Chemical Science

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Cite this: *Chem. Sci.*, 2011, **2**, 1086

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EDGE ARTICLE

Benzoquinone-derived sulfinyl imines as versatile intermediates for alkaloid synthesis: Total synthesis of (–)-3-demethoxyerythratidinone†

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Received 16th February 2011, Accepted 25th February 2011
DOI: 10.1039/c1sc00095k

The preparation and synthetic applications of benzoquinone monoketal-derived *N*-*tert*-butanesulfinyl imines is described. These synthetically versatile intermediates undergo highly diastereoselective 1,2-addition reactions with organometallic reagents to provide 4-aminocyclohexadienones in good yields. The utility of this methodology is demonstrated in a six-step enantioselective synthesis of (–)-3-demethoxyerythratidinone.

Introduction

The enantioselective preparation of chiral amines is an area of considerable interest in the discipline of organic chemistry. Chiral amines are prevalent in modern pharmaceutical agents and are the defining functionality of alkaloid natural products.[1] As part of studies aimed at the total synthesis of polycyclic alkaloid natural products, we recognized that enantioenriched 4-aminocyclohexadienones could serve as versatile synthetic intermediates for the preparation of erythrina,[2] hasubanan,[3] and acutumine[4] alkaloids (Fig. 1). Retrosynthetically, it was envisioned that 4-aminocyclohexadienones (**4**) could derive from the corresponding benzoquinone imine monoketals (**5**) *via* nucleophilic 1,2-addition.[5] Whereas Swenton and coworkers have previously reported 1,2-addition reactions of organolithium reagents to benzoquinone imine monoketals,[6] there are no general methods available to promote these reactions with control over the absolute stereochemistry of the newly formed C–N bond. As a result, these intermediates are underutilized in synthetic efforts. Herein we report a direct, general method to enantioselectively prepare a variety of 4-aminocyclohexadienones, and illustrate their synthetic utility in a six-step synthesis of (–)-3-demethoxyerythratidinone.

Synthesis plan

In considering general methods to prepare enantioenriched 4-aminocyclohexadienones (**4**) from benzoquinone imine monoketals (**5**), we sought to develop a reaction that would: 1) utilize a stable, easy-to-handle benzoquinone imine monoketal; 2) control the absolute configuration at C4; and 3) tolerate a variety of alkyl, aryl, and alkenyl nucleophiles. Moreover, we recognized that 4-aminocyclohexadienones such as **4** are highly susceptible to dienone-phenol rearrangements;[7] it was therefore critically important to identify a sufficiently electron-withdrawing nitrogen protecting group in order to disfavor deleterious rearrangements.

Despite considerable efforts targeting the preparation of enantioenriched chiral amines,[1] the asymmetric synthesis of α,α-disubstituted amines by nucleophilic 1,2-addition to ketimines remains a challenging problem.[8–12] Although successful catalytic reactions have emerged for enantioselective allylation[10] and Mannich-type reactions,[11] there are few reports of catalytic asymmetric addition of aryl or alkyl organometallic reagents to ketimines.[12] Hoveyda, Snapper, and coworkers have reported the Zr-catalyzed asymmetric addition of simple alkylzinc reagents to *o*-anisidine ketimines.[12b] Alternatively, Shintani, Hayashi, and

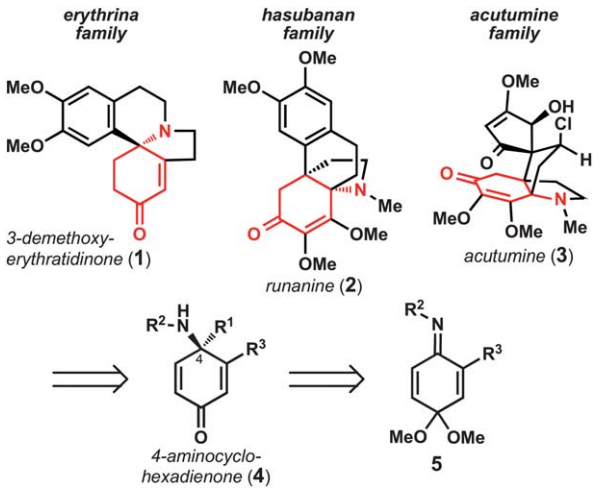

Fig. 1 Polycyclic alkaloids envisioned to arise from 4-aminocyclohexadienone **4**.

