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Graphical Abstract

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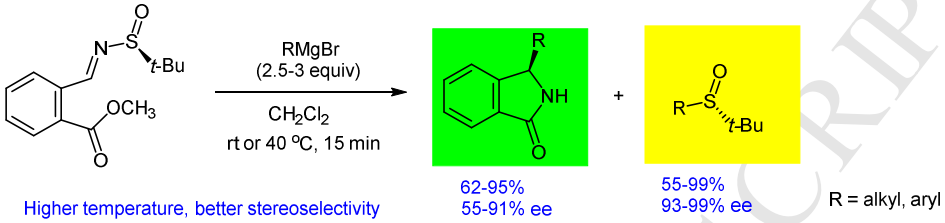

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Stereoselective synthesis of isoindolinones and *tert*-butyl sulfoxides

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ABSTRACT

A reaction of Grignard reagents with an optically pure *N*-sulfinylimine derived from methyl 2-formylbenzoate yields enantioenriched isoindolinones and *tert*-butyl sulfoxides. The products are formed by the addition of the nucleophile to *N*-sulfinylimine followed by cyclization to form *N*-*tert*-butylsulfinylisoindolinone, which readily undergoes substitution with a second equivalent of Grignard reagent. The reaction can be carried out in dichloromethane at room temperature or at elevated temperatures without any loss of stereoselectivity. The use of nucleophiles other than Grignard reagents has also been investigated.

1. Introduction

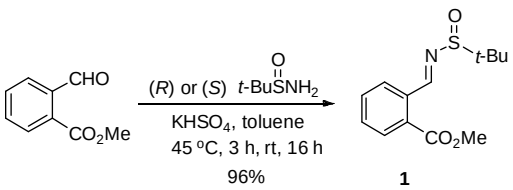
3-Substituted isoindolinones possess diverse biological properties, such as anxiolytic,[1] sedative-hypnotic,[2] anticancer,[3] antileukemic,[4] antihyper-glycemic,[5] antiviral[6] and antihypertensive[7] properties. They are also potent neurokinin-,[8] serotonin-,[9] and dopamine-receptor[10] inhibitors or antagonists. For many years, they have become the target of medicinal chemists, particularly in enantiomeric form. Most methods for the synthesis of optically active isoindolinones are based on the use of chiral auxiliaries. Some good examples are addition of Grignard reagents to chiral *N*-substituted phthalimides,[11] reaction of chiral Schiff bases of glycine with 2-cyanobenzaldehyde,[12] cyclization of chiral α-substituted benzylamines,[13] and alkylation of chiral *N*-acylisoindolinones.[14] Catalytic methods include Rh(I)-catalyzed arylation of 2-bromobenzaldimines followed by aminocarbonylation,[15] enantioselective addition of isoindolinones to imines,[16] aminoacid-catalyzed Mannich reaction followed by lactamization,[17] and cinchoninium-catalyzed intramolecular aza-Michael reactions.[18] A thorough review of asymmetric syntheses of 3-substituted isoindolinones was published by Massa et al. [19]

In this paper, we propose a straightforward method for the preparation of enantioenriched isoindolinones using Ellman's *tert*-butylsulfinamide methodology.[20] The same reaction may be used for obtaining optically pure *tert*-butyl sulfoxides.

2. Results and discussion

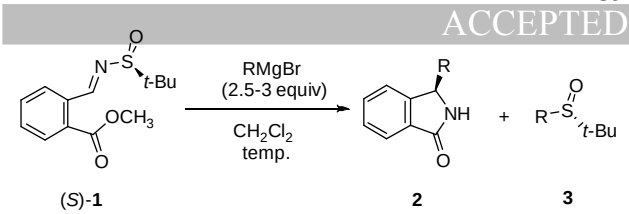
We tried to obtain isoindolinones by using the following-three step procedure: addition of Grignard reagent to *N*-sulfinylimine **1** derived from 2-carboxybenzaldehyde, removal of the sulfinyl group from the nitrogen atom, and cyclization. A similar stepwise procedure was described earlier by Xu and coworkers[21] by using a stereoselective addition of allylindium to *N*-sulfinylimine **1** followed by desulfinylation and cyclization to give 3-allylisoindolinones with excellent stereoselectivity. The free radical approach of this reaction was described by Rodríguez-Fernández et al.[22] by using tributyltin-mediated isopropyl iodide addition at -78 °C to *N*-sulfinylimine **1**. Our procedure allows preparation of numerous derivatives of 3-substituted isoindolinones, not only limited to 3-allyl or 3-isopropyl.

The starting methyl 2-[(*tert*-butyl-*N*-sulfinylimine)-methyl]benzoate **1** can be conveniently prepared by the condensation of commercially available optically pure *tert*-butylsulfinamide with methyl 2-formylbenzoate in the presence of $KHSO_4$ (Scheme 1).[23] The enantiomeric excess of *N*-sulfinylimine **1** was 98%.



Scheme 1. Substrate preparation.

Unexpectedly, we found that the desired isoindolinones could be formed directly in one step by using Grignard reagents. The second product of this reaction was found to be *tert*-butyl sulfoxide (Scheme 2). Apparently, Grignard reagent after the addition to the C=N bond further reacted, yielding a substitution product at the sulfur atom.

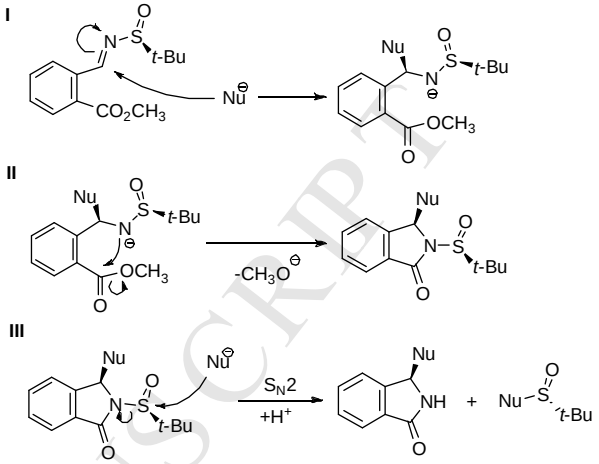


Scheme 2. Addition of Grignard reagents to *N*-sulfinylimine **1**.

