Lewis acid-catalyzed redox-neutral amination of 2-(3-pyrroline-1-yl)benzaldehydes via intramolecular [1,5]-hydride shift/isomerization reaction

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Abstract
Lewis acid-catalyzed redox-neutral amination of 2-(3-pyrroline-1-yl)benzaldehydes via intramolecular [1,5]-hydride shift/isomerization reaction has been realized, using the inherent reducing power of 3-pyrrolines. A series of N-arylpyrrole containing amines are obtained in high yields.

Introduction
The direct and selective functionalization of the inactive C(sp^3)–H bond constitute an economically attractive strategy for organic syntheses [1-10]. Until now, a number of transition metals can be used for the activation of C–H bonds [11-18]. Among the reported transformations, intramolecular redox processes based on direct functionalization of C(sp^3)–H bonds linking with α heteroatoms are useful for the synthesis of structurally diverse amines and ether derivatives [19-30]. On the other hand, compounds containing the N-arylpyrrole moiety serve as important building blocks for the synthesis of various complex molecules and exhibit a larger number of biological effects [31-33].

In 2009, Tunge's group disclosed that N-alkylpyrroles could be formed via a redox isomerization reaction (Scheme 1, reaction 1) [34-36]. Moreover, we recently realized a Lewis acid-catalyzed intramolecular redox reaction using an aldehyde group as the H-shift acceptor to afford (2-(1H-pyrrol-1-yl)phenyl)methanol (Scheme 1, reaction 2) [37]. As part of our interest in expanding the inherent reducing power of 3-pyrrolines, we
In our initial investigation, aldehyde 1a and dibenzylamine (2a) were chosen as the model reaction substrates. In the presence of 10 mol % PhCOOH, the reaction of 1a with 2a in DCE at rt for 24 h gave the trisubstituted amine 3a in 50% yield (entry 1, Table 1). Encouraged by this result, we screened readily available Brønsted and Lewis acids (Table 1). Except the Lewis acid AlCl3, other strong Brønsted acids and common Lewis acids could be used as the catalyst in this reaction, affording the desired products in excellent yields (entries 2–8, Table 1). Considering that ZnCl2 is cheaper and easy to handle, it was chosen as the catalyst for further optimization reactions. Furthermore, various solvents such as DCE, CH2Cl2, CHCl3, toluene, CH3CN and THF were examined. All the solvents afforded the desired product in satisfactory yields (entries 8–13, Table 1). Subsequently, the loading of dibenzylamine (2a) and the catalyst was examined. The results show that decreasing the amount of 2a to 1.2 equiv and ZnCl2 to 5 mol % did not affect the yield (entry 16, Table 1).

Finally, we established the optimized reaction conditions using ZnCl2 (5 mol %) as the catalyst and CH2Cl2 as the solvent, and running the reaction at room temperature or under reflux.

Under the optimized conditions, the results of the amination reaction of 2a with various 2-(3-pyrroline-1-yl)benzaldehydes 1 are shown in Scheme 2. The reactions proceeded smoothly to give the corresponding N-arylpize amines 3 in good to excellent yields (71–97% yields). Notably, the substitution of the benzene ring had little effect on the reaction since both electron-donating (3b, 3c) and electron-withdrawing groups (3d–i) were tolerated in the reaction.

Next, the scope of amines 2 was explored. The results are summarized in Scheme 3. Reaction of secondary amines possessing aryl–aryl, alkyl–alkyl and aryl–alkyl moieties yield the corresponding N-arylpize amines 3j–p in high yields (81–94% yields). Various cyclic secondary amines were also good substrates for this reaction, affording the desired products (3q, 3r, 3s) in good to high yields (77–98% yields) with DCE as the solvent under reflux conditions. The reaction with indoline, tetrahydroquinoline, and tetrahydroisoquinoline could also be realized to give products 3t, 3u, and 3v in good yields (76–88% yields), respectively. Finally, primary amines were examined. The reaction with excess benzylamine (5.0 equiv) in the presence of Zn(OTf)2 as the catalyst afforded the desired product...
Table 1: Optimization of the redox-neutral amination reaction.\(^{a}\)

