structural diversity of peptides, thereby facilitating the development of novel drugs.[1] Indolylglycine, a non-canonical amino acid, is regarded as an aromatic amino acid analog because of the electron-rich nature of the indolyl π-system, which might engage the electrostatic interactions such as π–π, cation–π, and NH–π interactions, similar to a canonical aromatic amino acid residue.[2] This amino acid unit can be constructed via the 1,2-addition of an indole nucleophile to imino carboxylic acid derivatives.[3] The most straightforward method to obtain this amino acid is the direct indolylation of a peptide bearing an imine moiety at its N-terminus.[4] Li and Correa independently reported the preparation of *N*-4-methoxyphenyl (PMP)-protected imino peptides by the combination of *tert*-butyl hydroperoxide (TBHP) and metal catalyst-mediated oxidation of the corresponding N-terminal glycine peptide and then directly adding an indole nucleophile to the imino peptide (Scheme 1-a). However, the harsh oxidative conditions accompanying the use of TBHP, which reacts with oxidation-labile groups, such as the sulfide group of the methionine residue,[5] can narrow the substrate scope of this reaction. Furthermore, the indolylation of *N*-PMP imines proceeds without a catalyst at ambient temperature;[4,6] therefore, stereoselectivity relies on the chirality and substituents of the substrate, which could hamper the diastereoselective at-will construction of the indolylglycine moiety. Indeed, previous protocols used only hydrophobic amino acid residue-containing peptides as substrates, and the diastereoselectivities of the obtained products were poor. During our efforts to develop asymmetric reactions,[7] we found that the readily available *N*-2-nitrophenylsulfenyl (Nps) imino amide is stable and can be used as a substrate for asymmetric indolylation catalyzed by chiral phosphoric acid (CPA)[8,9] (Scheme 1-b). Using the hydrophobic-anchor-linked[10] N-terminus of an *N*-Nps imino peptide consisting of glycine residues, we demonstrated, for the first time, the direct asymmetric indolylation of a peptidyl substrate controlled by an external catalyst.[9d] Based on this previous achievement, we anticipated that the *N*-Nps imine moiety could be installed in the presence of other amino acids bearing several functional groups under mild oxidation conditions (Scheme 1-c). In addition, we believe that the stereoselectivity of the product of the addition reaction could be controlled by the catalyst, rather than the chirality of the substrate; this capability would be valuable for synthesizing diverse peptides bearing indolylglycine. Herein we report the preparation and diastereoselective indolylation of *N*-Nps imino peptides with diverse chiral amino acids.



Scheme 1. Direct indolylation of *N*-protected imino peptides for the synthesis of indolylglycine-containing peptides.

Results and Discussion

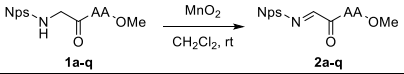
To verify the compatibility of the amino acid residues, we performed the MnO_2-mediated oxidation of *N*-Nps glycine dipeptides with various amino acid residues at the C-terminus (Table 1). The oxidation of **1a**–**1c**, which bear alkyl chains of various sizes, proceeded smoothly to give imino peptides **2a**–**2c** in good yield (entries 1–3). The reactions of serine and tyrosine gave the desired products when their hydroxy group was protected by benzyl or *t*-butyl groups, which are generally used

in standard peptide synthesis (entries 4–7). Residues bearing carboxylic acid derivatives were also tolerated (entries 8–11). Dipeptides **1l** and **1m**, which have basic amino acids at the C-terminus, could also be oxidized when the proper protective groups were used (entries 12 and 13). To our delight, methionine-containing substrate **1n** was successfully converted to the corresponding imine **2n** without oxidation of the sulfide moiety (entry 14). The reaction of the *N*-Cbz-protected histidine-containing substrate **1o** proceeded smoothly (entry 15). In peptide chemistry, tryptophan is often used without protecting the indole group. Unfortunately, the non-protected indole-containing dipeptide **1p** was not tolerated during MnO_2-mediated oxidation because of the lability of the indole ring under oxidative conditions (entry 16). This problem was solved by installing an electron-withdrawing Cbz group on the nitrogen atom of the indole (entry 17).

