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Asymmetric synthesis of dihydroquinazolinones via directed *ortho* metalation and addition to *tert*-butanesulfinyl imines

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Abstract—An asymmetric route to dihydroquinazolinones via the addition of *ortho* metalated substrates to *tert*-butanesulfinyl imines is reported. The scope of the nucleophile and electrophile components and the absolute stereochemical outcome are presented.

Dihydroquinazolinones represent an important class of biologically active molecules with utility in many therapeutic areas (Fig. 1).[1–3] Recently reported structures of this class include DPC-961, a potent second generation non-nucleoside reverse-transcriptase inhibitor for the treatment of HIV infection and SM-15811, an effective Ca^{2+}/Na^{+} ion exchanger inhibitor with potential utility for the management of ischemic heart disease.[2,3]

To the best of our knowledge, only two asymmetric approaches to 3,4-dihydroquinazolinones have been reported to date. Both these reports target the DPC-961 class of molecules and utilize either a chiral auxiliary or catalyst to mediate the asymmetric addition of acetylenic nucleophiles to generate the amine bearing stereocenter.[2,4] During our efforts to synthesize compounds of this structural class, we focused on the 2-(1-aminoalkyl)aniline retron present in the 3,4-dihydroquinazolinone core. We hypothesized that the addition of an *ortho* metalated aniline derivative to a *tert*-butanesulfinyl imine could provide this core in a diastereoselective manner.[5,6] Judicious choice of a directing group can provide the desired intermediate with differentially protected amine functionality.

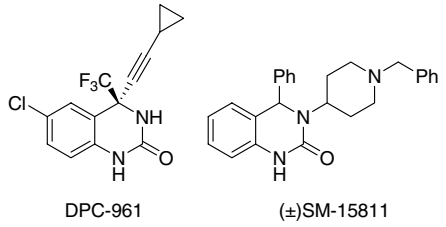

Figure 1. Representative dihydroquinazolinones.

Boc-protected aniline **1** and benzaldehyde sulfinyl imine **2** were chosen as the initial substrates to examine the feasibility of this reaction (Table 1). Directed *ortho* metalation of **1** with *sec*-BuLi in THF followed by electrophile addition did not afford any desired product **3**.[7] Fortunately, **3** was obtained in modest yield in the presence of one equivalent of TMEDA.[8,9] Increasing the stoichiometry of TMEDA resulted in improved yield but did not affect the diastereoselectivity of the reaction.

We then surveyed the reaction scope with respect to the nucleophilic component (Table 2). Electron withdrawing substituents at the *para* position were found to enhance the yields for this process (adducts **4**, **5**, and **6**). This trend was confirmed by the addition of *ortho* metalated *N*-Boc-4-methoxyaniline, which gave **7** in poor yield and selectivity.[10] *N*-Boc-2-aminopyridine was found to add with excellent yield and selectivity to afford adduct **8**. In contrast, the isomeric *N*-Boc-4-aminopyridine provided **9** with poor selectivity. The nature of the directing group is also critical for the success

Keywords: Dihydroquinazolinones; Asymmetric synthesis; Sulfinyl imines; Directed *ortho* metalation.
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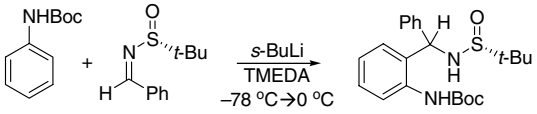
Table 1. Effect of TMEDA additive