The proposed mechanism is shown in Scheme 3. We assume that nucleophile addition to the *N*-sulfinylimine is followed by cyclization to form the corresponding *N*-*tert*-butylsulfinylisoindolinone, which finally undergoes a S_N2-type substitution with the second equivalent of Grignard reagent to form the products.

When we used more than two equivalents of an organomagnesium compound, the yield was excellent and the only products were isoindolinone and *tert*-butyl sulfoxide. The results are presented in Table 1. The enantioselectivity of isoindolinones strongly depends on the reaction conditions. The effects of different solvents, temperature, and additives are presented in Tables 2 and 3.

The best results were obtained when using dichloromethane as solvent (Table 2, entry 3). Additives, such as $AlMe_3$, CuI, or TMEDA, did not improve the ee. The presence of THF was also unfavorable. Solutions of organomagnesium reagents in THF provided low ee of isoindolinone (Table 2, entry 5). Therefore, we used solutions of Grignard reagents in diethyl ether. However, the ee remained medium. Decreasing the reaction temperature did not improve the results. The highest stereoselectivity was observed at 40 °C. The ee did not change significantly after 15 min and after several hours (Table 3, entry 3-5). Similar temperature dependence was observed for the BuLi addition to *O*-protected *N*-trimethylsilyl imines of (2*S*)-lactal.[24]



Scheme 3. Reaction mechanism.

Table 1 Synthesis of 3-substituted isoindolinones **2**[a]

Entry	*N*-Sulfinylimine	R	Temp. °C	Isoindolinone	Yield[b], %	Ee, %
1	(*R*)-**1**	Me	20	(*S*)-**2a**	90	68
2	(*R*)-**1**	*i*-Pr	40	(*S*)-**2b**	90	58
3	(*S*)-**1**	Bu	40	(*R*)-**2c**	95	71
4	(*S*)-**1**	Hex	0	(*R*)-**2d**	76	55
5	(*R*)-**1**	Bn	40	(*S*)-**2e**	71	91
6	(*R*)-**1**	Ph	40	(*S*)-**2f**	62	78
7	(*S*)-**1**	2-$MeOC_6H_4$	20	(*S*)-**2g**	88	11
8	(*S*)-**1**	4-ClC_6H_4	0	(*R*)-**2h**	99	80
9	(*R*)-**1**	4-ClC_6H_4	40	(*S*)-**2h**	91	81
10	(*S*)-**1**	*p*-Tol	40	(*R*)-**2i**	90	82

[a] The reactions were carried out on a 0.19-0.75 mmol scale under argon for 90 min except for entry 1, 120 min, entries 6 and 9, 20 min. 3 equiv of Grignard reagent were used.

[b] Isolated yield.

Table 2 Solvent and additives effect upon the addition of Grignard reagent for the preparation of isoindolinone **2c** [a]

Entry	*N*-Sulfinylimine	Grignard reagent	Solvent / Additive	Temp. °C	Yield[b], %	Ee, %
1	(*R*)-**1**	BuMgBr / Et_2O	THF	0	66	9
2	(*R*)-**1**	BuMgBr / Et_2O	PhMe	40	66	5
3	(*S*)-**1**	BuMgBr / Et_2O	CH_2Cl_2	40	95	71
4	(*R*)-**1**	BuMgBr / Et_2O	CH_2Cl_2 / $AlMe_3$	0	69	60
5	(*R*)-**1**	BuMgCl / THF	CH_2Cl_2 / $AlMe_3$	0	98	20
6	(*S*)-**1**	BuMgBr / Et_2O	CH_2Cl_2 / TMEDA	0	93	16
7	(*S*)-**1**	BuMgBr / Et_2O	CH_2Cl_2 / CuI	0	99	57

[a] The reaction was carried out on a 0.374 mmol scale under an atmosphere of argon. 3 equiv of Grignard reagent were used.

[b] Isolated yield.

Table 3 Temperature effect on Grignard addition for the preparation of isoindolinone **2c** [a]

Entry	*N*-Sulfinylimine	Grignard reagent	Solvent	Temp., °C/ time	Yield[b], %	Ee, %
1	(*R*)-**1**	BuMgBr	CH_2Cl_2	-20 / 180 min	76	30
2	(*R*)-**1**	BuMgBr	CH_2Cl_2	0 / 180 min	87	50
3	(*R*)-**1**	BuMgBr	CH_2Cl_2	40 / 15 min	98	68
4	(*R*)-**1**	BuMgBr	CH_2Cl_2	40 / 30 min	97	67
5	(*R*)-**1**	BuMgBr	CH_2Cl_2	40 / 240 min	99	70

[a] The reaction was carried out on a 0.374 mmol scale under an atmosphere of argon. 3 equiv of Grignard reagent were used.

[b] Isolated yield.

Table 4 Synthesis of *tert*-butyl sulfoxides **3** [a]

Entry	*N*-Sulfinylimine	R	Temp., °C	Sulfoxide	Yield[b], %	Ee, %
1	(*S*)-**1**	Bu	0	(*S*)-**3c**	99	98
2	(*R*)-**1**	Bu	0	(*R*)-**3c**	99	99
3	(*S*)-**1**	Bn	40	(*S*)-**3e**	79	93
4	(*S*)-**1**	Ph	-20	(*R*)-**3f**	55	99
5	(*S*)-**1**	2-$MeOC_6H_4$	20	(*R*)-**3g**	95	98
6	(*R*)-**1**	2-$MeOC_6H_4$	40	(*S*)-**3g**	88	98
7	(*R*)-**1**	4-ClC_6H_4	40	(*S*)-**3h**	95	97
8	(*R*)-**1**	*p*-Tol	40	(*S*)-**3i**	96	95

[a] The reaction was carried out on a 0.374 mmol scale under an atmosphere of argon. 3 equiv of Grignard reagent were used.

