Quinone-catalyzed oxidative deformylation: synthesis of imines from amino alcohols

Xinyun Liu, Johnny H. Phan, Benjamin J. Haugeberg, Shrikant S. Londhe and Michael D. Clift*

Abstract
A new method for imine synthesis by way of quinone-catalyzed oxidative deformylation of 1,2-amino alcohols is reported. A wide range of readily accessible amino alcohols and primary amines can be reacted to provide N-protected imine products. The methodology presented provides a novel organocatalytic approach for imine synthesis and demonstrates the synthetic versatility of quinone-catalyzed oxidative C–C bond cleavage.

Introduction
Imines are extremely versatile intermediates in organic chemistry [1-3]. Consequently, many synthetic methods have been developed for the preparation of imines (Scheme 1). The condensation of an amine with an aldehyde or ketone is the oldest and most commonly employed method for imine synthesis [4]. More recently, the catalytic dehydrogenation of amines mediated by metal and organic catalysts has begun to emerge as an alternative approach for the preparation of imines [5,6]. The majority of these methods involve cleavage of a C–H bond at the α-position of an amine substrate [7-28]. Methods that deliver imines through amine α-C–C bond cleavage are far less common [29-32] despite the fact that these methods employ renewable resources, such as amino acids and their derivatives, as starting materials. In fact, only a few reports describing the oxidative deformylation of amino alcohols have been published [33-35], and in all of these reports stoichiometric oxidants, such as NaIO₄ and Pb(OAc)₄, must be employed to enable the desired transformations. Given that 1,2-amino alcohols are readily accessible from feedstock chemicals such as styrenes [36-38] and amino acids [39], the development of a new methodology to transform these materials into high-value imine products under catalytic conditions has the potential to be broadly useful. Herein, we report a new method that utilizes quinone catalysis to enable the synthesis of imines via oxidative deformylation of amino alcohols.

Our group has recently reported the quinone-catalyzed decarboxylative homologation of α-amino acids [32], which
Scheme 1: Established methods for the preparation of imines vs this work.

demonstrated for the first time that quinone organocatalysts can be utilized to enable oxidative C–C bond cleavage to provide versatile imine intermediates. To further exploit the utility of this chemistry, we sought to develop a new method for the preparation of a wide range of imine products through the quinone-catalyzed deformylation of 1,2-amino alcohols. Such a transformation would not only facilitate rapid access to a variety of N-protected imines, but would also provide a novel approach for utilizing feedstock chemicals for the preparation of these valuable synthetic intermediates.

We envisioned a process wherein a 1,2-amino alcohol 1 would undergo condensation with an appropriate quinone catalyst 2 to deliver iminoquinone 3 (Scheme 2). Deformylation of 3 would

Scheme 2: Proposed catalytic cycle for quinone-catalyzed deformylation.
generate N-arylimine 4. Subsequent transamination with amine 6 would provide the desired imine product 7 and a reduced form of the catalyst 5, which would be expected to undergo oxidative turnover through one of two possible mechanisms (i.e., $5 \rightarrow 3$ or $5 \rightarrow 2$).

### Results and Discussion

With this plan in mind, we first explored the ability of several quinone catalysts to promote the dehydroxylation of 2-phenylglycinol (1a) to deliver N-PMP imine 7a (Table 1). We selected quinone catalysts (2a–c) that have previously been utilized in amine oxidation reactions [21,32,40,41], and began with reaction conditions similar to those developed for our quinone-catalyzed oxidative decarboxylation chemistry [32]. To our delight, the desired dehydroxylation product 7a was formed in 63% yield when catalyst 2a was employed (Table 1, entry 1). Quinone 2b failed to deliver imine 7a (Table 1, entry 2), but commercially available quinone 2c provided 7a in a promising 59% yield (Table 1, entry 3). Next, we examined the effect of base on the reaction using quinone 2c as the catalyst (Table 1, entries 4–7). Unfortunately, no improvement in reaction efficiency was observed when different bases were employed (Table 1, entries 4–6, 0–55% yield); however, exclusion of the base provided imine 7a in good yield (Table 1, entry 7, 85%). Decreasing the loading of catalyst 2c under these conditions reduced the yield of imine 7a (Table 1, entry 8, 64% yield), as did changing the identity of the catalyst (Table 1, entries 9 and 10, 62% and 0% respectively). Finally, we examined a range of solvents in an effort to further improve efficiency (Table 1, entries 11–17). No improvements in reaction efficiency were observed (Table 1, 0–72% yield), but it was noted that polar, protic solvents are critical in enabling the efficient dehydroxylation of phenylglycinol.

