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Grignard Addition to Imines Derived from Isatine: A Method for the Asymmetric Synthesis of Quaternary 3-Aminooxindoles

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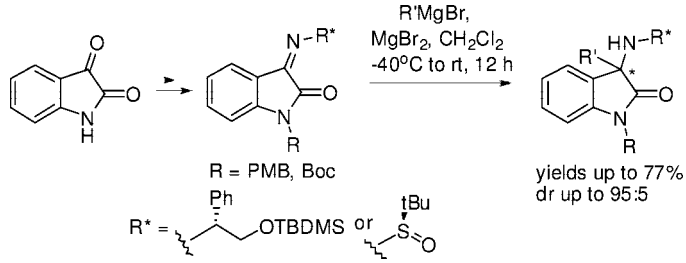

Addition of Grignard reagents to chiral imines derived from isatine afforded chiral, optically enriched 3-substituted 3-aminooxindoles in satisfactory yields and diastereoisomeric ratios. A general protocol is described for the addition of alkyl, alkenyl, and aryl Grignard reagents. In one case, the absolute configuration at C3 was determined and the selective *N*-deprotection was described, enabling further synthetic transformations of the reaction product.

Introduction

Oxindoles constitute a common structural motif in various natural products and biologically active compounds.[1] Among them, 3-substituted 3-amino-2-oxindoles are a useful class of compounds found in several drug candidates, including the potent gastrin/CCK-B receptor antagonist AG-041R (**1**)[2] and the vasopressin VIb receptor antagonist SSR-149415 (**2**),[3] a drug now in clinical trials for treatment of anxiety and depression (Figure 1). Moreover, several members of the indole alkaloid family of natural products contain skeleta that could potentially be accessed synthetically via 3-aminooxindoles, for instance the 3*H*-indole skeleton of the chartellines (e.g., chartelline C, **3**).[4]

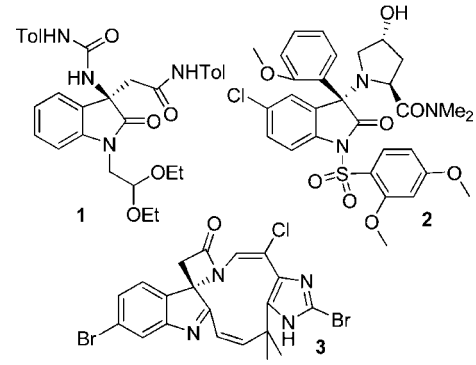

FIGURE 1. Selected bioactive quaternary aminooxindoles and a related natural compound.

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There are a number of reports on the enantioselective formation of quaternary carbon centers at the 3-position of oxindoles.[5] However, the direct enantioselective formation of an amine at this position has been elusive until now. Quaternary 3-aminooxindoles have previously been synthesized by few asymmetric methods, including intramolecular α-arylation of amides[6] and alkylation of 3-aminooxindoles.[7] Owing to the significance of this structural motif, the development of asymmetric synthetic methods for oxindoles bearing a nitrogen atom at the C3 stereogenic center is highly valuable. To the best of our knowledge, there is no example of asymmetric synthesis of quaternary 3-aminooxindoles, relying on nucleophiles addition to imines derived from isatine.

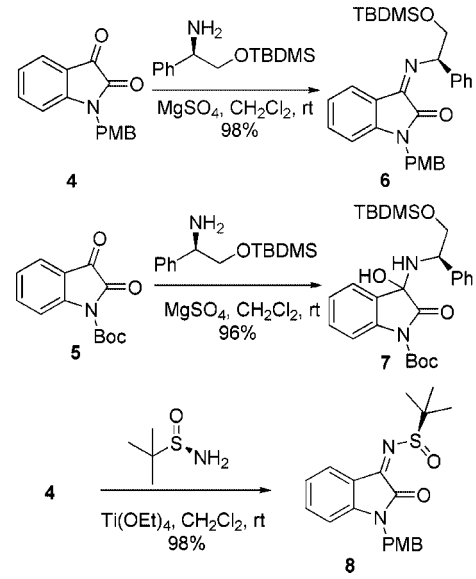
We report here the first asymmetric Grignard addition protocol to achieve this goal. The formation of quaternary carbon centers via addition of carbon nucleophiles to imine derivatives still constitutes a major challenge for synthetic chemistry.[8] There are a number of catalytic asymmetric methods employed to this end.[9] However, they still require a relatively large amount of complex, chiral catalysts, which are often expensive and difficult to obtain. Moreover, the majority of the literature in this field addresses the addition of organometallic reagents to aldimines, but not to ketimines. In fact, an additional challenge to this approach is that ketimines tend to have poor reactivity toward nucleophilic addition and are often activated by the addition of a Lewis acid.