[b] Isolated yield.

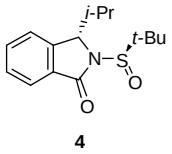


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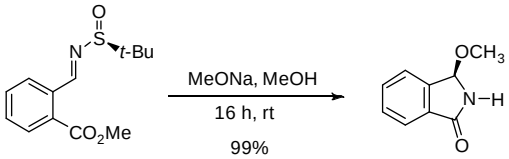
Figure 1 Transition product **4**

We could isolate the transition product **4** (major diastereomer) by using substoichiometric amounts of isopropylmagnesium chloride (Figure 1). Usually, at 40 °C the reaction was complete in minutes; however, at 0 °C and at room temperature, we used longer reaction times to obtain a better yield. The configuration at C-3 was established based on the optical rotation discussed in earlier literature. It was in agreement with the chelated transition state mechanism of the addition of Grignard reagents to *N*-sulfinylimines as proposed by Ellman[25] and Davis.[26] The yield of isoindolinones is usually very high, but the chromatographic isolation of the product might be difficult in some cases (e.g., 3-hexylisoindolinone **2d**). Isoindolinones with an aromatic substituent at C-3 may be purified by simple trituration with a hexane-diethyl ether mixture. *tert*-Butyl sulfoxides are easily soluble in such a solution. Poor results were obtained with ethynyl and allylmagnesium bromides. Chelating substituents, such as 2-methoxyphenyl, significantly lowered the ee. The use of *n*-butyllithium instead of *n*-butylmagnesium bromide also results in low ee for the isoindolinone.

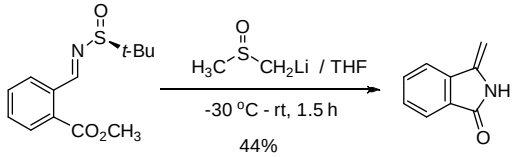
Moreover, the present reaction was particularly useful for the synthesis of enantiomerically pure *tert*-butyl sulfoxides **3** (Table 4). They were formed by a nucleophilic substitution of *N*-sulfinylisoindolinone (Scheme 2). The isoindolinone moiety seemed to be an excellent leaving group. Usually, the yields and the ee of sulfoxides were high when the reaction was carried out at room temperature or 0 °C. Considering that the ee of the *N*-sulfinylimine was 98 %, there was no loss of optical purity. At 40 °C, the ee decreased to 93-95 % (Table 4, entries 3 and 8). The presented approach might be useful because *tert*-butyl sulfoxides are valuable substrates in many reactions.[27] To the best of our knowledge, our synthesis of *tert*-butylsulfoxides can compete with existing methods in the literature.

The reaction of *N*-sulfinylimine **1** with strong nucleophiles was found very general. For example, the reaction with sodium methanolate yields 3-methoxy isoindolinone **5** (Scheme 4). The crude reaction mixture can be purified by simple trituration with hexane, which dissolves methyl *tert*-butylsulfinate.



1 **5** 70% ee

Scheme 4 Synthesis of 3-methoxyisoindolinone



1 **6**

Scheme 5 Addition of dimsyl lithium

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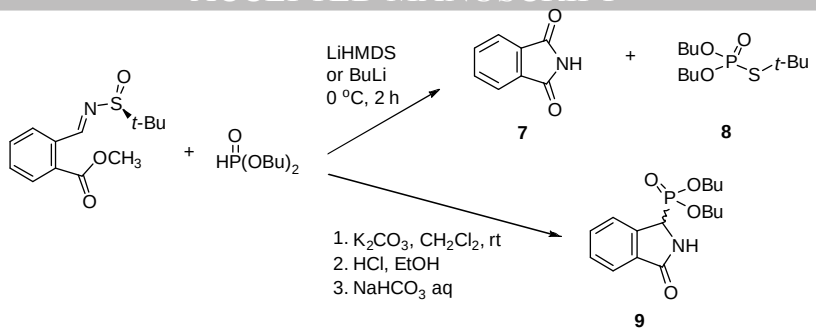

Scheme 6. Addition of dibutyl phosphonate

The reaction of dimsyl lithium with *N*-sulfinylimine **1** yields 3-methyleneisoindolinone **6** (Scheme 5). In this example, the addition of a sulfoxide anion is followed by the elimination of sulfenic acid. An analogous reaction with a carbanion obtained from dimethyl sulfone failed. The reaction of *N*-sulfinylimine **1** and a phosphonate anion generated by deprotonation with LiHMDS or *n*-BuLi unexpectedly yielded phthalimide as the main product (Scheme 6). We assumed that the addition of phosphonate to *N*-sulfinylimine was followed by the elimination of sulfenic acid and a reaction at the phosphorus atom to yield phthalimide **7** and *O,O*-dibutyl-*S*-*tert*-butyl phosphorothioate **8**.

The use of K_2CO_3 as a base resulted in the addition of a phosphonate anion to the C=N bond without subsequent cyclization. Routine removal of the *tert*-butylsulfinyl group with ethanolic HCl and alkalization yielded isoindolinone-3-phosphonate **9** in the racemic form.

3. Conclusions

An efficient one-step method for the synthesis of enantioenriched 3-substituted isoindolinones and *tert*-butyl sulfoxides from methyl 2-[(*N*-*tert*-butylsulfinylimine)methyl] benzoate and Grignard reagents was developed. The procedure is robust, reliable, and straightforward. High stereoselectivity was observed at room temperature and at 40 °C. In the case of poorly soluble 3-aryl substituted isoindolinones, the purification did not require chromatography. *N*-*tert*-Butylsulfinyl-isoindolinone is a very good sulfinylating agent, so the reaction with Grignard reagents produced enantiopure *tert*-butyl sulfoxides in good yields. The use of sodium methanolate as a nucleophile yielded 3-methoxyisoindolinone. The reaction with dimsyl lithium or lithium phosphonates yielded addition products that underwent further transformations.