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† Electronic supplementary information (ESI) available: Experimental details, characterization data and NMR spectral charts. CCDC reference numbers 780836. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1sc00095k

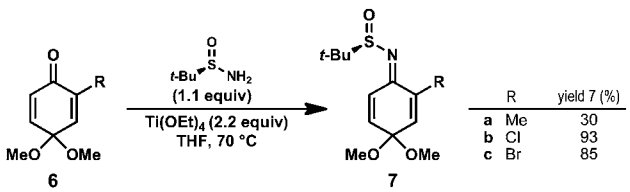
coworkers recently reported the Rh-catalyzed asymmetric addition of tetra-arylborates to *N*-tosyl ketimines.[12c] These two reports represent the state-of-the-art for asymmetric catalytic additions to ketimines; however, the limited scope of nucleophiles and the required use of *N*-aryl or *N*-tosyl protecting groups was not expected to be amenable to our desired synthetic applications (*vide infra*).

With these considerations in mind, it was hypothesized that benzoquinone monoketal-derived *N-tert*-butanesulfinimines could provide a unique solution. Pioneering studies by Ellman and coworkers have shown that *N-tert*-butanesulfinyl ketimines undergo highly diastereoselective 1,2-addition reactions with a variety of organometallic reagents.[9a,13] In addition, the *tert*-butanesulfinyl group can be cleaved using mildly acidic conditions. Furthermore, it was envisioned that the electron-withdrawing nature of the sulfinamide product would disfavor the dienone-phenol rearrangement. Taken together, these features of the *tert*-butanesulfinyl auxiliary were anticipated to prove advantageous in a synthetic context relative to existing asymmetric catalytic approaches.

Results and discussion

Known benzoquinone monoketals **6a–c** were prepared in one step from commercially available phenols.[14] Our preliminary studies determined that sulfinimine **7a** (R = Me) could be prepared directly from **6a** by treatment with *tert*-butanesulfinamide (1.1 equiv) and $Ti(OEt)_4$ at 70 °C for 72 h; however, the desired product was isolated in low yield (Scheme 1). Monitoring the yield of **7a** over time revealed that it was decomposing under the reaction conditions. It was hypothesized that use of a quinone monoketal bearing an electron-withdrawing substituent may enhance the rate of sulfinimine formation, allowing for shorter reaction times. Indeed, 2-chloro and 2-bromosulfinimines **7b** and **7c** were prepared under standard conditions[15] in 93% and 85% isolated yield, respectively. Halogenated substrates **7b** and **7c** possess the advantage of a functional handle for elaboration in natural product synthesis efforts. In both cases, the sulfinimine was formed exclusively as the *E*-imine isomer (as shown). Sulfinimines **7b** and **7c** were prepared on gram scale and were stable for months when stored at −20 °C.

With access to the quinone-derived sulfinimines **7b** and **7c**, experiments were conducted to evaluate their ability to undergo diastereoselective 1,2-addition reactions with *n*-butyllithium (Table 1, entries 1 and 3). Treatment of chlorosulfinimine **7b** with 1.1 equivalents *n*-butyllithium at −78 °C followed by quenching with 1N HCl provided 4-aminocyclohexadienone **8a** in 97 : 3 dr. The major diastereomer was obtained after silica gel chromatography in 90% isolated yield. Notably, hydrolysis of the dimethyl ketal cleanly occurred during the acidic workup; no products of dienone-phenol rearrangement were observed.



Scheme 1 Synthesis of benzoquinone monoketal-derived *N-tert*-butanesulfinimines.