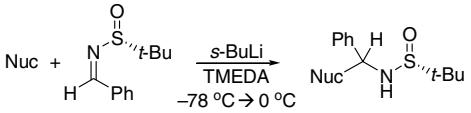


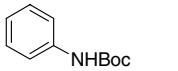
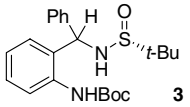
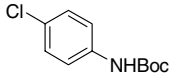
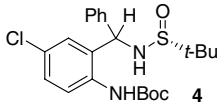
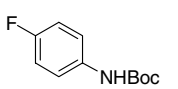
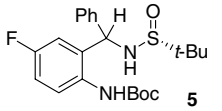
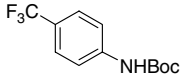
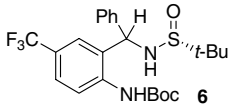
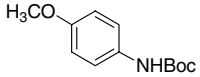
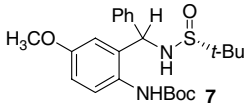
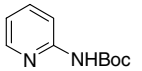
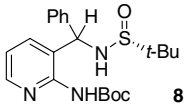
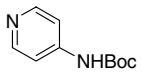
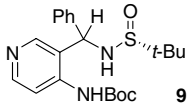
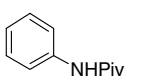
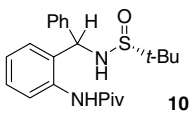
1 2 3

TMEDA (equiv)[a]	Yield (%)[b]	dr[c]
0	0	N/A
1	42	80:20
2	61	80:20
3	55	80:20

[a] With respect to the nucleophile.
[b] Combined isolated yield of diastereomeric mixture.
[c] Ratio determined by 400 MHz ^{1}H NMR analysis of the unpurified reaction mixture.

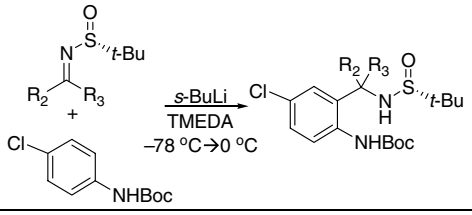
Table 2. Nucleophile scope

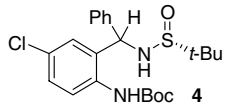
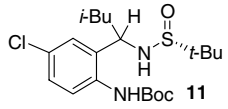
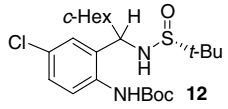
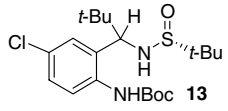
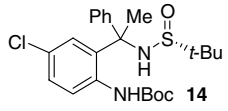
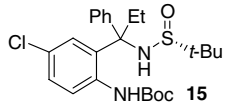
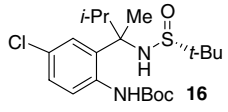


Nuc	Adduct	Yield (%)[a]	dr[b]
	 **3**	61	80:20
	 **4**	79	80:20
	 **5**	74	85:15
	 **6**	81	75:25
	 **7**	30	70:30
	 **8**	70	95:05
	 **9**	90	60:40
	 **10**	31	66:34

[a] Combined isolated yield of diastereomeric mixture.
[b] Ratio determined by 400 MHz ^{1}H NMR analysis of the unpurified reaction mixture.

Table 3. Electrophile scope



R_2	R_3	Adduct	Yield (%)[a]	dr[b]
Ph	H	 **4**	79	80:20
i-Bu	H	 **11**	80	66:34
c-Hex	H	 **12**	75	80:20
t-Bu	H	 **13**	42	66:34
Ph	Me	 **14**	<5[c]	N/A
Ph	Et	 **15**	37	91:09
i-Pr	Me	 **16**	<10[c]	N/A

[a] Combined isolated yield of diastereomeric mixture.
[b] Ratio determined by 400 MHz ^{1}H NMR analysis of the unpurified reaction mixture.
[c] Based on conversion observed by LC/MS.

of this reaction. Boc proved to be optimal, and variations such as pivalate gave the corresponding addition adduct **10** with severely diminished yield and selectivity.

Using *N*-Boc-4-chloroaniline as the nucleophile precursor, we surveyed the scope of the electrophilic component (Table 3). Sulfinyl imine derivatives of enolizable aldehydes underwent addition in high yield (adducts **11** and **12**). However, the selectivity of the addition was highly dependent on the steric nature of the aldimine. Both α-monosubstituted and α,α,α-trisubstituted aldimines gave the desired product with poor selectivity (adducts **11** and **13**), whereas α,α-disubstituted cyclohexylcarboxaldehyde sulfinyl imine proved to be comparable to **2** for this reaction.