4. Experimental

All reactions containing moisture or oxygen sensitive reagents were performed under argon using ballons. Tetrahydrofuran and diethyl ether were dried with sodium in the presence of benzophenone. Dichloromethane was dried with CaH_2. Methyl 2-formylbenzoate was obtained by alkylation of 2-formylbenzoic acid with CH_3I.[28] Butylmagnesium bromide in diethyl ether was obtained using standard procedure. Racemic sulfoxides for HPLC standards were prepared from rac-*tert*-butyl *tert*-butanethiosulfinate and Grignard reagents according to known procedure.[29] All other reagents were purchased from commercial sources and used without further purification. Column chromatography was performed using Acros Organics 60 Å silica gel with the indicated solvents. NMR spectra were recorded on a 400 MHz instrument and were referenced to residual solvent signals (chloroform δ = 7.26 and 77.0 ppm for ^{1}H NMR and ^{13}C NMR respectively). High-resolution mass spectra (HRMS) were obtained using an electrospray ionization (ESI) source. HPLC was performed using cyclohexane-isopropanol mixture at flow rate 0.5 mL/min and UV detection (230 nm or 250 nm). Commercial chiral ODH, AD and OJ type columns 5 μm, 250x4.6 mm were used.

*4.1. (R)-Methyl 2-[(N-t-butylsulfinylimine)methyl] benzoate (**1**)*

To a solution of (*R*)-*tert*-butylsulfinamide (400 mg, 3.3 mmol) and methyl 2-formylbenzoate (800 mg, 4.95 mmol) in dry toluene (80 mL) was added potassium hydrogen sulfate (900 mg, 6.6 mmol). The mixture was stirred at 45 °C for 3 hrs and 16 hrs at rt. After filtration the solution was evaporated to give yellow oil. Chromatography on silica gel using AcOEt:hexane 1:2.5 (v/v) gave the title compound as white crystals (0.767 g, 86%). Analogously was obtained second enantiomer. Spectroscopic data identical to reported:[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (s, 9H, *t*-Bu); 3.95 (s, 3H, OCH_3); 7.52-7.64 (m, 2H, Ar); 7.95 (dd, J =7.5 Hz, J =1.2 Hz, 1H, Ar); 8.02 (dd, J =7.9 Hz, J =1.2 Hz, 1H, Ar); 9.22 (s, 1H, CH=N). ^{13}C NMR ($CDCl_3$) δ: 22.6, 52.6, 57.9, 128.9, 130.4, 131.2, 131.3, 132.1, 134.5, 162.5, 167.0.

*4.2. General procedure for the addition of Grignard reagents to N-sulfinylimine (**1**).*

To a solution of *N*-sulfinylimine **1** (100 mg, 0.374 mmol) in dry dichloromethane (6 mL) was added etheral solution of Grignard reagent (1.12 mmol) at temperature indicated in Table 1. Reaction was quenched with aqueous NH_4Cl solution (6 mL). The organic layer was separated and aqueous layer was extracted with dichloromethane (3 x 10 mL). Organic extracts were dried with $MgSO_4$, filtered and evaporated. In the case of 3-aryl substituted isoindolinones resulting crystals may be triturated with hexane-diethyl ether (1:1) mixture to wash out *t*-butyl sulfoxide. Washings were further purified using column chromatography on silica gel.

*4.3. (S)-3-Methyl-2,3-dihydro-1H-isoindolin-1-one (**2a**).*

Following general procedure, (*R*)-*N*-sulfinylimine **1** (100 mg, 0.374 mmol) and 3M etheral solution of methylmagnesium bromide (0.49 mL, 1.48 mmol) were reacted for 120 min at rt. Product was purified using column chromatography on silica gel acetone:hexane 1:1 (v/v) yielding 46 mg of white crystals (90%). The spectroscopic data matched those reported in the literature:[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51 (d, J = 6.9 Hz, 3H, CH_3), 4.70 (q, J = 6.9 Hz, 1H, C3-H), 7.17 (br, 1H, N-H), 7.42-7.49 (m, 2H, Ar), 7.57 (td, J = 1.2 Hz, 7.5 Hz, 1H, Ar), 7.85 (dt, J = 0.8 Hz, 1.6 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 20.3, 52.5, 122.2,

123.7, 128.1, 131.5, 131.9, 148.9, 170.8. $[\alpha]_D^{20}$ = -18.7 (c = 0.97, CH_2Cl_2). lit. $[\alpha]_D^{17}$ = +42.7 (c = 0.43, $CHCl_3$) for (*R*) enantiomer.[30]

*4.4. (S)-3-Isopropyl-2,3-dihydro-1H-isoindolin-1-one (**2b**).*

Following general procedure, (*R*)-*N*-sulfinylimine **1** (100 mg, 0.374 mmol) and 2M etheral solution of isopropylmagnesium bromide (1.12 mmol) were reacted for 90 min at 40 °C. Product was purified using column chromatography on silica gel AcOEt:Hexane 1:1 (v/v) yielding 59 mg (90%) of white crystals. The spectroscopic data matched those reported in the literature.[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.72 (d, J = 6.9 Hz, 3H, CH_3), 1.09 (d, J = 6.9 Hz, 3H, CH_3), 2.26 (dsep, J = 3.7 Hz, 7.0 Hz, 1H, C-H), 4.56 (d, J = 3.7 Hz, 1H, N-C-H), 7.32 (br, 1H, N-H), 7.41-7.48 (m, 2H, Ar), 7.55 (td, J = 1.2 Hz, 7.4 Hz, 2H, Ar), 7.85 (d, J = 7.4 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 15.8, 19.5, 31.7, 62.4, 122.6, 123.6, 127.9, 131.6, 132.5, 146.6, 171.9. $[\alpha]_D^{20}$ = -21.78 (c = 0.895, CH_2Cl_2). lit. $[\alpha]_D^{18}$ = +22.6 (c = 0.70, $CHCl_3$) for enantiomer (*R*).[30]