With optimized conditions in hand, we next explored the scope of this methodology by employing a range of 1,2-amino alcohol substrates 1 (Table 2). As reported in Table 1, the reaction involving phenylglycinol gave the desired N-PMP imine 7a in 85% yield (Table 2, entry 1). ortho-Substitution of the arene is reasonably well-tolerated, as 2-methylphenylglycinol (1b) and 2-chlorophenylglycinol (1c) delivered the corresponding imines in 68% yield (Table 2, entries 2 and 3). The meta-fluoro derivative provided imine 7d in 60% yield (Table 2, entry 4). Electronic effects were studied by examining a series of para-substituted phenylglycinol derivatives (Table 2, entries 5–9). Both electron-donating and electron-withdrawing substituents were tolerated, but no obvious trends in the reactivity patterns were observed (47–77% yield). Thiophenyl amino alcohol 1j was also subjected to the optimized conditions and the corresponding imine 7j was formed in 47% yield (Table 2, entry 10). Unfortunately, aliphatic 1,2-amino alcohols, such as valinol (1k), failed to undergo dehydroxylation under the current conditions (Table 2, entry 11).

Next, we investigated the use of various amine reaction partners 6 to access a variety of imine products 7 from phenylglycinol (1a, Table 3). The reaction with aniline (6a, Table 3, entry 2, 68% yield) showed reduced reaction efficiency compared to that with para-anisidine (6a, Table 3, entry 1, 85% yield). When para-fluoroaniline (6m) was employed as the reaction partner, imine 7m was produced in a 77% yield (Table 3, entry 3). α-Branch amines are effective reaction partners, providing the corresponding imines 7n–p in modest yields (Table 3, entries 4–6, 42–66% yield). From these results, it can be concluded that increasing the steric bulk at the α-position of the

| Entry | Catalyst | Solvent | Base | Yield [%]| |
|-------|----------|---------|------|---------|---|
| 1     | 2a       | EtOH    | Et3N | 63      | |
| 2     | 2b       | EtOH    | Et3N | 0       | |
| 3     | 2c       | EtOH    | Et3N | 59      | |
| 4     | 2c       | EtOH    | DABCO| 55      | |
| 5     | 2c       | EtOH    | DBU  | 0       | |
| 6     | 2c       | EtOH    | K2CO3| 17      | |
| 7     | 2c       | EtOH    | none | 85      | |
| 8b    | 2c       | EtOH    | none | 64      | |
| 9     | 2a       | EtOH    | none | 62      | |
| 10    | 2b       | EtOH    | none | 0       | |
| 11    | 2c       | iPrOH   | none | 72      | |
| 12    | 2c       | H2O     | none | 47      | |
| 13    | 2c       | MeCN    | none | 28      | |
| 14    | 2c       | DMSO    | none | 13      | |
| 15c   | 2c       | THF     | none | 0       | |
| 16    | 2c       | PhMe    | none | 11      | |
| 17    | 2c       | CHCl3   | none | 3       | |

Table 1: Optimization of quinone-catalyzed oxidative dehydroxylation of phenylglycinol (1a).

