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Nucleophilic Imines and Electrophilic *o*-Quinone Methides, a Three-Component Assembly of Assorted 3,4-Dihydro-2*H*-1,3-benzoxazines

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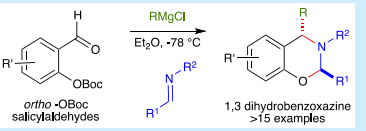
Supporting Information

ABSTRACT: A one-pot method for joining three separate components leading to an assortment of N-substituted 3,4-dihydro-2*H*-1,3-benzoxazines is described. The method involves the addition of a Grignard reagent to an *o*-OBoc salicylaldehyde in the presence of an imine. With a variety of components, 15 examples are presented, including the diastereoselective incorporation of chiral imines.

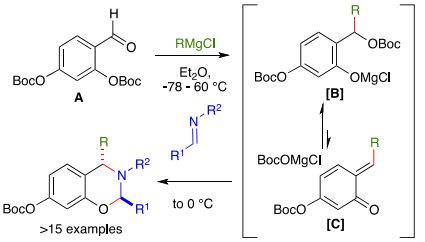


Imines are usually activated by addition of a Lewis acid for subsequent addition of carbon nucleophiles.[1] While Staudinger *β*-lactam construction is touted as an example of the reverse notion,[2a−c] it is usually deployed in Umpolung fashion,[2d] whereby an electrophilic ketene is first converted into a nucleophilic zwitterionic enolate by addition of an amine or phosphine for subsequent addition to an electron deficient imine.[2] Indeed, beyond a few scattered examples of *N*-acyl iminiums formed by acylation of Schiff bases,[3] we could find very few examples of imines serving as nucleophiles toward carbon.[4] In 2002, we and Schwarz separately reported the first examples of *o*-QMs engaging imines in this manner.[5a,6d] Since then, several other reports have appeared.[5b−d,8a,b] Nearly all among these have involved heating a Mannich base of a corresponding polycyclic *o*-phenolic compound, so as to yield a stable polyaryl *o*-QM.[5a−d,8a,b] The analogous reaction among less stable monocyclic *o*-QMs has remained almost unknown.[6d,8a,b]

Building upon our past experiences,[6] we supposed that an imine would engage an *o*-QM via its lone pair of electrons in a 1,4-conjugate addition, followed by an intramolecular cyclization of the developing phenoxide zwitterion onto the resulting iminium species. This sequence should provide an assortment of N-substituted 3,4-dihydro-2*H*-1,3-benzoxazines in a single pot in a manner that is more straightforward than that possible with other processes (Scheme 1).[5,7−9] We chose to focus on the reactivity of two *o*-QMs ([**C**]; R = -Ph or -Me) prepared *in situ* at low concentrations via the intermediacy of [**B**]. These intermediates would be generated from aldehyde **A**[6c] by addition of the appropriate Grignard reagent. We knew these two species displayed markedly different reactivity profiles, with the *β*-phenyl *o*-QM proving to be less reactive and more selective in its reactions with nucleophiles. Moreover, given our past investigations of *o*-QMs of differing substitutions and their reactions with a range of nucleophiles,[6] we expected to be able to extrapolate our findings for these two species to many other systems.

We began by examining imines **1**−**3**.[10] These presented aliphatic substituents on both their nitrogen and carbon atoms of the respective imine functionality (Figure 1). Using the

Scheme 1. General Method[a]



[a]The Grignard reagent is added to the OBoc salicylaldehyde at −78 °C in diethyl ether in the presence of the imine, and the reaction mixture is permitted to warm to 0 °C (over 6 h). Then, the reaction is quenched with an aqueous buffer (pH 2.6), and the mixture is extracted with ether, dried over sodium sulfate, concentrated, and chromatographed on deactivated silica gel.

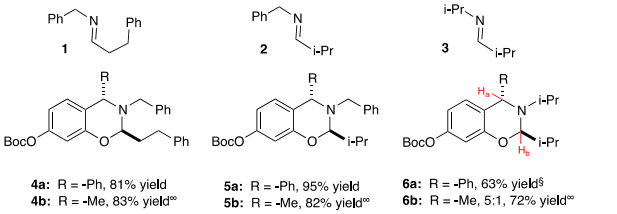


Figure 1. Class I imines. Yields estimated using CH_2Br_2 as a ^{1}H NMR standard. ∞NOE analysis, isolated yields 2−10% lower. §2 equiv of imine.

sequence outlined above, we were able to obtain the corresponding benzoxazines **4**−**6** in isolated yields ranging from 61 to 94%. Yields for unpurified adducts (63−95%), as computed by ^{1}H NMR comparison to a standard, were 2−10% higher than their respective isolated yields. Indeed, in our opinion, the former measurements were much more useful for interpreting structural and electronic effects on a reaction's outcome, whereas isolated yields revealed adduct stability.