Next, we screened the ideal indolylation conditions for *N*-2-Nps imino dipeptide **2a**, which possesses a sterically demanding valine residue, and indole **3a** (Table 2). CPA (*R*)-**4a** efficiently promoted the reaction, but no diastereoselectivity was observed in the resultant products (entry 1). The introduction of bulky substituents at the 3,3'-positions improved the stereoselectivity of the products (entries 2 and 3). The 6,6'-TIPS group-substituted catalyst (*R*)-**4d** further improved the ratio of **5aa** and *epi*-**5aa** to 91:9 (entry 4). The addition of MS3Å also improved both the chemical yield and stereoselectivity of the products, and the catalyst loading could be reduced to 5 mol% without a significant loss of yield (entries 5 and 6). We attempted to determine the conditions under which *epi*-**5aa** is preferentially produced using an (*S*)-series of catalysts. To our surprise, (*S*)-**4a**, which possesses relatively less bulky substituents at the 3,3'-positions, gave products with high stereoselectivity (entry 7). By contrast, the use of bulkier catalysts, such as (*S*)-**4b**, **4c**, or **4d**, resulted in diminished stereoselectivity (entries 8–10). Neither the addition of MS3Å nor a decrease in the catalyst loading improved the diastereoselectivity of the products (entries 11 and 12). The absolute configurations of **5aa** and *epi*-**5aa** were determined by derivatization to the authentic known compound with **5aa** and comparison of their ^{1}H NMR spectra (see Supporting Information for details).

The optimal conditions for producing each diastereomer in our hands, we next examined the scope and limitation of the substrate (Scheme 2). In addition to the reaction of **2a**, those of

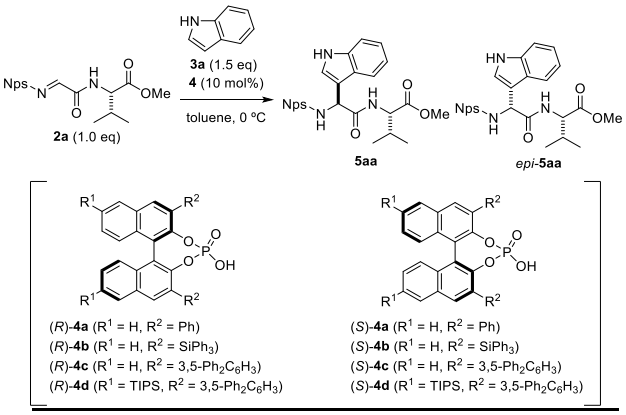
Table 1. Preparation of *N*-Nps imino peptides by MnO_2-mediated oxidation.[a]



Entry	AA	1	Time (min)	2	Yield (%)[b]
1	Val	**1a**	60	**2a**	79
2	Ala	**1b**	60	**2b**	81
3	Phe	**1c**	30	**2c**	86
4	Ser (Bn)	**1d**	30	**2d**	71
5	Ser (*t*-Bu)	**1e**	30	**2e**	81
6	Tyr (Bn)	**1f**	90	**2f**	75
7	Tyr (*t*-Bu)	**1g**	30	**2g**	84
8	Gln $(Bn)_2$	**1h**	60	**2h**	76
9	Asn (Tr)	**1i**	30	**2i**	88
10	Glu (Bn)	**1j**	60	**2j**	69
11	Asp (*t*-Bu)	**1k**	30	**2k**	77
12	Lys (Cbz)	**1l**	60	**2l**	77
13	Arg $(Cbz)_2$	**1m**	90	**2m**	84
14	Met	**1n**	60	**2n**	83
15	His (Cbz)	**1o**	90	**2o**	74
16	Trp	**1p**	30	**2p**	0
17	Trp (Cbz)	**1q**	60	**2q**	94

[a] The reactions were carried out using **1** (1 equiv) and MnO_2 (20 equiv) in CH_2Cl_2. [b] Isolated yield.