*4.5. (R)-3-Butyl-2,3-dihydro-1H-isoindolin-1-one (**2c**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (100 mg, 0.374 mmol) and 2M etheral solution of *n*-butylmagnesium bromide (0.561 mL, 1.123 mmol) were reacted for 90 min at 40 °C. Product was purified using column chromatography on silica gel AcOEt:Hexane 1:1 v/v) yielding 69 mg of white crystals (98%). The spectroscopic data matched those reported in the literature:[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.90 (t, J = 7 Hz, 3H, CH_3), 1.22-1.50 (m, 4H, CH_2), 1.59-1.70 (m, 1H, CH_2), 1.90-2.0 (m, 1H, CH_2), 4.62 (dd, J = 4.5 Hz, 7.8 Hz, 1H, C3-H), 7.37 (br, 1H, N-H), 7.41-7.48 (m, 2H, Ar), 7.56 (td, J = 1.2 Hz, 7.4 Hz, 1H, Ar), 7.84 (d, J = 7.4 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 13.9, 22.6, 27.6, 34.2, 57.0, 122.4, 123.7, 127.9, 131.7, 131.9, 147.8, 171.3. $[\alpha]^{20}_D$ = +21.62 (c = 0.555, CH_2Cl_2). lit. $[\alpha]_D^{17}$ = +30.7 (c = 0.55, $CHCl_3$) for (*R*) isomer.[30]

*4.6. (R)-3-Hexyl-2,3-dihydro-1H-isoindolin-1-one (**2d**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (202 mg, 0.75mmol) and 2M etheral solution of *n*-hexylmagnesium bromide (1.13 mL, 2.25 mmol) were reacted for 90 min at 0 °C and left overnight at rt. Product was purified using column chromatography on silica gel (acetone-hexane 1:2 v/v) yielding 120 mg of white crystals (76%). The spectroscopic data matched those reported in the literature:[31] ^{1}H NMR (400 MHz, $CDCl_3$): δ: 0.86 (t, J =6.8Hz, 3H, CH_3); 1.23-1.50 (m, 9H); 1.58-1.69 (m. 1H); 1.89-2.0 (m. 1H); 4.61 (dd, J =4.6Hz, 7.9 Hz, 1H, C3-H); 7.13 (br. 1H, NH); 7.41-7.48 (m, 2H, Ar.); 7.56 (dt, J =7.5Hz, 1.2Hz, 1H, Ar); 7.84 (d, J =7.5Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$): δ = 14.0; 22.5; 25.5; 29.2; 31.6; 34.6; 56.9; 122.4; 123.7; 128.0; 131.7; 131.8; 147.7; 170.6. $[\alpha]_D^{20}$ = +37.4 (c = 1.7, CH_2Cl_2). lit. $[\alpha]_D^{18}$ = +26.9 (c = 0.77, $CHCl_3$) for (*R*) isomer.[30]

*4.7. (S)-3-Benzyl-2,3-dihydro-1H-isoindolin-1-one (**2e**).*

Following general procedure, (*R*)-*N*-sulfinylimine **1** (80mg, 0.3 mmol) and 2M etheral solution of benzylmagnesium bromide (0.33 mL, 0.66 mmol) were reacted at 40 °C for 90 min. Product was purified using column chromatography on silica gel using acetone:hexane 1:3 (v/v) to give 48 mg of white crystals (71%). The spectroscopic data matched those reported in the literature:[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.82 (dd, J = 8.7 Hz, 13.7 Hz, 1H, C3-CH_2), 3.22 (dd, J = 5.4 Hz, 13.7 Hz, 1H, C3-CH_2), 4.80 (dd, J = 5.4 Hz, 8.7 Hz, 1H, C3-H), 6.75 (br, 1H, N-H), 7.21-7.36 (m, 6H, Ar), 7.47 (t, J = 7.3 Hz, 1H, Ar), 7.55 (td, J = 1.2 Hz, 7.5 Hz, 1H, Ar), 7.84 (d, J = 7.5 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 41.3, 57.9, 122.7, 123.8, 127.1, 128.3, 128.7, 129.2, 131.6, 131.9, 136.8, 146.8, 170.4. $[\alpha]_D^{20}$ = -53.4 (c = 0.5, CH_2Cl_2). lit. $[\alpha]_D^{17}$ = +42.7 (c = 0.43, $CHCl_3$) for (*R*) enantiomer.[30]

*4.8. (S)-3-Phenyl-2,3-dihydro-1H-isoindolin-1-one (**2f**).*

Following general procedure, (*R*)-*N*-sulfinylimine **1** (60 mg, 0.225 mmol) and 3M etheral solution of phenylmagnesium bromide (0.23 mL, 0.674 mmol) were reacted at 40 °C for 15 min. Product was purified using column chromatography on silica gel using acetone:hexane 1:3 (v/v) to give 29 mg of white crystals (62%). The spectroscopic data matched those reported in the literature:[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.62 (s, 1H, C3-H); 6.39 (br, 1H, N-H); 7.22-7.29 (m, 3H, Ar); 7.31-7.39 (m, 3H, Ar); 7.45-7.54 (m, 2H, Ar); 7.90 (dd, J = 1.6 Hz, 6.2 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 60.7, 123.3, 123.8, 126.8, 128.4, 128.5, 129.1, 130.7, 132.3, 138.4, 147.9, 171.0. $[\alpha]_D^{20}$ = +50.9 (c = 0.62, CH_2Cl_2). Lit. $[\alpha]_D^{17}$ =-81.1 (c 0.34, $CHCl_3$) for (*R*) enantiomer.[30]