---

**Table 1:** Optimization of quinone-catalyzed oxidative dehydroxylation of phenylglycinol (1a).

- **Entry**
- **Catalyst**
- **Solvent**
- **Base**
- **Yield [%]**

1. **2a** EtOH Et3N 63
2. **2b** EtOH Et3N 0
3. **2c** EtOH Et3N 59
4. **2c** EtOH DABCO 55
5. **2c** EtOH DBU 0
6. **2c** EtOH K2CO3 17
7. **2c** EtOH none 85
8b **2c** EtOH none 64
9. **2a** EtOH none 62
10. **2b** EtOH none 0
11. **2c** iPrOH none 72
12. **2c** H2O none 47
13. **2c** MeCN none 28
14. **2c** DMSO none 13
15c **2c** THF none 0
16. **2c** PhMe none 11
17. **2c** CHCl3 none 3

* Determined by 1H NMR using benzyl ether as an internal standard.
*10 mol% quinone was used.
*Reaction carried out at 50°C.
Table 2: Quinone-catalyzed oxidative deformylation of various amino alcohols.

| Entry | Amino alcohol 1 | Product 7 | Yield [%]a |
|-------|----------------|-----------|------------|
| 1     | 1a, R = H      | 7a, R = H | 85         |
| 2     | 1b, R = Me     | 7b, R = Me| 68         |
| 3     | 1c, R = Cl     | 7c, R = Cl| 68         |
| 4     | 1d             | 7d        | 60         |
| 5     | 1e, R = Me     | 7e, R = Me| 68         |
| 6     | 1f, R = OMe    | 7f, R = OMe| 77         |
| 7     | 1g, R = Cl     | 7g, R = Cl| 66         |
| 8     | 1h, R = F      | 7h, R = F | 54         |
| 9     | 1i, R = CF₃    | 7i, R = CF₃| 47         |
| 10    | 1j             | 7j        | 47         |
| 11    | 1k             | 7k        | 0          |

aDetermined by 1H NMR using benzyl ether as an internal standard (average of two replicates).

amine results in decreased reaction efficiency. Phenethylamine (6q) provided only a 17% yield of the corresponding imine (7q, Table 3, entry 7), potentially due to its increased nucleophilicity, which may result in inhibition of catalysis via condensation with quinone 2c. We also tested several electron deficient amides (6r–t) in these reactions (Table 3, entries 8–10). Unfortunately, only sulfinamide 6t provided the desired imine 7t (Table 3, entry 10, 22% yield). In all three cases, a significant amount of benzaldehyde was observed, indicating that electron deficient primary amides (such as 6r–t) are either incapable of promoting transimination, or the resulting imines (7r–t) are hydrolyzed under the current reaction conditions. Notably, imines 7n [42-45] and 7t [46-48] are useful imines for diastereoselective 1,2-addition reactions.

Following these substrate scope studies, we next examined the quinone-catalyzed C–C bond cleavage of analogous substrates (Scheme 3). First, we tested isomeric amino alcohol iso-1a, which provided imine 7a in a yield comparable to that observed when phenylglycinol was used as a substrate. Notably, the mechanism of this reaction likely involves initial formation of benzaldehyde, followed by condensation with para-anisidine,
Table 3: Quinone-catalyzed oxidative deformylation using various amine reaction partners.

| Entry | Amine 6 | Product 7 | Yield [%]a |
|-------|---------|-----------|------------|
| 1     | 6a, R = OMe | 7a, R = OMe | 85         |
| 2     | 6l, R = H   | 7l, R = H   | 68         |
| 3     | 6m, R = F   | 7m, R = F   | 77         |
| 4     | 6n         | 7n         | 66         |
| 5     | 6o         | 7o         | 42         |
| 6     | 6p         | 7p         | 56         |
| 7     | 6q         | 7q         | 17         |
| 8     | 6r         | 7r         | 0          |
| 9     | 6s         | 7s         | 0          |
| 10    | 6t         | 7t         | 22         |

aDetermined by 1H NMR using benzyl ether as an internal standard (average of two replicates).