Table 2. Screening of the diastereoselective indolylation conditions.[a]



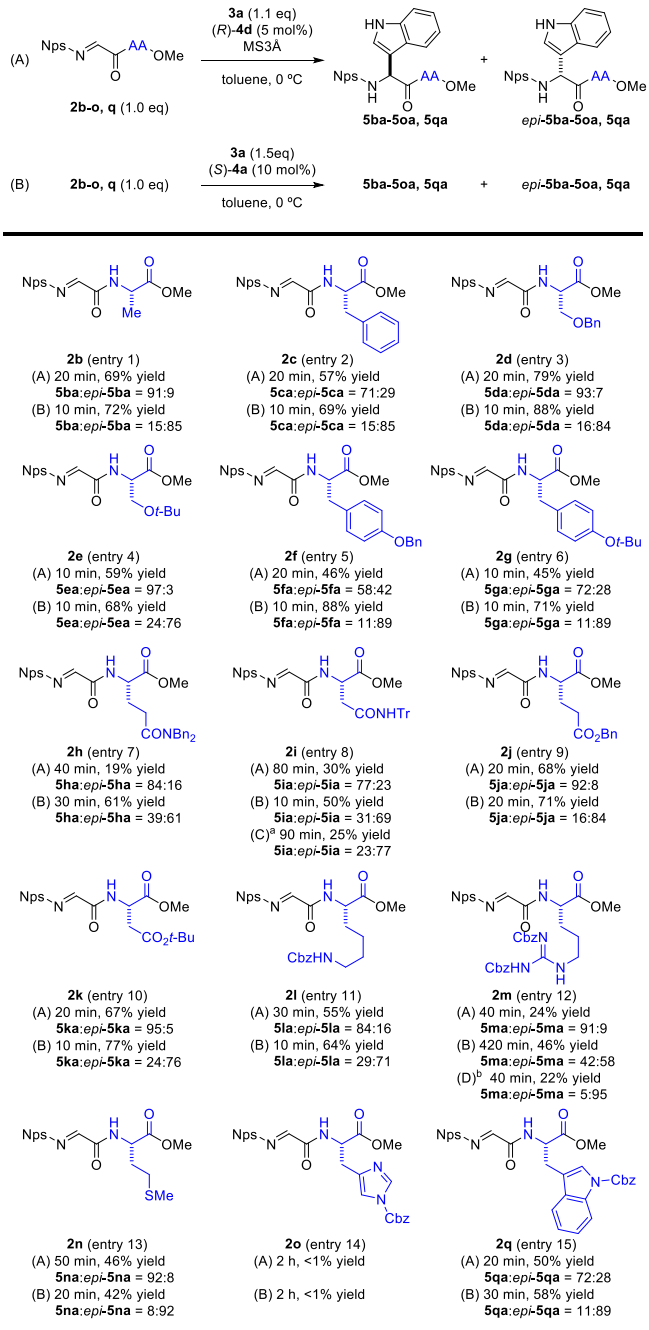
Entry	4	Time (min)	Yield (%)[b]	**5aa**:*epi*-**5aa**[c]
1	(*R*)-**4a**	60	73	50:50
2	(*R*)-**4b**	120	62	85:15
3	(*R*)-**4c**	120	78	86:14
4	(*R*)-**4d**	120	55	91:9
5[d]	(*R*)-**4d**	120	73	94:6
6[d][e]	(*R*)-**4d**	20	72	95:5
7	(*S*)-**4a**	60	72	7:93
8	(*S*)-**4b**	120	71	31:69
9	(*S*)-**4c**	120	50	19:81
10	(*S*)-**4d**	120	42	14:86
11[d]	(*S*)-**4a**	60	70	12:88
12[d][e]	(*S*)-**4a**	20	74	13:87

[a] The reactions were carried out using **2a** (0.10 mmol), **3a** (0.15 mmol), and **4** (10 μmol) in toluene. [b] Combined isolated yield of **5aa** and *epi*-**5aa**. [c] Determined by ^{1}H NMR analysis of the mixture of **5aa** and *epi*-**5aa**. [d] MS3Å (30 mg) was added. [e] **3a** (0.11 mmol) and **4** (5.0 μmol) were used.