The feasibility of utilizing ketimines in this reaction sequence was also examined (Table 3). The sulfinyl imine

derivative of acetophenone proved to be a poor substrate, but we were pleasantly surprised to find that the *tert*-butylsulfinyl imine of propiophenone gave adduct **15** with high selectivity albeit in modest yield. The ketimine derivative of 3-methyl-2-butanone did not afford **16** under these conditions. Enolization is the primary non-productive reaction pathway of ketimines, as has been previously documented in the literature.[11] This was confirmed by quenching ketimine reactions with MeOH-d_4, and observing significant deuteration of the ketimine component by LC/MS analysis of the unpurified reaction mixture.[12]

X-ray quality single crystals of enantiomerically pure **12** could not be obtained from any of the crystallization conditions tested. However, *rac*-**12** proved to be more amenable to crystallization, and the relative stereochemistry was determined by single crystal X-ray analysis of this racemic material.[13] These results, shown as a perspective drawing of *rac*-**12** in Figure 2, establish the relative configuration of the two chiral centers to be either *S*, *R* or *R*, *S* for S1 and C19, respectively.

The relative stereochemical outcome for the addition of *ortho* metalated nucleophiles is *opposite* to that generally documented in the literature.[6] We speculate that due to the bidentate chelating nature of the nucleophile or the presence of TMEDA, a Zimmerman–Traxler-like transition state with 'internal' activation of the sulfinyl imine is not feasible. The reversal of facial selectivity could result from external activation of the sulfinyl imine, presumably from the lithium counterion that is not strongly associated with the nucleophile. Addition occurs at the less hindered back face of the electrophile through an acyclic transition state (Fig. 3).[14]

We chose the Na^+/Ca^{2+} ion exchanger inhibitor SM-15811 as a target to illustrate the utility of this methodology towards the synthesis of a biologically active 3,4-dihydroquinazolinone (Scheme 1).[3] Adduct **3** was used as the starting building block.[15] Selective deprotection

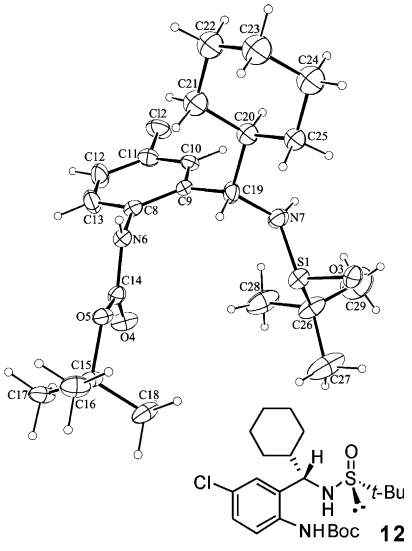


Figure 2. X-ray structure of *rac*-**12**.

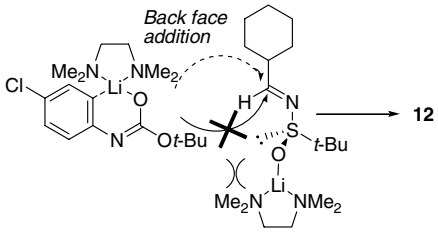
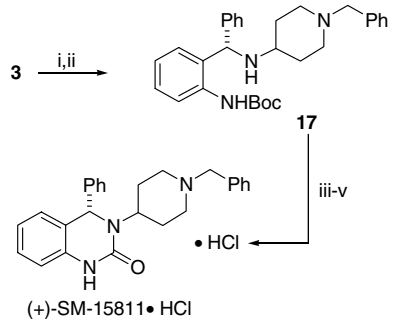


Figure 3. Rationalization of stereochemical outcome.



Scheme 1. Reagents and conditions: (i) HCl, Et_2O, 95%; (ii) $NaBH(OAc)_3$, *N*-benzylpiperidin-4-one, 81%; (iii) TFA, CH_2Cl_2, 92%; (iv) CDI, CH_2Cl_2, 83%; (v) HCl, CH_2Cl_2, 100%.

of the chiral auxiliary was effected in high yield with 2 equiv HCl in the presence of the acid labile Boc protective group. The resulting hydrochloride salt underwent a reductive amination with *N*-benzyl-4-piperidinone under standard conditions to afford **17**.