Results and Discussion

We decided to investigate the arylation, alkylation, and alkenylation of imines derived from isatin substrates using chiral auxiliaries at the nitrogen atom, in order to achieve the synthesis of 3-substituted 3-aminooxindoles. Among the numerous chiral amines widely used as a nitrogen-linked stereocontrol element with ketone precursors, we selected commercially available (*R*)-phenylglycinol and Ellman's (*R*)-*tert*-butanesulfinamide. Both auxiliaries are reported[10] to perform effectively in Grignard additions, activating the C=N bond for nucleophilic addition and exerting a powerful stereodirecting effect. Finally, the removal of both the auxiliaries is described to occur usually in high yields under mild conditions.

Since we reasoned that it would be preferable to avoid interaction with indole N−H in the addition reactions, the starting substrates were conveniently prepared respectively from N-*p*-methoxybenzylisatine **4**[11] and from N-Boc-isatine **5**[12] (Scheme 1). Both PMB and Boc protecting groups are well suited for selective removal of the auxiliaries, in view of potential subsequent synthetic transformations of the obtained addition compounds. In addition, we think that the sterically demanding Boc could also exert a favorable additional stereodirecting effect. By reaction with *O*-TBDMS (*R*)-phenylglycinol,[13] in the presence of TsOH in toluene at reflux, isatine **4** afforded imine **6** quantitatively. Under the same conditions, starting from the *N*-Boc-protected isatine **5**, we could isolate only the aminal **7** as a nearly single diastereisomer at C3. We regard compound **7** as a synthetic equivalent of the desired imine for the addition reaction. The *tert*-butanesulfinylimine **8** was obtained from **4** with (*R*)-*tert*-butanesulfinamide in the presence of 2 equiv of $Ti(OEt)_4$ in THF under reflux. Compounds **6** and **8** have been respectively obtained as 4:1 and 3:2 mixtures of imine isomers on the NMR time scale.

SCHEME 1. Synthesis of N-Protected Isatine-Based Imines 6 and 8 and of Aminal 7



The addition of Grignard reagents was first investigated starting from the imine **6** (Table 1). With 1.1 equiv of allylMgBr, at −40 °C in CH_2Cl_2, the addition occurred without Lewis acid (entry 1) to give the amino derivative **9a** in 41% yield (68:32 dr), easily separable from the minor diastereoisomer by flash-chromatography. Compound **9a** was crystalline, and its single-crystal X-ray analysis unequivocally established the relative configuration, from which the absolute configuration of the stereocenter at C-3 was deduced as (*S*).

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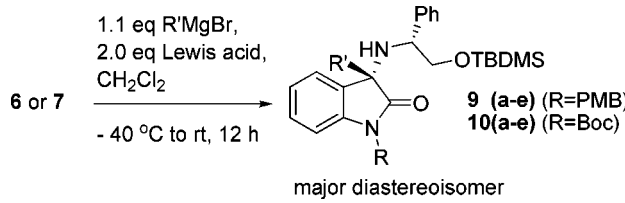
TABLE 1. Addition of Grignard Reagents across Substrates 6 and 7



entry	substrate	R'MgX	L.A.	product	yield %[a]	dr[b]
1	**6**	allylMgBr		**9a**	41	68:32
2	**6**	allylMgBr	BF_3·OEt_2	**9a**	55	55:45
3	**6**	allylMgBr	$Yb(OTf)_3$	**9a**	27	59:41
4[c]	**6**	allylMgBr	$MgBr_2$	**9a**	43	70:30
5	**6**	allylMgBr	$MgBr_2$	**9a**	77	80:20
6	**6**	isopropylMgBr	$MgBr_2$	**9b**	53	80:20
7	**6**	vinylMgBr	$MgBr_2$	**9c**	0	
8	**6**	*p*-Cl-PhMgBr	$MgBr_2$	**9d**	48	75:25
9	**6**	*p*-OMe-PhMgBr	$MgBr_2$	**9e**	62	70:30
10	**7**	allylMgBr	$MgBr_2$	**10a**	48	95:5
11	**7**	isopropylMgBr	$MgBr_2$	**10b**	54	75:25
12	**7**	vinylMgBr	$MgBr_2$	**10c**	34	80:20
13	**7**	*p*-Cl-PhMgBr	$MgBr_2$	**10d**	53	75:25
14	**7**	*p*-OMe-PhMgBr	$MgBr_2$	**10e**	61	95:5

[a] Yield of the major diastereoisomer after flash chromatography. [b] Determined by mass balance after chromatography. [c] Toluene was used instead of CH_2Cl_2.