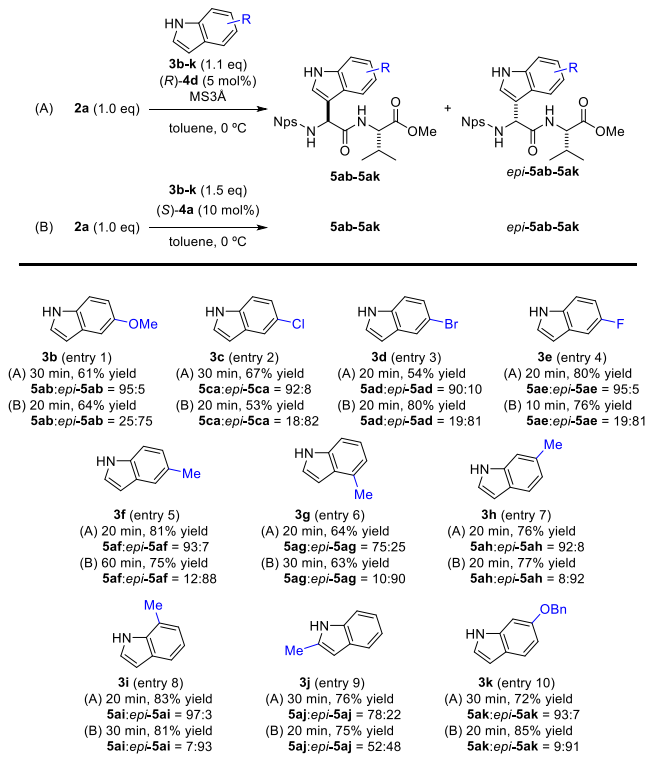
imines **2b**, **2j**, and **2n** proceeded with high diastereoselectivity when (*R*)-**4d** or (*S*)-**4a** (entries 1, 9, and 13) was used. Although catalyst (*R*)-**4d** converted serine-, glutamine-, glutamic acid-, aspartic acid-, and lysine-containing imines **2d**, **2e**, **2h**, **2k**, and **2l** to the corresponding adducts **5da**, **5ea**, **5ha**, **5ka**, and **5la**, respectively, with good stereoselectivity, the diastereoselectivity of the reactions of the same substrates catalyzed by (*S*)-**4a** were moderate (entries 3, 4, 7, 10, and 11, respectively). In the case of arginine-containing imine **2m**, (*R*)-**4d** produced **5ma** with high diastereoselectivity, albeit in low yield. By contrast, the stereoselectivity of the reaction catalyzed by (*S*)-**4a** was low. Improvement of the diastereoselectivity using (*S*)-catalyst could be achieved in the use of (*S*)-**4d** (entry 12). Imines **2c**, **2f**, **2g**, and **2q**, which contain phenylalanine, tyrosine, or tryptophan, could be stereoselectively converted to *epi*-**5ca**, **5fa**, **5ga**, and **5qa**, respectively, in the presence of (*S*)-**4a**. However, the stereoselectivity of the products of the reaction of the same substrates catalyzed by (*R*)-**4d** were unsatisfactory (entries 2, 5, 6, and 15). Unfortunately, **2i** afforded low diastereoselectivity under both conditions catalyzed by (*R*)-**4d** or (*S*)-**4a** and slightly better diastereoselectivity was observed with (*S*)-**4d** than with (*S*)-**4a** (entry 8). Histidine-containing imine **2o** afforded negligible amounts of the expected adducts under both conditions using (*R*)-**4d** or (*S*)-**4a** (entry 14). In these reactions, significant amounts of the substrates were recovered, and the transfer of the Cbz group from **2o** to **3a**[11] was not observed; therefore, we speculate that the failure of the reaction may be attributed to the deactivation of the catalyst caused by the basic imidazole moiety.