| entry | catalyst          | X  | Y   | solvent | yield (%)\(^{b}\) |
|-------|-------------------|----|-----|---------|------------------|
| 1     | PhCOOH            | 1.5| 10  | DCE     | 50               |
| 2     | CF\(_3\)COOH      | 1.5| 10  | DCE     | 87               |
| 3     | p-TsOHH\(_2\)O    | 1.5| 10  | DCE     | 90               |
| 4     | Sc(OTf)\(_3\)     | 1.5| 10  | DCE     | 94               |
| 5     | Cu(OTf)\(_2\)     | 1.5| 10  | DCE     | 94               |
| 6     | Zn(OTf)\(_2\)     | 1.5| 10  | DCE     | 97               |
| 7     | AlCl\(_3\)        | 1.5| 10  | DCE     | 76               |
| 8     | ZnCl\(_2\)        | 1.5| 10  | DCE     | 95               |
| 9     | ZnCl\(_2\)        | 1.5| 10  | CH\(_2\)Cl\(_2\)  | 97               |
| 10    | ZnCl\(_2\)        | 1.5| 10  | CHCl\(_3\)    | 95               |
| 11    | ZnCl\(_2\)        | 1.5| 10  | toluene  | 94               |
| 12    | ZnCl\(_2\)        | 1.5| 10  | CH\(_2\)CN    | 96               |
| 13    | ZnCl\(_2\)        | 1.5| 10  | THF      | 71               |
| 14    | ZnCl\(_2\)        | 1.2| 10  | CH\(_2\)Cl\(_2\) | 97               |
| 15    | ZnCl\(_2\)        | 1.0| 10  | CH\(_2\)Cl\(_2\) | 93               |
| 16    | ZnCl\(_2\)        | 1.2| 5   | CH\(_2\)Cl\(_2\) | 95               |
| 17    | ZnCl\(_2\)        | 1.2| 2   | CH\(_2\)Cl\(_2\) | 91               |

\(^{a}\)1a (0.5 mmol), 2a (X equiv), catalyst (Y mol %), solvent (5 mL), room temperature, 24 h. \(^{b}\)Isolated yield.

Scheme 2: Substrate scope of aryl aldehydes 1. Reagents and conditions: 1 (0.3 mmol), 2a (1.2 equiv), ZnCl\(_2\) (5 mol %), CH\(_2\)Cl\(_2\) (3.0 mL). \(^{a}\)Room temperature. \(^{b}\)DCE, reflux.
Scheme 3: Substrate scope of amines 2. Reagents and conditions: 1a (0.5 mmol), 2 (1.2 equiv), ZnCl₂ (5 mol %), CH₂Cl₂ (5.0 mL), rt. Reflux. Zn(OTf)₂ (5 mol %), n-butyamine (5.0 equiv), DCE, reflux. p-TsOH·H₂O (5 mol %), PhNH₂ (5.0 equiv), CH₂Cl₂, rt.

3w in 98% yield. However, when n-BuNH₂ was used as the substrate, the yield was reduced to 33% even under high temperature. Notably, according to the ¹H NMR spectrum of the crude product, the reaction with phenylamine using Zn(OTf)₂ as the catalyst afforded only the corresponding imine product, indicating that the [1,5]-hydride shift/isomerization reaction did not occur. To our delight, this reaction proceeded smoothly at room temperature to give the desired N-arylpyrrole amine 3y in high yield (99% yield) when p-TsOH·H₂O was used as the catalyst instead of Zn(OTf)₂.

Conclusion
In conclusion, Lewis acid-catalyzed redox-neutral amination of 2-(3-pyrroline-1-yl)benzaldehydes via intramolecular [1,5]-hydride shift/isomerization reaction has been realized. Various types of amines and 2-(3-pyrroline-1-yl)benzaldehydes are well tolerated in this reaction, affording the corresponding N-arylpyrrolamines in good to high yields. Further studies on synthetic applications of [1,5]-hydride shift/isomerization reactions that utilize the inherent reducing power of 3-pyrrolines are underway in our laboratory.

Experimental
General procedure for the preparation of N-arylpyrroles 3: A mixture of benzaldehyde 1 (0.3–0.5 mmol), amine 2 (1.2 equiv) and ZnCl₂ (5 mol %) were stirred in dichloromethane or DCE (5.0 mL) at room temperature or reflux and monitored by TLC. After completion of the reaction (about...
24 h), the solvent was removed by evaporation and the residue was purified by flash column chromatography on silica gel to give N-arylpyrrole 3.

Supporting Information

Supporting Information File 1
Experimental details, analytical data, and copies of the \(^1\)H and \(^{13}\)C NMR spectra of the final products.

[http://www.beilstein-journals.org/bjc/issue/ supplementary/1860-5397-10-306-S1.pdf]