The allylation was more efficiently promoted by 2 equiv of $MgBr_2$ (entry 5), with CH_2Cl_2 as solvent of choice, with respect to as well noncoordinating toluene (entry 4). Lowering or increasing the temperature of the reaction and, alternatively, the equivalents of $MgBr_2$, gave a lower range of yields. When the Lewis acid was changed to BF_3·Et_2O or $Yb(OTf)_3$, a marked lower diastereoselectivity was obtained (entries 2 and 3), thus suggesting the best choice of $MgBr_2$ as imine activator and substrate coordinating agent.

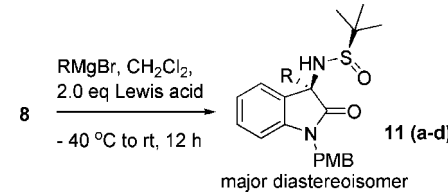
In order to explore the scope of the Grignard addition to imine **6**, we substituted allylMgBr with other commonly available Grignard reagents. All reactions were carried out utilizing the conditions summarized in Table 1 (entries 6−9). A major diastereoisomer was always detected and isolated, with yields up to 62%, except with vinylmagnesium bromide. It should be noted that imine **6** reacts smoothly with the more reactive Grignard reagents derived from stabilized carbanions (as allylmagnesium bromide). On the other hand, the starting isatine **4** was predominantly recovered, together with N-deprotected isatine, when more basic reagents, such as vinylmagnesium bromide (entry 7), were employed.

It was found that amines **10a**−**e** could be synthesized in moderate yields (up to 61%) and in good diastereoselectivity (up to 95:5), starting from aminal **7**, under the optimized conditions (entries 10−14). A Boc protecting group seemed to be beneficial when vinylmagnesium bromide was used, allowing the α-vinyl quaternary amine **10c** to be isolated (entry 12) in high dr, albeit in rather low yield.

In all reactions, both on **6** and **7**, in addition to the desired addition product, we could recover consistent amounts of isatine (**4** or **5**), deriving from hydrolysis during work up of the unreacted starting material. All efforts to completely consume the starting substrate, by increasing the equivalents of Grignard reagent (up to five), were uneffective.

Similar results, in terms of yields and dr, were obtained when imine **8**, containing the (*R*)-*tert*-butanesulfinamide chiral auxiliary, was used as substrate. With this more sterically demanding auxiliary, a higher excess of Grignard reagent turned out to be necessary. Evaluation of Lewis acid additives for addition of 2 equiv of allylmagnesium bromide (entries 1−5, Table 2) revealed that the best results were obtained in the presence of $MgBr_2$ also in this case. Ellman has used trimethylaluminium to increase the reaction yield of organomagnesiums with *tert*-butanesulfinyl aldimines,[14] but in our case, a lowering of yield was observed, although the diastereoselectivity was slightly enhanced (entry 4). In this case, the lower isolated yield could possibly be also attributed to a competitive methyl transfer from the $AlMe_3$ additive to the imine carbon. Finally, yield of amine **11a** further increased (entry 6) when 5 equiv of Grignard reagent was used. Under these conditions, good results were obtained also with isopropylmagnesium bromide and with *p*-methox-

TABLE 2. Addition of Grignard Reagents across Imine 8



entry	RMgX (equiv)	L.A.	product	yield (%)	dr
1	allylMgBr (2.0)		**11a**	32[a]	54:46[c]
2	allylMgBr (2.0)	BF_3·OEt_2	**11a**	30[a]	61:39[c]
3	allylMgBr (2.0)	$Yb(OTf)_3$	**11a**	35[a]	65:35[c]
4	allylMgBr (2.0)	$AlMe_3$	**11a**	25[a]	89:11[c]
5	allylMgBr (2.0)	$MgBr_2$	**11a**	38[a]	80:20[c]
6	allylMgBr (5.0)	$MgBr_2$	**11a**	46[a]	85:15[c]
7	isopropylMgBr (5.0)	$MgBr_2$	**11b**	52[a]	78:22[c]
8	vinylMgBr (5.0)	$MgBr_2$	**11c**	0	
9	*p*-OMePhMgBr (5.0)	$MgBr_2$	**11d**	53[b]	70:30[d]