We also screened the scope of indole nucleophiles (Scheme 3). Both electron-rich indole **3b** and electron-poor indoles **3c**–**3e** gave one of the expected epimers with good diastereoselectivity, depending on the chirality of the catalysts used (entries 1–4). Next, the effect of the substituent position was evaluated. All indoles possessing a methyl group at either the 4, 5, 6, or 7 positions could be used to synthesize the epimers of the adduct (entries 5–8). When 2-methylindole **3j** was used in the reaction, (*R*)-**4d** induced stereoselectivity at a sufficient level, whereas (*S*)-**4a** resulted in the synthesis of both epimers **5aj** and *epi*-**5aj** at almost the same ratio (entry 9). 6-Benzyloxyindole **3k**, which can be used to synthesize a mimetic of tyrosine, was also applicable (entry 10).

The mechanism of stereoinduction during indolylation was rationalized using DFT calculations. The transition-state geometries of the model reactions of substrate **6** and indole **3a** to give **8** and *ent*-**8** using catalysts (*R*)- or (*S*)-**7**, corresponding to the reactions in Table 2, entry 1, and Scheme 1, entry 1-B,

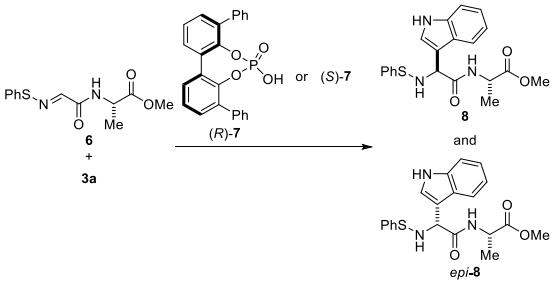


Scheme 2. Scope of the Substrate. [a] condition C: (*S*)-**4d** (5 mol%), **3a** (1.1 equiv), and MS3Å (30 mg) was used. [b] condition D: (*S*)-**4d** (10 mol%), **3a** (1.1 equiv), and MS3Å (30 mg) was used.



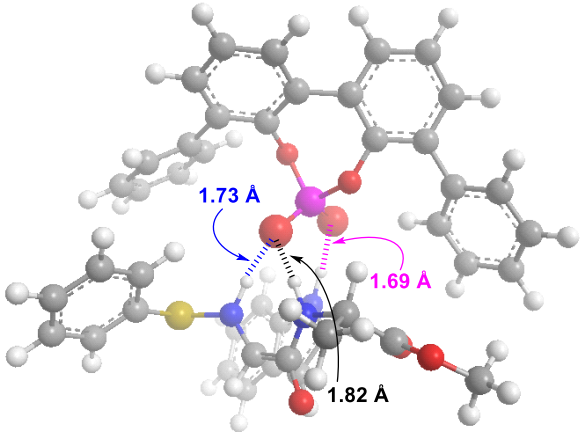
Scheme 3. Scope of the indole nucleophile.

respectively,[12] were optimized at the B3LYP/6-31G* level of theory, and the dispersion-corrected energies were calculated at the M06-2X/6-311+G** level of theory (Scheme 4). All transition states (Figures 1 and 2) involved three hydrogen-bonding interactions between the OH of CPA and C=N of **6** (blue line), the P=O of CPA and amide NH of **6** (black line), and the P=O of CPA and NH of **3a** (magenta line). No apparent steric repulsion