Acid mediated Boc deprotection and isolation of the free base using SCX ion exchange chromatography[16] gave the requisite diamine, which underwent cyclization in the presence of carbonyl diimidazole to complete the synthesis of SM-15811, which was characterized as its hydrochloride salt.[17,18] This asymmetric synthesis was completed in five steps from commercially available materials.

In conclusion, the addition of *ortho* metalated substrates to *tert*-butane sulfinyl imines provides a useful intermediate for the enantioselective synthesis of 3,4-dihydroquinazolinones. The modular approach presented by this work facilitates the synthesis of diverse members of this class of molecules from readily available materials utilizing a short reaction sequence.

Acknowledgments

We thank Philippe G. Nantermet and James C. Barrow for helpful discussions, and Joan Murphy for mass spectral data.

Supplementary data

^1H NMR spectral data and high resolution mass spectral data for all compounds, ^{13}C NMR and specific rotation data for major products that were isolated as single

diastereomers. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.067.

References and notes

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6. Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011.
7. For a comprehensive review on directed *ortho* metalation see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
8. TMEDA has been documented to break down alkyllithium aggregates, increasing their basicity. We suspect this results in enhanced nucleophilicity of the *ortho* metalated anion under our conditions. See: Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, UK, 1974, The addition of TMEDA before or after the orthometalation step gave identical results.
9. Representative procedure: To a solution of *tert*-butyl phenyl carbamate (0.346 g, 1.79 mmol) in 10 mL THF at −78 °C was added *sec*-BuLi (3.90 mL of a 0.92 M solution, 3.58 mmol). TMEDA (0.540 mL, 3.58 mmol) was added, and the solution was warmed to −10 °C over 2 h. The reaction was cooled to −78 °C, and 2-methyl-*N*-(phenylmethylene)propane-2-sulfinamide (0.250 g, 1.194 mmol) in 2 mL THF was added via cannula (0.5 mL THF rinse). The reaction was allowed to warm to −20 °C over 15 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl and diluted with EtOAc. The layers were separated, the organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was typically purified using normal phase silica gel chromatography.
10. The presence of an electron withdrawing group on the nucleophile gives higher isolated yields under our conditions. We speculate that charge delocalization due to an electron withdrawing group results in diminished aggregation or enhanced nucleophilicity.
11. The addition of organolithium and Grignard reagents to ketimines generally do not proceed in high yield, and imine **16** is a particularly poor substrate for nuclephilic addition. Lewis acid activated addition of organolithium reagents provide optimal results. See: Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883.
12. Comparing the differences in reactivity between imine substrates **14** and **15** illustrates the fine balance between nucleophile addition and enolization for ketimines under our conditions.
13. Crystallographic data (excluding structure factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 283338. Copies of this data may be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
14. This transition state model is in accord with that proposed by Davis to explain the reversal of stereochemistry observed in the Lewis acid mediated addition of BnMgCl to glyoxylate sulfinyl imines. See: Davis, F. A.; McCoull, W. *J. Org. Chem.* **1999**, *64*, 3396.
15. Diastereomerically pure **3** was utilized for the synthesis of (+)-SM-15811. The 80:20 mixture of **3** obtained under our reaction conditions was separated using a chiral stationary phase. See Supplementary data for additional details.
16. A Varian prepacked straight barrel solid phase extraction cartridge packed with a benzenesulfonic acid sorbent was utilized for this step. See Supporting information for additional details.
17. The synthesis and biological activity of *racemic* SM-15811 has been reported in the literature (Ref. 3), hence we are unable to establish the identity of the active enantiomer.
18. The absolute stereochemistry for (+)-SM-15811 was assigned in analogy to the relative stereochemistry obtained for adduct *rac*-**12** by single crystal X-ray.