[a] Yield of the major diastereoisomer after flash chromatography. [b] Determined by mass balance of the reaction mixture. [c] Determined by mass balance after chromatography. [d] Determined by ^1H NMR integration of crude reaction products.

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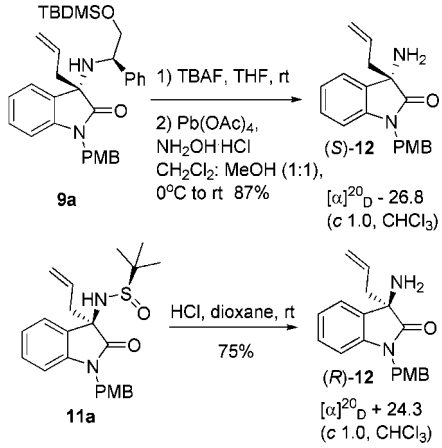
SCHEME 2. Synthesis and Configurational Assignment of (*S*)-12 and (*R*)-12 in Enantiopure Form



yphenylmagnesium bromide (entries 7 and 9), while also in this case, no reaction occurred when vinylmagnesium bromide was employed (entry 8).

We then tested the feasibility of the amino group deprotection both on **9a** and **11a**. In this way, the configuration of the major diastereoisomer was assigned for **11a** as 3*R* by correlation of the derived amine **12** with the corresponding (*S*)-**12**, obtained after desilylation and removal of the (*R*)-phenylglycinol side chain from **9a** (Scheme 2). To our knowledge, amines (*S*)-**12** and (*R*)-**12** have never been reported before, all the more so in nonracemic form.

A working model to explain the observed diastereoselectivities is shown in Figure 2. For both **6** and **8**, we postulate an initial $MgBr_2$-promoted equilibration of the *E*/*Z* ketimine mixtures to the *E* isomers and simultaneous activation to nucleophilic attack, through chelation of the oxindole oxigen and imine nitrogen. On this basis, we propose that the stereochemical outcome can be explained by 1,3-allylic strain, which favors the shown conformations. Delivery of the nucleophile would occur from the less hindered faces, that is from the *re* face in the case of **6** and from the *si* face in the case of **8**. According to this interpretation, use of a solvent with a low coordinating ability such as methylene chloride would maximize the complexation of the $MgBr_2$ with the substrate.

The observed selectivity is in accordance with the models proposed in the case of ketimines containing an α-coordinating group, such as a nitrogen or a chlorine atom, both in the case of phenylglycinol[15] or *tert*-butanesulfinamide[16] as chiral auxiliaries.

Conclusions

In summary, we have demonstrated the first method for the asymmetric addition of Grignard reagents to ketimines derived from isatine, affording chiral, optically enriched 3-substituted-3-aminooxindoles. The satisfactory stereoselectivity observed for the addition reactions with two different chiral auxiliaries is particularly noteworthy since the diastereoselective formation of quaternary stereocenters has always been a challenge, especially when ketimines are used as starting materials. Despite

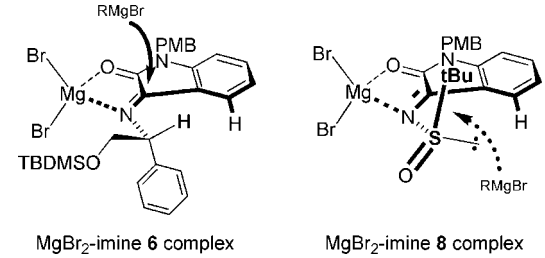


FIGURE 2. Explanation of stereochemical outcomes.

the moderate yields for these substrates, it is significant to note the difficulty in synthesizing these highly substituted and hindered amines derivatives with current methods.

Application of these protocols to the synthesis of lead compounds for the medicinal chemistry is in progress and will be reported in the due course.