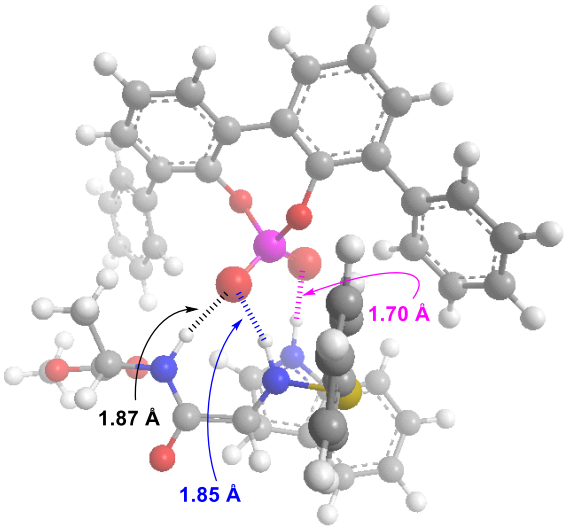
Scheme 4. Model reactions for DFT calculations.

(a) Transition state to give **8**



$\Delta E^{\ddagger}$ = 0.02 kcal/mol

(b) Transition state to give *epi*-**8**

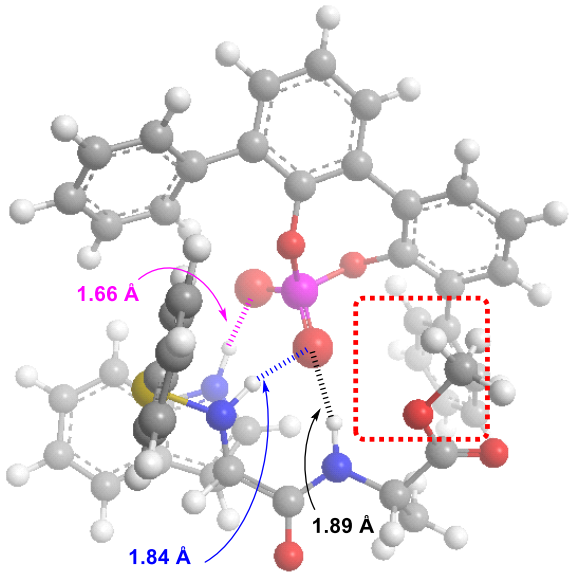


$\Delta E^{\ddagger}$ = 0.00 kcal/mol

Figure 1. The transition state models with (*R*)-**7**.

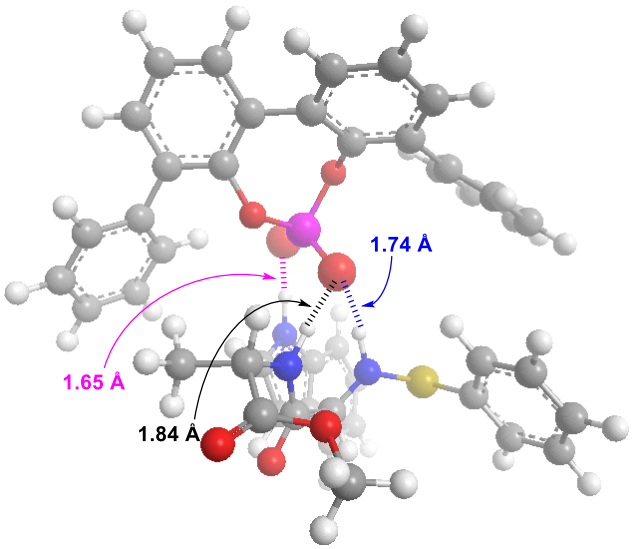
was observed in the transition states when (*R*)-**7** was used (Figure 1), and the energies of these transition states were nearly identical ($\Delta\Delta E^{\ddagger}$ = 0.02 kcal/mol), which is comparable with the experimental result (dr 50:50; Table 2, entry 1). In the transition state of the reaction to give **8**, sufficient space was available for additional substituents around the phenyl groups at the 3,3'-positions of CPA (Figure 1-a), whereas the area around one of the phenyl groups (the left one in Figure 1-b) was crowded in the transition state to give *epi*-**8**. This finding clearly explains the results of entries 2–6 in Table 2, which reveals that CPA bearing bulky substituents at the 3,3'-positions gives **5aa**, the product corresponding to **8**, as the major product. In the transition state of the reaction to give **8** with (*S*)-**7**, steric repulsion was observed between the alanine moiety of **6** and the phenyl group of (*S*)-**7**, as shown by the red dashed square in

(a) Transition state to give **8**



$\Delta E^{\ddagger}$ = 1.39 kcal/mol

(b) Transition state to give *epi*-**8**



$\Delta E^{\ddagger}$ = 0.00 kcal/mol

Figure 2. The transition state models with (*S*)-**7**.