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References

1. Godula, K.; Sames, D. Science 2006, 312, 67–72. doi:10.1126/science.114731
2. Bergman, R. G. Nature 2007, 446, 391–393. doi:10.1038/446391a
3. Alberico, D.; Scott, M. E.; Lautens, M. Chem. Rev. 2007, 107, 174–238. doi:10.1021/cr0509760
4. Davies, H. M. L.; Manning, J. R. Nature 2008, 451, 417–424. doi:10.1038/nature06465
5. Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. Angew. Chem., Int. Ed. 2009, 48, 5094–5115. doi:10.1002/anie.200806273
6. Jazzar, R.; Hilse, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. Chem. – Eur. J. 2010, 16, 2654–2672. doi:10.1002/chem.200902374
7. Lyons, T. W.; Sanford, M. S. Chem. Rev. 2010, 110, 1147–1169. doi:10.1021/cr900184e
8. Yu, J.-Q.; Shi, Z. Top. Curr. Chem. 2010, 292, 1–345. doi:10.1007/978-3-642-12356-6
9. Davies, H. M. L.; Du Bois, J.; Yu, J.-Q. Chem. Soc. Rev. 2011, 40, 1855–1856. doi:10.1039/C1CS10091b
10. Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. Acc. Chem. Res. 2012, 45, 826–839. doi:10.1021/ar200194b
11. Ackermann, L.; Vicente, R.; Kapdi, A. R. Angew. Chem., Int. Ed. 2009, 48, 9792–9826. doi:10.1002/anie.200902996
12. Seregin, I. V.; Gevorgyan, V. Chem. Soc. Rev. 2007, 36, 1173–1193. doi:10.1039/B606984N
13. Daugulis, O.; Do, H.-Q.; Shabashov, D. Acc. Chem. Res. 2009, 42, 1074–1086. doi:10.1021/ar900058
14. Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. Chem. Soc. Rev. 2011, 40, 5068–5083. doi:10.1039/C1CS15082k
15. Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. Angew. Chem., Int. Ed. 2012, 51, 10236–10254. doi:10.1002/anie.201202369
16. Collet, F.; Dodd, R. H.; Dauban, P. Chem. Commun. 2009, 5061–5074. doi:10.1039/b805820f
17. Arockiam, P. B.; Bruneau, C.; Dianne, P. H. Chem. Rev. 2012, 112, 5879–5918. doi:10.1021/cr300153j
18. Jordan-Hore, J. A.; Johansson, C. C. C.; Gulisas, M.; Beck, E. M.; Gaunt, M. J. J. Am. Chem. Soc. 2008, 130, 16184–16186. doi:10.1021/ja806543s
19. Tobisu, M.; Chatani, N. Angew. Chem., Int. Ed. 2006, 45, 1683–1684. doi:10.1002/anie.200503866
20. Pan, S. C. Beilstein J. Org. Chem. 2012, 8, 1374–1384. doi:10.3762/bjoc.8.159
21. Peng, B.; Maulide, N. Chem. – Eur. J. 2013, 19, 13274–13287. doi:10.1002/chem.201301522
22. Haibach, M. C.; Seidel, D. Angew. Chem., Int. Ed. 2014, 53, 5010–5036. doi:10.1002/anie.201306498
23. Verboom, W.; van Dijk, B. G.; Reinhoudt, D. N. Tetrahedron 1983, 24, 3923–3926. doi:10.1016/S0040-4020(00)84316-8
24. Zhang, C.; Murarka, S.; Seidel, D. J. Org. Chem. 2009, 74, 419–422. doi:10.1021/jo902325x
25. Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. Chem. Lett. 2009, 38, 524–525. doi:10.1246/cl.2009.524
26. Vadola, P. A.; Carrera, I.; Sames, D. J. Org. Chem. 2012, 77, 6689–6702. doi:10.1021/jo300685n
27. Mori, K.; Kawasaki, T.; Akiyama, T. Org. Lett. 2012, 14, 1436–1439. doi:10.1021/ol301808w
28. He, Y.-P.; Wu, H.; Chen, D.-F.; Yu, J.; Gong, L.-Z. Chem. – Eur. J. 2013, 19, 5232–5237. doi:10.1002/chem.201300052
29. Pastine, S. J.; Sames, D. Org. Lett. 2005, 7, 5429–5431. doi:10.1021/ol052283
30. Jurburg, I. D.; Peng, B.; Wöstefeld, E.; Wasserloos, M.; Maulide, N. Angew. Chem., Int. Ed. 2012, 51, 1950–1953. doi:10.1002/anie.201108639
31. Yan, R.-L.; Luo, J.; Wang, C.-X.; Ma, C.-W.; Huang, G.-S.; Liang, Y.-M. J. Org. Chem. 2010, 75, 5395–5397. doi:10.1021/jo10122k
32. Galliford, C. V.; Scheidt, K. A. J. Org. Chem. 2007, 72, 1811–1813. doi:10.1021/jo0624086
33. Jalal, S.; Sarkar, S.; Bera, K.; Malli, S.; Jana, U. Eur. J. Org. Chem. 2013, 4823–4828. doi:10.1021/jo30100172
34. Pahadi, N. K.; Paley, M.; Jana, R.; Waetzig, S. R.; Tunge, J. A. J. Am. Chem. Soc. 2009, 131, 16626–16627. doi:10.1021/ja907357g
35. Deb, I.; Das, D.; Seidel, D. Org. Lett. 2011, 13, 812–815. doi:10.1021/ol1031359
36. Ramakumar, K.; Tunge, J. A. Chem. Commun. 2014, 50, 13056–13058. doi:10.1039/C4CC06369D
37. Du, H.-J.; Zhen, L.; Wen, X.; Xu, Q.-L.; Sun, H. Org. Biomol. Chem. 2014, 12, 9716–9719. doi:10.1039/C4OB02009J

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