Experimental Section

(*R*)-3-(2-(*tert*-Butyldimethylsilyloxy)-1-phenylethylimino)-1-(4-methoxybenzyl)indolin-2-one 6. To a solution of **4** (500 mg, 1.87 mmol) in 10 mL of dry CH_2Cl_2 under nitrogen atmosphere were added *O*-TBDMS-(*R*)-phenylglycinol[17] (470 mg, 1.87 mmol) and $MgSO_4$ (2 g). The reaction was stirred at room temperature for 24 h. The solution was then filtered through a pad of Celite and evaporated under reduced pressure to obtain **6** (oil, 917 mg, 98%) as a 4:1 mixture of imine isomers. The compound was used without further purification: $R_f = 0.35$ (hexane/EtOAc 8:1); $[\alpha]^{25}_D = -28.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.88 (d, $J = 7.6$ Hz, 0.2H), 7.73 (d, $J = 7.4$ Hz, 0.8H), 7.64−7.59 (m, 2H), 7.38 (t, $J = 7.4$ Hz, 1.6H), 7.34−7.23 (m, 4.4H), 7.07 (t, $J = 7.4$ Hz, 0.8H), 7.01 (t, $J = 7.6$ Hz, 0.2H), 6.86 (d, $J = 8.5$ Hz, 2H), 6.81 (t, $J = 6.4$ Hz, 0.8H), 6.77 (d, $J = 7.9$ Hz, 0.2H), 6.71 (d, $J = 7.9$ Hz, 0.8H), 5.57 (t, $J = 6.7$ Hz, 0.2H), 4.97 (d, $J = 15.5$ Hz, 0.2H), 4.90 (br, d, $J = 15.2$ Hz, 1H), 4.78 (d, $J = 15.2$ Hz, 0.8H), 4.18−4.12 (m, 0.4H), 4.02 (d, $J = 6.4$ Hz, 1.6H) 3.80 (s, 3H), 0.82 (s, 7.2H), 0.79 (s, 1.8H), 0.02 (s, 2.4H), −0.02 (s, 2.4H), −0.03 (s, 0.6H), −0.08 (s, 0.6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 159.9 and 159.5, 155.0 and 153.7, 147.5 and 145.4, 141.9 and 141.0, 133.5 and 133.1, 129.6−127.7 (9C), 123.5, 123.2 and 122.9, 122.7, 114.9 (2C), 110.7 and 109.8, 70.1 and 69.7, 69.0 and 65.7, 55.9, 44.0 and 44.6, 26.5 (3C), 18.9, −3.7 (2C); HRMS (ESI) calcd for $C_{30}H_{36}N_2O_3Si$ 500.2495, found 500.2488.

***tert*-Butyl 3-((*R*)-2-(*tert*-Butyldimethylsilyloxy)-1-phenylethylamino)-3-hydroxy-2-oxoindoline-1-carboxylate 7.** To a solution of **5** (550 mg, 2.22 mmol) in 10 mL of dry CH_2Cl_2 under nitrogen atmosphere were added (*R*)-phenylglycinol (540 mg, 2.22 mmol) and $MgSO_4$ (2 g). The reaction was stirred at room temperature for 3 h. The solution was filtered through a pad of Celite and evaporated under reduced pressure to afford a yellow foamy solid which was used in the next step without further purification (1.025 g, 96%): $R_f = 0.65$ (hexane/EtOAc = 4:1); $[\alpha]^{25}_D = +16.0$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 8.47 (d, $J = 8.1$ Hz, 1H), 8.37 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.59 (m, 2H), 7.40−7.29 (m, 5H), 7.04 (t, $J = 8.1$ Hz, 1H), 5.14 (dt, $J = 7.8$, 4.6 Hz, 1H), 4.03 (dd, $J = 10.3$, 4.4 Hz, 1H), 3.91(dd, $J = 10.3$, 4.6 Hz, 1H), 2.30−2.08 (br, s, 1H), 1.57 (s, 9H), 0.89 (s, 9H), 0.00 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 191.3, 162.5, 152.8, 143.3, 139.2, 136.3, 134.5, 126.5 (2C), 127.7, 128.9 (2C), 121.1, 119.1, 118.2, 81.0, 66.1, 55.0, 28.3 (3C), 25.8 (3C), 18.3, −5.5, −5.6; HRMS (ESI) calcd for $C_{27}H_{38}N_2O_5Si$ 498.2550, found 498.2546.