Similar levels of diastereoselectivity were observed for the corresponding bromide **7c**.[16] A survey of solvents indicated that ethereal solvents were optimal, with Et_2O or THF providing the highest levels of diastereoselectivity. A variety of organolithium and organomagnesium reagents were evaluated in order to assess the substrate scope of the reaction. Alkyllithiums provided uniformly high diastereoselectivities (Table 1, entries 1, 3–7); however, addition of phenyllithium proceeded with lower levels of stereocontrol (entries 2 and 8).[17] Fortunately, improved diastereoselectivity was observed using substituted aryllithiums (entries 9–11). With less reactive nucleophiles, improved yields were obtained by employing 2 equivalents (entries 9–13, 16). In the case of allyl and propargyl nucleophiles, the readily available Grignard reagents were utilized instead of the corresponding organolithium reagents. Notably, the products shown in Table 1 *cannot be prepared enantioselectively through any other previously reported methods.*

The vinyl halide moiety of the enantioenriched sulfinamide products provides a useful handle for further elaboration. For example, vinyl bromide **8e** (R^1 = Me) undergoes a variety of palladium-catalyzed cross-coupling reactions, allowing access to the corresponding arene-, alkyne- and allyl-substituted products (Scheme 2, **9**, **11**, and **12**, respectively). On the other hand, vinyl bromide **8n** (R^1 = allyl) can be coupled with vinyl tributylstannane and treated with Hoveyda-Grubbs second generation catalyst[18] to provide bicycle **10** in excellent yield over two steps.

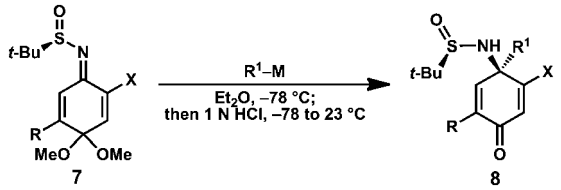
Having developed a method to prepare enantioenriched 4-aminocyclohexadienones, we sought to highlight this enabling reaction in a total synthesis of the erythrina alkaloid (–)-3-demethoxyerythratidinone (Fig. 1).[19] 3-Demethoxyerythratidinone (**1**) was isolated from *Erythrina lithosperma* in 1973, and is a representative member of the erythrina family of natural products.[20] There have been several total syntheses of **1**, the first of which was reported by Tsuda in 1984.[21] However, there are only three total syntheses of enantioenriched **1** reported to date;[22] thus, the enantioselective synthesis of this natural product remains a significant challenge. The spirocyclic core of (–)-**1** was anticipated to derive directly from *N-tert*-butanesulfinyl imine **7c** by a one-pot intermolecular 1,2-addition followed by intramolecular *N*-alkylation.

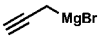
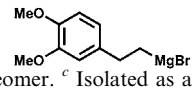
In the forward sense, we were pleased to find that addition of aryllithium **13**[23] (generated *in situ* at −78 °C from the corresponding aryl bromide by lithium-halogen exchange) to bromosulfinimine **7c** provided spirocycle **14** (>98:2 dr), which was isolated in 74% yield as a single diastereomer (Scheme 3). This highly convergent reaction provides direct access to the key spirocyclic amine with excellent levels of stereocontrol.

Exposure of sulfinamide **14** to vinyl stannane **15** in the presence of $Pd_2(dba)_3$ and $AsPh_3$ at 100 °C furnished the corresponding enol ether in 85% yield.[24] Sulfinamide deprotection and *in situ* acid-mediated condensation was effected by treatment of the enol ether with 2N HCl for 2 min at 0 °C to provide tetracycle **16**. Notably, use of weaker acids or stirring for longer periods resulted in substantially diminished yields due to competitive decomposition of **16**.

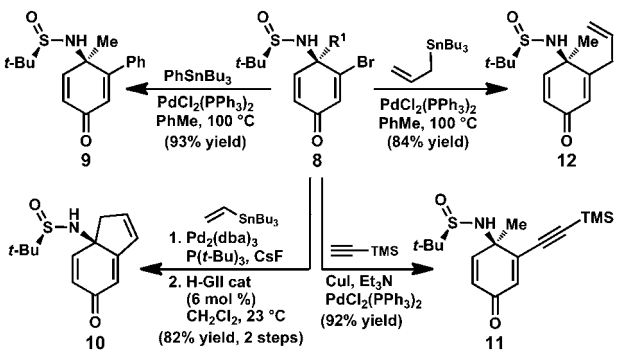
Completion of the synthesis was achieved by selective hydrogenation of triene **16** to furnish (–)-**1** in 65% yield. At six steps

Table 1 Scope of the diastereoselective 1,2-addition of organometallic reagents to benzoquinone monoketal-derived sulfinimines.