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Both compounds **4** and **5** were observed to form as a single diastereomer as determined by ^{1}H NMR (presumably >30:1).[11] Subsequent NOE experiments established that the major stereoisomer possessed a *trans* configuration regarding the R and R^1 substituents.[11] Only bis-isopropyl adduct **6b** displayed a small amount of the corresponding *cis* isomer (**6b**, 5:1 *trans*:*cis*). These diastereomers displayed distinctive and useful ^{1}H NMR shifts for their corresponding H_A and H_B protons enabling rapid assignment ($\Delta\delta$ for H_A + 0.15 ppm for *trans*:*cis*) and ($\Delta\delta$ for H_B − 0.04 ppm for *trans*:*cis*).

Next, we examined the N-arylated imines **7** and **8**[12] (Figure 2). The respective benzoxazines **9** and **10** were again observed

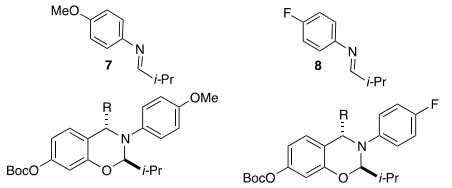

Figure 2. Class II imines. Yields estimated using CH_2Br_2 as an ^{1}H NMR standard. ∞NOE analysis. §2 equiv of imine.

to form as a single diastereomer assumed to be >30:1 by ^{1}H NMR. These formed in amounts slightly smaller than those observed for the prior examples shown in Figure 1. Electron-donating and -withdrawing groups on the *N*-aryl portion of the imine had little effect on reaction outcomes. The *trans* stereochemical arrangement of the R and R^1 substituents was again deduced by NOE analysis and coupling data. Refluxing compound **9b** in deuterated chloroform was found to degrade the diastereomeric ratio (from >30:1 to 1:1 *trans*:*cis*). Diastereomers again displayed different ^{1}H NMR shifts for their corresponding H_A and H_B protons that facilitated assignment ($\Delta\delta$ for H_A + 0.60 ppm for *trans*:*cis*) and ($\Delta\delta$ for H_B − 0.20 ppm for *trans*:*cis*). However, because these imine adducts proved to be unstable toward chromatography, we were unable to purify them further. Nevertheless, these products proved to be sufficiently pure for NMR characterization.

Bis-arylated class III imines **11**−**13**,[13] in which both the carbon and the nitrogen atoms were arylated, led to disappointing results (Figure 3). We estimated that 15−31%

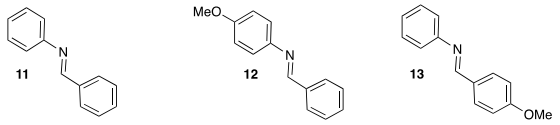

Figure 3. Class III imines, unreactive and adducts very unstable.

of the corresponding benzoxazine adducts had formed from our NMR analyses of their respective reaction mixtures. However, these adducts proved to be even more unstable than the class II adducts described above (Figure 2), and unfortunately, we were unable to thoroughly characterize and identify the products.

Next, we examined imines **14**−**22**, which displayed assorted aliphatic groups on the nitrogen atom and various aryl substituents on the carbon atom of their respective imines (Figure 4). Almost all of the corresponding benzoxazine products **23**−**31** formed in reasonable yields. While these