(*R*)-*N*-(1-(4-Methoxybenzyl)-2-oxoindolin-3-ylidene)-2-methylpropane-2-sulfinamide 8. To a solution of **4** (500 mg, 1.87

(15) (a) Steinig, A. G.; Spero, D. M. *J. Org. Chem.* **1999**, *64*, 2406–2410. (b) Spero, D. M.; Kapadia, S. R. *J. Org. Chem.* **1997**, *62*, 5537–5541.

(16) (a) Denolf, B.; Mangelinckx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2007**, *9*, 187–190. (b) Barrow, J. C.; Ngo, P. L.; Pellicore, J. M.; Selnick, H. G.; Nantermet, P. G. *Tetrahedron Lett.* **2001**, *42*, 2051–2054.

(17) This product was prepared according to the procedure reported in: Palomo, C.; Aizpurua, J. M.; Balentová, E.; Jimenez, A.; Oyarbide, J.; Fratila, R. M.; Miranda, J. I. *Org. Lett.* **2007**, *9*, 101–104.

mmol) in 5 mL of dry CH_2Cl_2 under nitrogen atmosphere at room temperature were added $Ti(OEt)_4$ (1 mL, 3.74 mmol) and (*R*)-2-methyl-2-propanesulfinamide (225 mg, 1.87 mmol). The solution was refluxed until complete disappearance of the starting materials. The reaction was quenched with 4 mL of saturated aqueous solution of $NaHCO_3$. The biphasic solution was filtered through a pad of Celite and the organic phase extracted with water. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to afford **8** (oil, 681 mg, 98%) as a 3:2 mixture of imine isomers. The compound was used without further purification: R_f = 0.8 (hexane/EtOAc 1:1); $[\alpha]^{25}_D = -50.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.61 (dd, *J* = 7.4, 1.0 Hz, 0.4H), 7.50 (pseudo td, *J* = 7.8, 1.2 Hz, 0.4H), 7.36 (td, *J* = 7.8, 1.0 Hz, 0.6H), 7.32−7.26 (m, 2.6H), 7.10 (td, *J* = 7.6, 0.8 Hz, 0.4H), 7.05 (t, *J* = 7.7, Hz, 0.6H), 6.90−6.85 (m, 2H), 6.82 (d, *J* = 7.8 Hz, 0.4H), 6.76 (d, *J* = 7.8 Hz, 0.6H), 4.91 (br,d, *J* = 15.6 Hz, 0.6H), 4.88 (s, 0.8H), 4.84 (d, *J* = 15.6 Hz, 0.6H), 3.80 (s, 1.2H), 3.79 (s, 1.8H), 1.45 (s, 5.4H), 1.25 (s, 3.6H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 159.5 and 155.3, 159.4, 150.8 and 148.0, 138.3 and 135.3, 129.7 and 128.2, 128.9 (2C), 126.9 and 126.5, 125.4 and 123.8, 123.5, 117.7 and 113.7, 114.4 (2C), 111.0 and 110.0, 56.0, 55.3, 43.6, 22.3, and 22.1 (3C); HRMS (ESI) calcd for $C_{20}H_{22}N_2O_3S$ 370.1351, found 370.1359.

General Optimized Procedure for the Grignard Addition to 6 or 7. A suspension of substrate (**6** or **7**, 0.20 mmol) and $MgBr_2$ (80 mg, 0.40 mmol) in 6 mL of dry CH_2Cl_2 under nitrogen atmosphere was stirred for 20 min at −40 °C. The desired Grignard reagent (0.22 mmol) was then slowly added. The reaction mixture was stirred for 1 h at − 40 °C and for 12 h at room temperature. The reaction was quenched with 5 mL of a saturated aq NH_4Cl solution, and the organic phase was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated under reduced pressure. The crude addition product was purified by flash chromatography.

Spectroscopic data of major diastereoisomers are reported below.