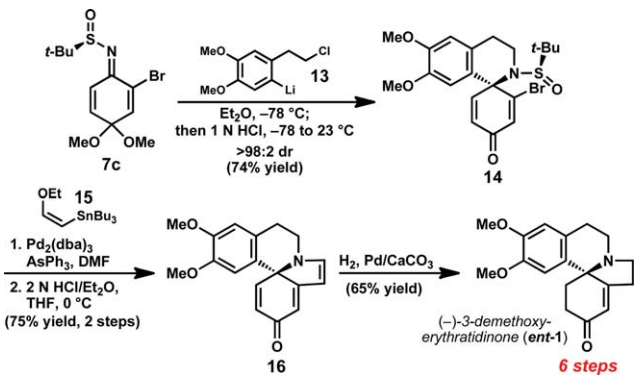


Entry	X	R	R[1]-M (equiv)	pdt	dr[a]	Yield (%)[b]
1	Cl	H (**7b**)	*n*-BuLi (1.1)	**8a**	97:3	90
2	Cl	H	PhLi (1.1)	**8b**	78:22	76
3	Br	H (**7c**)	*n*-BuLi (1.1)	**8c**	98:2	88
4	Br	H	EtLi (1.1)	**8d**	98:2	96
5	Br	H	MeLi (1.1)	**8e**	98:2	91
6	Br	Cl (**7d**)	MeLi (1.1)	**8f**	97:3	92[c]
7	Br	Me (**7e**)	MeLi (1.1)	**8g**	98:2	91
8	Br	H	PhLi (1.1)	**8h**	80:20	74
9	Br	H	*o*-MeC_6H_4Li (2.0)	**8i**	97:3	86
10	Br	H	*m*-MeC_6H_4Li (2.0)	**8j**	91:9	79
11	Br	H	*p*-MeC_6H_4Li (2.0)	**8k**	91:9	78
12	Br	H	 (2.0)	**8l**	98:2	68[d]
13	Br	H	(2.0)	**8m**	98:2	71[d]
14	Br	H	 (1.1)	**8n**	87:13	82[d]
15	Br	H	 (1.1)	**8o**	> 97:3	91
16	Br	H	 (2.0)	**8p**	> 98:2	99[c,d,e]
17	Br	H	 (1.1)	**8q**	96:4	82[d]

[a] Determined by HPLC. [b] Isolated yield of major diastereomer. [c] Isolated as a mixture of diastereomers. [d] Reaction conducted in THF. [e] Reaction conducted at 0 °C.



Scheme 2 Synthetic transformations of sulfinamide **8**.



Scheme 3 Enantioselective synthesis of (–)-3-demethoxyerythratidinone.

and 26% overall yield, this represents the shortest enantioselective synthesis of **1** reported to date, and illustrates the strategic advantage provided by the ability to promote diastereoselective 1,2-additions to benzoquinone monoketal-derived sulfinimines.

Conclusions

In conclusion, the preparation and synthetic applications of sulfinimines derived from benzoquinone monoketals is reported. This methodology provides the first direct access to a variety of enantioenriched 4-aminocyclohexadienones which possess synthetic handles for further elaboration to alkaloid natural products. The utility of this methodology was demonstrated in a short, enantioselective total synthesis of the natural product 3-demethoxyerythratidinone. The further application of benzoquinone monoketal-derived sulfinimines to the synthesis of alkaloid natural products is the focus of ongoing research in our laboratory.

Acknowledgements

We thank Drs. Michael Day and Larry Henling for X-ray crystallographic structural determination, as well as Prof. Brian Stoltz, Dr. Scott Virgil, and the Caltech Center for Catalysis and Chemical Synthesis for access to analytical equipment. We thank the Gates Millennium Scholars Program (R.N.) and the Amgen Scholars Program (K.V.C.) for fellowship support. Andrew Lim is acknowledged for assistance in the preparation of compound **10**. HRMS and X-ray crystallographic data were obtained on instruments purchased through awards to the California Institute of Technology by the NSF CRIF program (CHE-0639094, CHE-0541745). Financial support from the California Institute of Technology is gratefully acknowledged.

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