*4.9. (S)-3-(2-Methoxyphenyl)-2,3-dihydro-1H-isoindolin-1-one (**2g**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (50 mg, 0.188 mmol) and 1M etheral solution of o-methoxyphenylmagnesium bromide (0.56 mL, 0.56 mmol) were reacted at 20 °C for 90 min. Product was purified using column chromatography on silica gel using AcOEt:hexane 1:1 (v/v) to give 40 mg of white crystals (88%). The spectroscopic data matched those reported in the literature:[32] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.95 (s, 3H, OCH_3), 6.13 (s, 1H, C3-H), 6.58 (br, 1H, N-H), 6.87 (td, J = 0.8 Hz, 7.4 Hz, 1H, Ar), 6.98 (dd, J = 0.8 Hz, 8.2 Hz, 1H, Ar), 7.05 (dd, J = 1.6 Hz, 7.4 Hz, 1H, Ar), 7.26-7.32 (m, 1H, Ar), 7.39-7.49 (m, 2H, Ar), 7.52 (td, J = 1.2 Hz, 7.4 Hz, 1H, Ar), 7.88 (dd, J = 1.2 Hz, 7.0 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 54.6, 55.5, 110.7, 120.9, 123.7, 123.8, 126.5, 128.2, 129.4, 131.5, 131.9, 147.3, 157.2, 170.8.

*4.10. (R)-3-p-Chlorophenyl-2,3-dihydro-1H-isoindolin-1-one (**2h**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (80 mg, 0.3 mmol) and 1M etheral solution of p-chlorophenylmagnesium bromide (0.9 mL, 0.9 mmol) were reacted at 0 °C for 90 min. Product was purified using column chromatography on silica gel using acetone:hexane 1:3 (v/v) to give 73 mg of white crystals (99%). The spectroscopic data matched those reported in the literature:[33] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.60 (s, 1H, C3-H), 6.74 (br, 1H, N-H), 7.18-7.24 (m, 3H, Ar), 7.30-7.35 (m, 2H, Ar), 7.45-7.55 (m, 2H, Ar), 7.89 (dd, J = 1.6 Hz, 6.6 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 60.0, 123.2, 123.9, 128.2, 128.6, 129.3, 130.6, 132.5, 134.4, 136.9, 147.5, 170.9. $[\alpha]_D^{20}$ = -113.7 (c = 0.7, CH_2Cl_2). lit. $[\alpha]_D^{20}$ =+ 42.2 (c 1.0, CH_2Cl_2).[33]

*4.11. (R)-3-p-Tolyl-2,3-dihydro-1H-isoindolin-1-one (**2i**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (80 mg, 0.3 mmol) and 0.5M etheral solution of *p*-tolylmagnesium bromide (1.8 mL, 0.9 mmol) were reacted at 40 °C for 90 min. Product was purified using column chromatography on silica gel using acetone:hexane 1:3 (v/v) to give 61 mg of white crystals (90%). The spectroscopic data matched those reported in the literature:[33] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.34 (s, 3H, CH_3), 5.59 (s, 1H, C3-H), 6.52 (br, 1H, N-H), 7.12-7.18 (m, 4H, Ar), 7.22 (d, J = 7.4 Hz, 1H, Ar), 7.43-7.53 (m, 2H, Ar), 7.88 (dd, J = 1.2 Hz, 6.6 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 21.1, 60.5, 123.3, 123.8, 126.7, 128.3, 129.7, 130.7, 132.3, 135.3, 138.4, 148.1, 170.8. $[\alpha]_D^{20}$ = -100.5 (c = 0.75, CH_2Cl_2). lit. $[\alpha]_D^{20}$ =+29.2 (c = 1.0, CH_2Cl_2).[33]

*4.12. (S)-tert-Butyl-butyl sulfoxide (**3c**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (60 mg, 0.225 mmol) and 2M etheral solution of *n*-butylmagnesium bromide (0.34 mL, 0.674 mmol) were reacted at 0 °C for 90 min. Column chromatography on silica gel using ethyl acetate:hexane 1:1 (v/v) gave 32 mg of oil (88%). The spectroscopic data matched those reported in the literature:[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.95 (t, J = 7.3 Hz, 3H, CH_3), 1.23 (s, 9H, *t*-Bu), 1.38-1.59 (m, 2H, CH_2), 1.67-1.90 (m, 2H, CH_2), 2.38-2.49 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 13.7, 22.2, 22.8, 25.7, 45.3, 52.6. $[\alpha]_D^{20}$ = -97.9 (c = 1.25, CH_2Cl_2). Lit. $[\alpha]_D$ = -129 (c = 1.02, acetone) for (*S*) enantiomer.[34]

*4.13. (S)-Benzyl tert-butyl sulfoxide (**3e**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (100 mg, 0.374 mmol) and 2M etheral solution of benzylmagnesium bromide (0.415 mL, 0.823 mmol) were reacted at 40 °C for 90 min. Column chromatography on silica gel using acetone:hexane 1:3 (v/v) gave 58 mg of oil (79%). The spectroscopic data matched those reported in the literature:[35] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.32 (s, 9H, *t*-Bu), 3.62 and 3.82 (AB, J = 12.8 Hz, 2H), 7.28-7.38 (m, 5H, Ar). ^{13}C NMR ($CDCl_3$) δ: 23.0, 52.8, 53.6, 127.9, 128.7, 129.9, 131.9. $[\alpha]_D^{20}$ = -181.7 (c = 1.12, CH_2Cl_2). Lit. $[\alpha]_D$ = -191.1 (c = 1.0, $CHCl_3$) for (*S*) enantiomer.[36]

*4.14. (R)-tert-Butyl-phenyl sulfoxide (**3f**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (100 mg, 0.374 mmol) and 3M etheral solution of phenylmagnesium bromide (0.374 mL, 1.122 mmol) were reacted at -20 °C for 90 min. Column chromatography on silica gel using acetone:hexane 1:3 (v/v) gave 38 mg of oil (56%). The spectroscopic data matched those reported in the literature:[37] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (s, 9H. *t*-Bu), 7.43-7.50 (m, 3H, Ar), 7.55-7.60 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ: 22.7, 55.7, 126.2, 128.3, 131.1, 139.9. $[\alpha]_D^{20}$ = +152.3 (c = 0.96, CH_2Cl_2). Lit. $[\alpha]_D^{22}$ = +174.6 (c = 1.0, $CHCl_3$) for (*R*) enantiomer.[37]