Figure 2-a. This adverse interaction may explain why the energy of this transition state is 1.39 kcal/mol higher than that to give *ent*-**8** (Figure 2-b), which is comparable with the experimental result (dr 16:84; Table 3, entry 1-B). This interaction may also explain why (*S*)-**4a**, which bears a relatively less bulky phenyl group, can realize diastereoselective addition to produce (*R*)-adducts.

Conclusion

We have developed a protocol to synthesize *N*-Nps imino peptides. We confirmed that the functional groups generally used in peptide synthesis are well tolerated during MnO_2-mediated oxidation. In addition, the prepared imines can be used for CPA-catalyzed indolylation. In the reaction using valine-derived imino peptide **2a**, the epimers **5aa** and *epi*-**5aa** were obtained using the appropriate catalysts. Although some other peptides with different amino acid residues did not produce adducts with good stereoselectivity, the trends observed apply to a wide range of peptides and indole nucleophiles. The application of the proposed methodology to the development of biologically active peptides is currently underway and will be reported in due course.

Experimental Section

MnO_2-mediated oxidation (2a): To a solution of **1a** (1.40 g, 4.09 mmol) in CH_2Cl_2 (100 mL) was added MnO_2 (7.11 g, 81.8 mmol) at rt and stirred at the same temperature for 1 h. Then, the insoluble materials were removed by filtration through Celite®. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (hexane/EtOAc 2:1) to afford **2a** (1.10 g, 79%) as a yellow oil: $[\alpha]_{26}^{D}$ +116.2 (*c* 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.0 Hz, 1H), 8.29 (d, *J*. = 8.0 Hz, 1H), 8.22 (s, 1H), 7.79 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.28 (br m, 1H), 4.64 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.81 (s, 3H), 2.30 (septet d, *J* = 7.0, 5.0 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 161.0, 153.4, 142.3, 137.5, 134.3, 126.0, 125.3, 56.9, 52.1, 31.2, 18.7, 17.6. IR (NaCl) ν 2964, 1740, 1674, 1437, 1335, 1150 cm^{-1}. LRMS (ESI) *m/z* 362 (M + Na^+, 100). HRMS (ESI) (*m/z*) [M + K^+] calcd for $C_{14}H_{17}KN_3O_5S$; 378.0526, found, 378.0528.

Asymmetric Friedel–Crafts-type reaction using (*R*)-4d. A 95:5 mixture of 5aa and *epi*-5aa: To a mixture of **2a** (36.1 mg, 0.106 mmol), indole **3a** (13.7 mg, 0.116 mmol), and MS3Å (30 mg) in toluene (1.0 mL) was added (*R*)-**4d** (5.9 mg, 5.3 μmol) at 0 ºC, and the mixture was stirred at the same temperature for 20 min and then directly purified by silica gel column chromatography (hexane/EtOAc 2:1 to 1:1) to give a 95:5 mixture of **5aa** and *epi*-**5aa** (36.1 mg, 72%,) as a yellow oil: $[\alpha]_{23}^{D}$ +31 (*c* 1.00, $CHCl_3$). The ratio of **5aa** and *epi*-**5aa** was determined based on the integration area of ^{1}H NMR signals at 3.63 and 3.71 ppm.