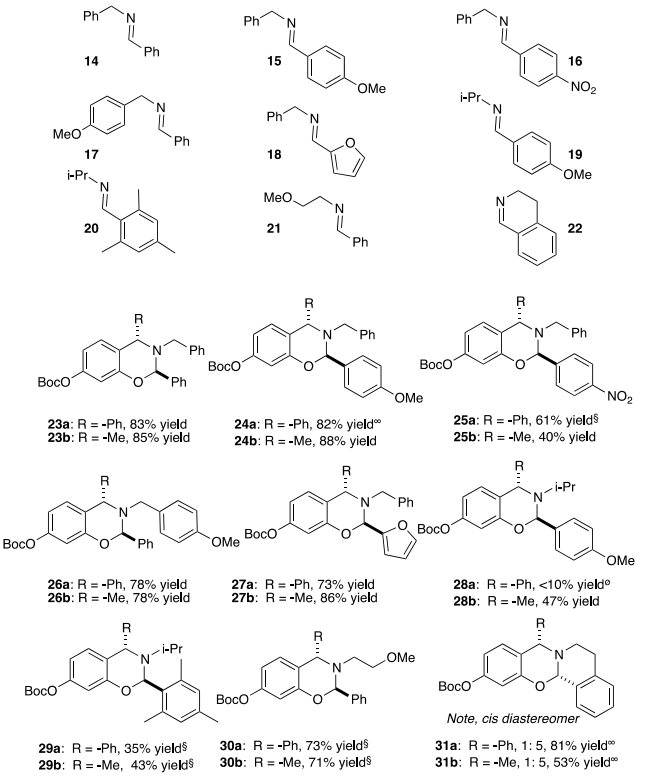

Figure 4. Class IV imines. Average yields estimated using CH_2Br_2 as a ^{1}H NMR standard in three or four runs, isolated yields 2−15% lower. ∞NOE analysis. §2 equiv of imine. **23b** previously prepared by us as shown in ref 6d.

adducts were more difficult to purify than those in Figure 1, they proved to be more chromatographically stable than those found in Figure 2. The *trans* diastereomer was again produced exclusively in nearly all of the cases (>30:1). Nitro-substituted imine **16** participated in the reaction, though the use of 2 equiv improved the adduct yield. Results for imines **14** and **17** indicated to us that inductive electronic effects in the aliphatic portion of the imine had little effect, as the yields for adducts **23** and **26** were similar. On the other hand, steric encumbrance in the aliphatic portion of the imine, chiefly when near the nitrogen atom, as in isopropyl imines **19** and **20**, was found to severely impede formation of products **28** and **29** with the mesityl derivative providing no improvement.[14] The *Z*-configured cyclic imine **22** afforded the *cis* diastereomer in a 1:5 ratio for both phenyl adduct **31a** and methyl adduct **31b** as established by NOE analysis and coupling data ($\Delta\delta$ for H_A + 0.10 ppm for *trans*:*cis*) and ($\Delta\delta$ for H_B + 0.05 ppm for *trans*:*cis*). We note that others, who have reported structures resembling compound **31** constructed through orthogonal procedures involving oxidation of the corresponding 2-[3,4-dihydroisoquinolin-2-(1*H*)-yl]phenol, may have mistakenly assigned these adducts as their corresponding *trans* isomers.[16]

We were curious to determine if our one-step kinetic *o*-QM method compared favorably with traditional thermodynamic procedures, whereby a benzylic amine is first synthesized from an aryl ketone by reductive amination and then treated with the appropriate aldehyde to yield similar benzoxazines (Scheme 2). This fairly mild thermodynamic protocol is reported to generally favor the *trans* diastereomer as the major isomer, just as our kinetic *o*-QM method had.[11] However, this thermodynamic process cannot access structures resembling

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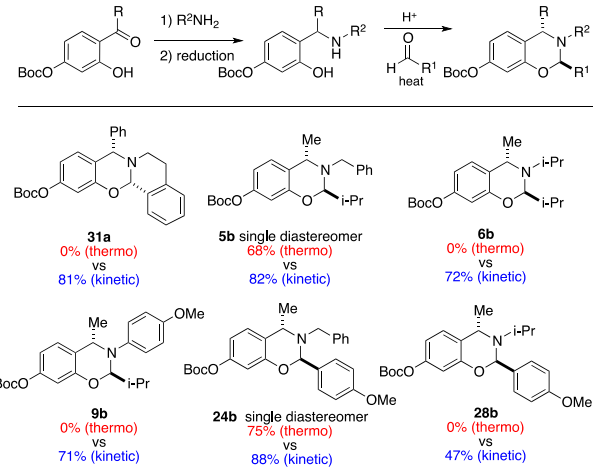
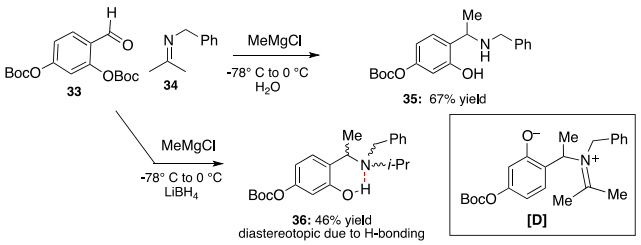
Scheme 2. Preparation of Prior Adducts Using the Multistep Thermodynamic Process and Comparison with Our One-Pot Kinetic Method