*4.15. (R)-tert-Butyl-2-methoxyphenyl sulfoxide (**3g**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (50 mg, 0.288 mmol) and 1M etheral solution of o-methoxyphenylmagnesium bromide (0.56 mL, 0.561 mmol) were reacted at 20 °C for 90 min. Column chromatography on silica gel using ethyl acetate:hexane 1:1 (v/v) gave 38 mg of yellow crystals (95%). The spectroscopic data matched those reported in the literature:[38] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (s, 9H, *t*-Bu), 3.83 (s, 3H, OCH_3), 6.90 (d, J = 8.1 Hz, 1H, Ar), 7.13 (t, J = 7.5 Hz, 1H, Ar), 7.42 (t, J = 8.1 Hz, 1H, Ar), 7.75 (dd, J = 1.4 Hz, 7.7 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 22.8, 55.4, 57.3, 110.6, 120.9, 127.3, 128.5, 132.2, 157.0. $[\alpha]_D^{20}$ = +262.8 (c = 1.05, CH_2Cl_2). Lit. $[\alpha]_D$ = +281.9 (c = 1.0, EtOH) for (*R*) enantiomer.[38]

*4.16. (S)-para-Chlorophenyl-tert-butyl sulfoxide (**3h**).*

Following general procedure, (*R*)-*N*-sulfinylimine **1** (100 mg, 0.374 mmol) and 1M etheral solution of *p*-chlorophenylmagnesium bromide (1.123 mL, 1.123 mmol) were reacted at 40 °C for 20 min. Column chromatography on silica gel using acetone:hexane 1:3 (v/v) gave 77 mg of oil (95%). Analogously was obtained second enantiomer. The spectroscopic data matched those reported in the literature:[39] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.12 (s, 9H, *t*-Bu), 7.41-7.45 (m, 2H, Ar), 7.47-7.51 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ: 22.6, 55.9, 127.5, 128.6, 137.3, 138.4. $[\alpha]_D^{20}$ = -146.9 (c = 1.05, CH_2Cl_2).

*4.17. (S)-tert-Butyl-p-tolyl sulfoxide (**3i**).*

Following general procedure, (*R*)-*N*-sulfinylimine **1** (100 mg, 0.374 mmol) and 0.5 M etheral solution of *p*-tolylmagnesium bromide (2.25 mL, 1.123 mmol) were reacted at 40 °C for 30 min. Column chromatography on silica gel using acetone:hexane 1:3 (v/v) gave 71 mg of oil (96%). The spectroscopic data matched those reported in the literature:[40] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.15 (s, 9H, *t*-Bu), 2.41 (s, 3H, CH_3), 7.26-7.30 (m, 2H, Ar), 7.45-7.49 (m, 2H, Ar). ^{13}C NMR ($CDCl_3$) δ: 21.3, 22.6, 55.5, 126.1, 129.0, 136.6, 141.4. $[\alpha]_D^{20}$ = -165.8 (c = 0.96, CH_2Cl_2). Lit. $[\alpha]_D^{20}$ = -144.9 (c = 0.046, EtOH) for (*S*) enantiomer.[40]

*4.18. (R,S$_S$)-N-tert-butylsulfinyl-3-isopropyl-2,3-dihydro-1H-isoindolin-1-one (**4**).*

Following general procedure, (*S*)-*N*-sulfinylimine **1** (100 mg, 0.374 mmol) and 2M solution of isopropylmagnesium chloride in THF (0.468 mL, 0.936 mmol) were reacted at rt for 90 min. Column chromatography on silica gel using ethyl acetate:hexane 1:1 (v/v) gave 52 mg of white crystals (50%); mp 127-130 °C. IR (ATR): 1701, 1084, 1055, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.50 (d, J = 6.6 Hz, 3H, CH_3), 1.19 (d, J = 7 Hz, 3H, CH_3), 1.37 (s, 9H, *t*-Bu), 3.05 (dsep. J = 3.7 Hz, 7.0 Hz, 1H, C-H), 5.15 (d, J = 3.3 Hz, 1H, C3-H), 7,43-7.51 (m, 2H, Ar), 7.58 (td, J = 1.2 Hz, 7.4 Hz, 1H, Ar), 7.87 (d, J = 7.4 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 14.5, 19.5, 23.7, 30.7, 60.8, 68.1, 123.6, 124.7, 128.5, 130.4, 132.6, 144.5, 169.8. HRMS (ESI) m/z calcd for $C_{15}H_{22}NO_2S$ $(M+H)^+$ 280.1366, found: 280.1364. $[\alpha]_D^{20}$ =+4.6 (c =1.1, CH_2Cl_2).

*4.19. (S)-3-Methoxy-2,3-dihydro-1H-isoindolin-1-one (**5**).*

To a solution of sodium methoxide in methanol (0.035M, 3 mL, 0.1 mmol) was added (*S*)-*N*-sulfinylimine **1** (50 mg, 0.187 mmol) at rt. The solution was left overnight at rt. Methanol was evaporated. Sat. NH_4Cl solution was added to the residue and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. White crystals were washed with hexane and dried under vacuum. Yield 31 mg (46%). The spectroscopic data matched those reported in the literature:[41] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.15 (s, 3H, OCH_3), 6.00 (d, J = 0.8 Hz, 1H, C3-H), 6.37 (br, 1H, N-H), 7.52-7.58 (m, 2H, Ar), 7.61-7.65 (m, 1H, Ar), 7.83-7.86 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 51.8, 84.5, 123.6, 123.7, 129.9, 132.1, 132.5, 142.7, 170.6. HRMS (ESI) m/z calcd for $C_9H_9NO_2$ $(M+H)^+$ 164.0705, found: 164.0706. $[\alpha]_D^{20}$ = +78.1 (c = 0.88, CH_2Cl_2).