To deliver imine 7a. Vicinal diamine 8 was also a compatible substrate, delivering imine 7a in 63% yield. Finally, we subjected diol 9 to the optimal reaction conditions; no product was observed, indicating that condensation between the substrate and catalyst to form an iminoquinone intermediate is likely required for productive reactivity.
Scheme 3: Studies of quinone-catalyzed C–C bond cleavage in related substrates.

To demonstrate the synthetic utility of this methodology, we performed a sequential oxidative deformylation/Mukaiyama–Mannich addition under our previously reported conditions for decarboxylative amino acid homologation (Scheme 4) [32]. In this reaction sequence, (thio)silyl ketene acetal 10 was united with 2-phenylglycinol and para-anisidine in a two-step, one-pot process to provide β-amino acid derivative 11 in a 60% yield. The overall reaction sequence provides a unique method for the production of the high-value β-amino acid derivatives [49,50] from 1,2-amino alcohols.

Scheme 4: Sequential oxidative deformylation/Mukaiyama–Mannich addition using phenylglycinol.

Conclusion

In conclusion, we have developed a novel method for the synthesis of imines from 1,2-amino alcohols. This chemistry features an unprecedented application of quinone organocatalysis to enable oxidative deformylation under aerobic conditions. Future work will involve mechanistic studies and the development of new catalysts to expand the scope of this chemistry.

Supporting Information

Supporting Information File 1
Experimental procedures, compound characterization data, and copies of 1H and 13C NMR spectra. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-13-282-S1.pdf]

Acknowledgements

Financial support from the NSF (EPS-0993806) and The University of Kansas is gratefully acknowledged. Additional support for this work was provided by the National Institutes of Health Graduate Training Program in Dynamic Aspects of Chemical Biology Grant T32 GM08545 from NIGMS (to B. J. H.). Support for NMR instrumentation was provided by NIH Shared Instrumentation Grants No. S10OD016369 and S10RR024664, and NSF Major Research Instrumentation Grant No. 0320648.

ORCID® iDs

Michael D. Clift - https://orcid.org/0000-0001-6441-9802

References

1. Kobayashi, S.; Ishitani, H. Chem. Rev. 1999, 99, 1069–1094. doi:10.1021/cr980414z
2. Adams, J. P. J. Chem. Soc., Perkin Trans. 1 2000, 125–139. doi:10.1039/a808142e
3. Kobayashi, S.; Mori, Y.; Fossey, J. S.; Saltar, M. M. Chem. Rev. 2011, 111, 2626–2704. doi:10.1021/cr100204f
4. Schiff, H. Justus Liebigs Ann. Chem. 1864, 131, 118–119. doi:10.1002/jlac.18641310113
5. Patil, R. D.; Adimurthy, S. Asian J. Org. Chem. 2013, 2, 726–744. doi:10.1002/ajoc.201300012
6. Chen, B.; Wang, L.; Gao, S. ACS Catal. 2015, 5, 5851–5876. doi:10.1021/acscatal.5b01479
7. Ell, A. H.; Samec, J. S. M.; Brasse, C.; Bäckvall, J.-E. Chem. Commun. 2002, 1144–1145. doi:10.1039/b202117j
8. Murahashi, S.-i.; Okano, Y.; Sato, H.; Nakaue, T.; Komiy, N. Synlett 2007, 1675–1678. doi:10.1055/s-2007-94051
9. Zhu, B.; Angeloci, R. J. Chem. Commun. 2007, 21, 2157–2159. doi:10.1039/b705955e
10. Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. Org. Lett. 2009, 11, 4568–4571. doi:10.1021/ol901816b
11. Allen, J. M.; Lambert, T. H. J. Am. Chem. Soc. 2011, 133, 1260–1262. doi:10.1021/ja109617y
12. Patil, R. D.; Adimurthy, S. Adv. Synth. Catal. 2011, 353, 1695–1700. doi:10.1002/adsc.201100100
13. Prades, A.; Peris, E.; Albrech, M. Organometallics 2011, 30, 1162–1167. doi:10.1021/o101146y