(*S*)-3-Allyl-3-((*R*)-2-(*tert*-butyldimethylsilyloxy)-1-phenylethylamino)-1-(4-methoxybenzyl)indolin-2-one 9a: R_f = 0.2 (hexane/EtOAc 9:1); $[\alpha]^{25}_D = +95.1$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.28 (d, *J* = 6.8 Hz, 1H), 7.227.16 (m, 4H), 7.08 (t, *J* = 7.4, 1H), 6.99−6.94 (m, 4H), 6.76 (d, *J* = 8.7 Hz, 2H), 6.53 (d, *J* = 7.7 Hz, 1H), 5.59 (ddt, *J* = 17.3, 10.1, 7.5 Hz, 1H), 5.16 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.06 (dd, *J* = 10.1, 1.5 Hz, 1H), 4.53 (d, *J* = 15.6 Hz,1H), 3.83 (d, *J* = 15.6 Hz, 1H), 3.76 (s, 3H), 3.62 (m, 2H), 3.52 (dd, *J* = 13.7, 9.0 Hz, 1H), 3.06−2.73 (br, s, 1H), 2.68 (dd, *J* = 13.2, 7.5 Hz, 1H), 2.53 (dd, *J* = 13.2, 7.5 Hz, 1H), 0.93 (s, 9H), 0,10 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 177.9, 158.8, 143.0, 139.6, 131.3, 128.9, 128.6−128.4 (6C), 128.1, 127.6 (2C), 127.5, 124.7, 121.8, 113.9 (2C), 109.1, 67.9, 64.5, 60.9, 55.2, 43.5, 42.9, 25.9 (3C), 18.2, −5.45 (2C); HRMS (ESI) calcd for $C_{33}H_{42}N_2O_3Si$ 542.2965, found 542.2972.

***tert*-Butyl 3-allyl-3-((*R*)-2-(*tert*-butyldimethylsilyloxy)-1-phenylethylamino)-2-oxoindoline-1-carboxylate 10a:** R_f = 0.13 (hexane/EtOAc 9:1); $[\alpha]^{25}_D = -7.3$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 1:1 mixture of rotamers, δ) 8.01 (d, *J* = 8.2 Hz, 0.5H), 7.88 (d, *J* = 8.2 Hz, 0.5H), 7.59 (d, *J* = 7.9 Hz, 0.5H), 7.55 (d, *J* = 7.9 Hz, 0.5H), 7.39−7.21 (m, 4H), 7.20−7.06 (m, 4H), 5.71 (pseudo sept, *J* = 8.1 Hz, 1H), 5.28 (d, *J* = 11.4 Hz, 1H), 5.22 (d, *J* = 14.7 Hz, 1H), 4.95 (dt, *J* = 7.3, 3.6 Hz, 1H), 3.83 (br, d, *J* = 10.2 Hz, 1H), 3.70 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.17−3.05 (m, 1H), 2.97 (dd, *J* = 13.8, 7.1 Hz, 1H), 1.48 (s, 4.5H), 1.45 (s, 4.5H), 0.81 (s, 4.5H), 0.79 (s, 4.5H), −0.1 (s, 3H), −0.14 (s, 1.5H), −0.20 (s, 1.5H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1 mixture of rotamers, δ) 174.15, 154.0 and 153.9, 140.3 and 140.2, 138.3 and 138.2, 132.8 and 132.7, 130.6, 129.8, 129.1, 128.9, 128.2, 127.3, 127.15 (2C), 124.7 and 123.8, 124.1 and 124.0, 121.6 and 121.5, 80.4, 78.1, 66.8 and 66.6, 55.4, 43.5 and 43.3, 29.1 (3C), 26.4 (3C), 18.7, −3.6, −3.7; HRMS (ESI) calcd for $C_{30}H_{42}N_2O_4Si$ 522.2914, found 522.2908.

General Procedure for the Grignard Addition to 8. A suspension of substrate (0.20 mmol) and $MgBr_2$ (80 mg, 0.40 mmol) in 6 mL of dry CH_2Cl_2 under nitrogen atmosphere was stirred for 20 min at −40 °C. The desired Grignard reagent (1.00 mmol) was then slowly added. The reaction mixture was stirred for 1 h at −40 °C and for 12 h at room temperature. The reaction was quenched with 5 mL of a saturated aq NH_4Cl solution, and the organic phase was extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated under reduced pressure. The crude addition product was purified by flash chromatography.

Spectroscopic data of major diastereoisomers are reported below.