tetracycle **31**, because introduction of piperidine followed by reduction affords a tertiary amine, and as such, it cannot participate in formation of the corresponding benzoxazine. In our hands, the traditional thermodynamic process afforded adducts **5b** and **24b** with selectivity identical to that from our kinetic method albeit in lower yields, 68% and 75%, respectively. However, in our hands, the thermodynamic protocol failed to yield adducts **6b** and **28b**. We suspect the steric encumbrance of the isopropyl residue thwarts adduct formation in these examples. We were also surprised by our inability to prepare compound **9b** using a thermodynamic process. However, an exhaustive literature search reveals no examples of 3-*N*-arylated benzo-[1,3]-oxazines displaying substituents at both their 2 and 4 positions being prepared in this manner; only adducts substituted at one position or the other were prepared. This suggests that stronger steric effects are operating among N-arylated systems.

Next, we assessed the reaction of trisubstituted aliphatic imine **34** in reactions with our two *o*-QMs (Scheme 3).

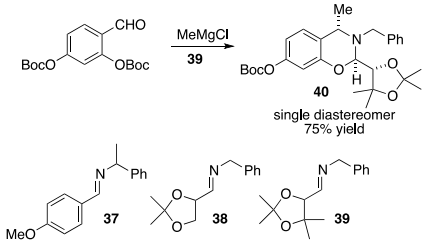
Scheme 3. Outcomes with Trisubstituted Cyclic Imines



Application of phenyl magnesium chloride to aldehyde **33** in the presence of imine **34** failed to afford anything identifiable. However, when the reaction was initiated with methyl magnesium chloride, benzylic amine **35** was cleanly formed upon aqueous workup. We believe these varying outcomes can be attributed to the more reactive *β*-methylated *o*-QM, and the more sterically encumbered nature of intermediate [**D**], which foiled cyclization. Our thinking was also supported by the sequential addition of lithium tetraborohydride to the reaction mixture, prior to aqueous workup, which resulted in benzylic tertiary amine **36** as a 1:1 mixture of diastereomers.[15]

Finally, we decided to challenge these *o*-QM intermediates with various chiral imines in the hope of observing diastereoselective outcomes (Scheme 4). Imines **37**−**39** were

Scheme 4. Diastereoselective Reactions Achieved



separately prepared and independently deployed in combination with methyl Grignard reagent. The first two imines underwent reaction but afforded poor selectivity (1:1 and 2.5:1 ratios, respectively). However, imine **39** led to desired benzoxazine adduct **40** as a single diastereomer in a respectable 75% isolated yield. X-ray analysis confirmed the relative structure to be that which is shown.[17]

In conclusion, we have developed a straightforward one-pot method that delivers an assortment of 3,4-dihydro-2*H*-[1,3]-benzoxazines. While this reaction may appear to be an inverse demand [4+2] cycloaddition, we believe it instead to be a 1,4-conjugate addition that results in a carbon-functionalized iminium species that then undergoes phenolate cyclization. This notion is supported by the following evidence. First, the reaction proves to be diastereoselective for *trans* adducts, even in the absence of secondary orbital effects as shown by bis-aliphatic examples [Figure 1 (**1**−**3**)]. Second, both nitrogen-arylated (Figure 2) and carbon-arylated (Figure 4) *E*-imines afford *trans* adducts; these different imine classes should have favored dissimilar diastereomers as their secondary orbital effects work in opposite directions. Third, in the case of a trisubstituted imine, we are able to selectively hydrolyze or reduce intermediate [**D**] before cyclization (Scheme 3). Lastly, our mechanistic rationale of a stepwise process led us to design imine **39**, which has proven to be very diastereoselective in this reaction. It is our assertion that this method provides a greater range and scope compared to those of prior methods for constructing this motif. Our studies further show that this method can deliver very encumbered systems that cannot be prepared by current thermodynamic processes. Lastly, our findings provide a road map for implementation of this method in future enantioselective applications, which we believe are needed for privileged benzylic amines of medicinal value.[18]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02655.

Experimental procedures, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1936973 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cam-

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Notes

The authors declare no competing financial interest.

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