Hexane washings contained methyl *tert*-butanesulfinate. The spectroscopic data matched those reported in the literature.[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (s, 9H, *t*-Bu), 3.80 (s, 3H, OCH_3).

*4.20. 3-Methylene-2,3-dihydro-1H-isoindolin-1-one (**6**).*

To the solution of dimethylsulfoxide (64 mg, 0.82 mmol) in THF (4 mL) was added butyllithium solution in hexane (2.5M, 0.3 mL, 0.748 mmol) at -30 °C. Resulting mixture was stirred at -30 °C for 30 min and the solution of (*R*)-*N*-sulfinylimine **1** (50 mg, 0.187 mmol) in THF (2 mL) was added dropwise. Stirring was continued for 90 min while the reaction mixture was warmed slowly to rt. Sat. NH_4Cl solution was added and the aqueous layer was extracted with ethyl acetate (2 x 5 mL) and CH_2Cl_2 (1 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. Product was purified using column chromatography on silica gel AcOEt:Hexane 2:1 (v/v). Yield 24 mg of yellow crystals (44%). The spectroscopic data matched those reported in the literature:[43] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.01 (d, J = 2.0 Hz, 1H, =CH), 5.22 (d, J = 2.0 Hz, 1 H, =CH), 7.52 (td, J = 0.8 Hz, 7.4 Hz, 1H, Ar), 7.62 (td, 0.8 Hz, 7.4 Hz, 1H, Ar), 7.71 (d, J = 7.4 Hz, 1H, Ar), 7.86 (d, J = 7.8 Hz, 1H,

Ar), 8.72 (br, 1H, N-H). ^{13}C NMR ($CDCl_3$) δ: 90.8, 120.2, 123.3, 129.5, 130.0, 132.2, 137.1, 139.8, 169.1.

*4.21. Reaction of lithium dibutyl phosphonate with N-sulfinylimine **1**.*

To the solution of dibutyl phosphonate (99 mg, 0.722 mmol) in diethyl ether (2 mL) was added dropwise *n*-butyllithium solution in hexane (2.5M, 0.28 mL, 0.70 mmol) at 0 °C. After 15 min a solution of (*S*)-*N*-sulfinylimine **1** (62 mg, 0.23 mmol) in diethyl ether (3 mL) was added. The reaction mixture was stirred at 0 °C for 2 hrs and quenched with sat. NH_4Cl solution. The resulting mixture was then extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The obtained crystals of phthalimide **7** were washed with ether- hexane 1:1 (v/v) mixture. Yield 9 mg (16%). The spectroscopic data matched those reported in the literature:[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.74-7.79 (m, 2H, Ar), 7.85-7.92 (m, 2H, Ar).

The washings were evaporated and purified using column chromatography on silica gel AcOEt:Hexane 1:2.3 (v.v) to give *O*,*O*-dibutyl-*S*-*t*-butyl phosphorothioate **8** (oil) 55 mg (90%). IR (ATR): 1251, 1020, 976, 610 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.3 Hz, 6H), 1.34-1.45 (m, 4H), 1.53 (d, J = 1.3 Hz, 9H), 1.62-1.70 (m, 4H), 3.98-4.14 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 13.6, 18.7, 32.2 (J = 7.1 Hz), 32.7 (J = 6.4 Hz), 49.8 (J = 4.5 Hz), 67.0 (J = 7.1 Hz). ^{31}P NMR ($CDCl_3$) δ: 25.3. HRMS (ESI) m/z calcd for $C_{12}H_{28}O_3PS$ $(M+H)^+$ 283.1491, found: 283.1488.

*4.22. Dibutyl 2,3-dihydro-1H-isoindolin-1-one-3-phosphonate (**9**).*

To a solution of (*S*)-*N*-sulfinylimine 1 (50 mg, 0.187 mmol) and dibutyl phosphonate (77 mg, 0.562 mmol) in dry dichloromethane (3 mL) was added K_2CO_3 (130 mg, 0.935 mmol). The reaction mixture was stirred for 24 h. Precipitate was centrifuged and the solution was evaporated. The residue was dissolved in ethanolic 4M HCl solution (0.1 mL) and the mixture was left for 24 h. The solution was made alkaline with sat. $NaHCO_3$ solution and extracted with dichloromethane (3 x 5 mL). Organic extracts were dried with $MgSO_4$, filtered and evaporated. Product was purified using column chromatography on silica gel AcOEt:Hexane 3:1 v/v). 42 mg (70%) of white crystals. IR (ATR): 3219, 1694, 1657, 991 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.80 (t, J = 7.4 Hz, 3H, CH_3), 0.89 (t, J = 7.4 Hz, 3H, CH_3), 1.13-1.43 (m, 6H, CH_2x3), 1.55-1.64 (m, 2H, CH_2), 3.64-3.73 (m, 1H, O-CH), 3.86-3.95 (m, 1H, O-CH), 4.02-4.15 (m, 2H, O-CH_2), 4.95 (d, J = 13.6 Hz, 1H, C3-H), 6.62 (br, 1H, N-H), 7.54 (t, J = 7.4 Hz, 1H, Ar), 7.62 (td, J = 1.2 Hz, 7.4 Hz, 1H, Ar), 7.73-7.77 (m, 1H, Ar), 7.89 (dd, J = 0.8 Hz, 7.4 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ: 13.4 (J = 7.1 Hz), 18.5 (J = 13.5 Hz), 32.2 and 32.4 (J = 5.6 Hz), 54.1 (J = 156.0 Hz), 67.0 and 67.5 (J = 7.1 Hz), 124.0 (J = 1.1 Hz), 124.1 (J = 2.6 Hz), 128.8 (J = 2.2 Hz), 131.7 (J = 4.9 Hz), 132.1 (J = 2.6 Hz), 140.1 (J = 6.4 Hz), 170.7 (J = 3.0 Hz). ^{31}P NMR ($CDCl_3$) δ: 14.0. HRMS (ESI) m/z calcd for $C_{16}H_{25}NO_4P$ $(M+H)^+$ 326.1516, found: 326.1515.

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