(*R*)-*N*-((*R*)-3-Allyl-1-(4-methoxybenzyl)-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide 11a: R_f = 0.44 (hexane/EtOAc 1:1); $[\alpha]^{25}_D = -52.4$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.54 (d, *J* = 7.4 Hz, 1H), 7.26−7.15 (m, 3H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.77 (d, *J* = 7.4 Hz, 1H), 5.53 (ddt, *J* = 17.1, 9.9, 7.3 Hz, 1H), 5.17 (dd, *J* = 17.1, 1.3 Hz, 1H), 5.08 (dd, *J* = 9.9, 1.3 Hz, 1H), 4.89 (d, *J* = 15.4 Hz, 1H), 4.81 (d, *J* = 15.4 Hz, 1H), 3.79 (s, 3H), 2.90 (dd, *J* = 13.3, 6.8, 1H), 2.80 (dd, *J* = 13.3, 7.8, 1H), 1.71−1.62 (br, s, 1H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 176.6, 143.2, 131.1, 130.4, 130.2, 129.3 (2C), 129.0, 128.2, 126.4, 123.5, 121.6, 114.8 (2C), 110.1, 64.5, 57.2, 55.9, 44.1, 44.0, 23.1 (3C); HRMS (ESI) calcd for $C_{23}H_{28}N_2O_3S$ 412.1821, found 412.1817.

(*S*)-3-Allyl-3-amino-1-(4-methoxybenzyl)indolin-2-one (*S*)-12. To a solution of **9a** (100 mg, 0.18 mmol) in 1 mL of dry THF under nitrogen atmosphere at room temperature was added TBAF (239 μL, 0.24 mmol, 1 M THF solution). The solution was stirred for 1 h. The reaction was then quenched with 2 mL of NaOH 1 M and extracted three times with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure to afford the crude product, which was used in the next step without further purification (75 mg): R_f = 0.11 (hexane/EtOAc 3:7); $[\alpha]^{25}_D = -45.2$ (*c* 1, $CHCl_3$).

To a solution of the obtained alcohol (75 mg, 0.17 mmol) in CH_2Cl_2/MeOH (1:1, 2 mL) at 0 °C and under nitrogen atmosphere, $Pb(OAc)_4$ (77 mg, 0.17 mmol, 1 equiv) was added, and the solution was stirred at 0 °C for one hour. After complete consumption of the starting material, $NH_2OH \cdot HCl$ (182 mg, 2.63 mmol) was added. After 30 min, the reaction was quenched with aqueous $NaHCO_3$ and the solid residue was filtered through a pad of Celite; the biphasic solution was diluted with water and the organic layer was extracted with EtOAc. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The resulting yellow oil was purified by flash chromatography (EtOAc/hexane 5:1) to afford **(*S*)-12** (48 mg, 87% overall yield): R_f = 0.27 (EtOAc); $[\alpha]^{25}_D = -26.8$ (*c* 1, $CHCl_3$).

(*R*)-3-Allyl-3-amino-1-(4-methoxybenzyl)indolin-2-one (*R*)-12. To a solution of **11a** (20 mg, 0.05 mmol) in 300 μL of dioxane was added a HCl saturated dioxane solution (122 μL, 10 equiv) at room temperature. The reaction mixture was stirred for 15 min. The reaction was quenched with 4 mL of aqueous $NaHCO_3$, and the organic phase was extracted with CH_2Cl_2, dried, and evaporated under reduced pressure to afford pure **(*R*)-12** (12 mg, 75%), as an oil: $[\alpha]^{25}_D = +24.3$ (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 7.40 (d, *J* = 7.5 Hz, 1H), 7.27−7.18 (m, 3H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 7.5 Hz, 1H), 5.56 (m, 1H), 5.11 (d, *J* = 16.9 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.98 (d, *J* = 15.9 Hz, 1H), 4.69 (d, *J* = 15.9 Hz, 1H), 3.79 (s, 3H), 2.68 (dd, *J* = 13.2, 6.4 Hz, 1H), 2.59 (dd, *J* = 13.2, 8.3 Hz, 1H), 2.00 (br, s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, δ) 180.6, 159.8, 143.1, 132.0, 129.5, 129.4 (2C), 128.5, 124.6, 123.4, 120.4 (2C), 114.8 (2C), 109.9, 61.6, 55.9, 44.2, 44.0; HRMS (ESI) calcd for $C_{19}H_{20}N_2O_2$ 308.1525, found 308.1530.

Supporting Information Available: Spectroscopic data of compounds **9b**,**d**,**e**, **10b**−**e**, and **11b**,**d**; ^{1}H NMR and ^{13}C NMR spectra of compounds **6**−**12**; crystallographic data of compound **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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