Data of **5aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.29 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.95 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.45 (ddd, *J* = 8.0, 7.0, 1.5 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29–7.15 (m, 4H), 6.48 (br m, 1H), 4.82 (d, *J* = 4.0 Hz, 1H), 4.57 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.63 (s, 3H), 2.14 (septet d, *J* = 7.0, 5.0 Hz, 1H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 171.8, 171.6, 144.7, 142.7, 136.4, 133.6, 125.8, 125.6, 124.8, 124.7, 124.3, 122.8, 120.2, 119.1, 112.2, 111.6, 61.2, 57.7, 52.1, 31.1, 19.0, 17.8. IR (NaCl) ν 2966, 1737, 1665, 1509, 1337, 1150 cm^{-1}. LRMS (ESI) *m/z* 495 (M + K^+, 100), 479 (M + Na^+, 5). HRMS (ESI) (*m/z*) [M + Na^+] calcd for $C_{22}H_{24}N_4NaO_5S$; 479.1365, found, 479.1363.

Data of *epi*-**5aa**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 8.24 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.82 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.47 (td, *J* = 8.0, 1.5 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.24–7.13 (m, 4H), 6.70 (br m, 1H), 4.79 (d, *J* = 4.0 Hz, 1H), 4.61 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.11 (m, 1H), 3.71 (s, 3H), 2.12 (septet d, *J* = 7.0, 5.0 Hz, 1H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 171.3, 144.2, 142.9, 136.4, 133.8, 125.9, 125.2, 124.8, 124.6, 124.5, 122.6, 120.1, 119.1, 112.0, 111.7, 60.7, 57.2, 52.2, 31.2, 18.9, 17.4. IR (NaCl) ν 2962, 1737, 1644, 1509, 1337, 1151 cm^{-1}. LRMS (ESI) *m/z* 479 (M + Na^+, 95). HRMS (ESI) (*m/z*) [M + Na^+] calcd for $C_{22}H_{24}N_4NaO_5S$; 479.1365, found, 479.1364.

Asymmetric Friedel–Crafts-type reaction using (*S*)-4a. A 7:93 mixture of 5aa and *epi*-5aa: To a solution of **2a** (19.2 mg, 56.6 μmol) and indole **3a** (10.6 mg, 90.5 μmol) in toluene (0.6 mL) was added (*S*)-**4a** (2.8 mg, 5.6 μmol) at 0 ºC, and the mixture was stirred at the same temperature for 60 min and then directly purified by silica gel column chromatography (hexane/EtOAc 2:1) to give a 7:93 mixture of **5aa** and *epi*-**5aa** (19.8 mg, 72%) as a yellow oil: $[\alpha]_{25}^{D}$ –67 (*c* 0.92, $CHCl_3$). The ratio of **5aa** and *epi*-**5aa** was determined based on the integration area of ^{1}H NMR signals at 3.63 and 3.71 ppm.

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Keywords: diastereoselectivity • indolyl glycine • *N*-Nps imino peptide • non-canonical amino acid-containing peptide • organocatalysis

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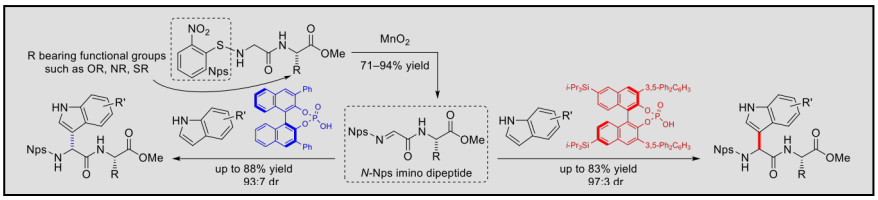
[12] We also performed the reaction of **2b**, **3a**, and (*R*)-**4a** and found that the reaction gave the adducts **5ba** and *epi*-**5ba** in 50:50 ratio as similar as that described in entry 1 in Table 1.

Entry for the Table of Contents



Preparation of *N*-2-Nitrophenylsulfenyl imino dipeptides bearing various functional groups was successfully achieved using MnO_2-mediated oxidation. We also realized the highly diastereoselective indolylation of the iminopeptides, which allows selective access to each diastereomer of the adduct from the same substrate using an appropriate chiral phosphoric acid catalyst. The origin of the diastereoselectivity was elucidated by DFT calculations.