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COMMUNICATION

Visible light-induced intramolecular cyclization reactions of diamines: a new strategy to construct tetrahydroimidazoles†

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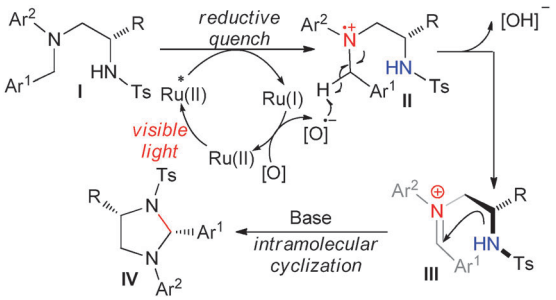
A new and efficient synthesis of highly substituted tetrahydroimidazole derivatives by means of visible light-induced intramolecular cyclization reactions has been described. This photoredox catalytic reaction exhibited high diastereoselectivity and afforded the desired products in good yields.

Recently, the use of the visible light to initiate organic reactions has attracted much attention[1] because of its natural abundance, ease of use, non-toxicity and potential applications.[2] For instance, [2 + 2] or [3 + 2] cycloaddition reactions and a tin-free reductive dehalogenation reaction, which are initiated by photoredox catalysts under visible light irradiation,[3] have been reported by the research groups of Yoon[4] and Stephenson,[5] respectively. Moreover, the highly reactive iminium intermediate, which can be generated from the oxidation of tertiary amines through photoredox catalysis, has also been successfully used for further functionalization.[6] Notably, MacMillan and co-workers disclosed an enantioselective alkylation of aldehydes by merging photoredox catalysis with organocatalysis.[7] These seminal investigations have shown the great potential of visible light photocatalysis in synthetic chemistry. However, to our knowledge, visible light-induced asymmetric reactions are still rare.

On the other hand, the tetrahydroimidazole moiety is a common structural subunit present in various natural products, many of which display a wide range of biological activities.[8] As a result, great efforts have been devoted to the development of a straightforward access to optically active tetrahydroimidazoles. An elegant method to prepare tetrahydroimidazoles is the condensation reaction of 1,2-diamine with aldehydes, although *in situ* removal of water is needed to increase the reaction efficiency.[9] Very recently, the Wu group disclosed a concise synthesis of tetrahydroimidazoles through 1,3-dipolar cycloadditions of azomethine ylides with fluorinated imines.[10] Despite these advances, the development of a strategically new route to highly substituted tetrahydroimidazoles in a stereoselective manner is desirable.



Scheme 1 Visible light induced the asymmetric synthesis of tetrahydroimidazole derivatives.

As part of our ongoing programme on the development of carbon- and heterocycle-oriented methodologies,[11] we envisioned that the enantiomerically pure substrate **I**, which was derived from commercially available natural amino acids, could be oxidized to iminium intermediate **III** in the presence of photoredox catalysts and O_2 under visible light irradiation. Followed by an intramolecular cyclization, the biologically important tetrahydroimidazole **IV** could be diastereoselectively obtained by the induction of the chirality of substrates (Scheme 1). In this communication, we describe the preliminary results of this study.

Our initial study began with the reaction of the enantiomerically pure diamine **1a** prepared from L-phenylananine in the presence of 5.0 mol% $Ru(bpy)_3Cl_2$ with O_2 under visible light irradiation. As highlighted in Table 1, the reaction media had a significant effect on the reaction efficiency (Table 1, entries 1–4). Some solvents, such as DMF and CH_3CN, which were widely used in photoredox catalytic reactions,[4,5] did not work well in this reaction (Table 1, entries 1 and 2). To our delight, the proposed cyclization reaction underwent smoothly when it was performed in ethanol or methanol albeit with fair diastereoselectivity (Table 1, entries 3 and 4). To further improve the reaction efficiency, we then examined the influence of a base on this process (Table 1, entries 5–10). Initial experiments revealed that the use of ^{t}BuOK gave optimal results (93% yield and 4 : 1 dr, Table 1, entry 10). Further optimization showed that the catalyst loading could be decreased to 1.0 mol% without a significant loss in the yield or diastereoselectivity (Table 1, entry 11).

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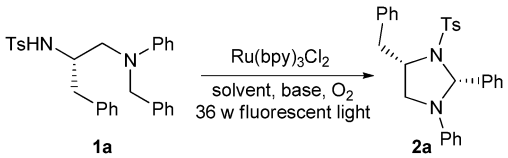
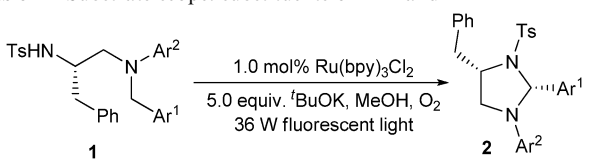
Table 1 Optimisation of reaction conditions[a]



Entry	Solvent	Base	Time/h	Yield[b] (%)	dr[c]
1	DMF	DBU	24	0	—
2	CH_3CN	DBU	10	27	nd[d]
3	EtOH	DBU	8	72	2 : 1
4	MeOH	DBU	8	89	3 : 1
5	MeOH	—	24	0	—
6	MeOH	TMG[g]	8	84	2 : 1
7	MeOH	Et_3N	24	23	nd
8	MeOH	K_2CO_3	16	93	1 : 1
9	MeOH	NaOH	9	84	2.5 : 1
10	MeOH	^{t}BuOK	9	93	4 : 1
11[e]	MeOH	^{t}BuOK	9	93	4 : 1
12[f]	MeOH	^{t}BuOK	48	92	10 : 1

[a] Unless otherwise specified, all reactions were carried out with **1a** (0.2 mmol), $Ru(bpy)_3Cl_2$ (5.0 mol%), base (5.0 equiv.) and O_2 in the solvent (4 mL) under visible light irradiation at RT. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude products. [d] nd = not determined. [e] 1.0 mol% $Ru(bpy)_3Cl_2$ was used. [f] After completion of reaction, DCM (1.0 mL) was added and stirring was continued for 48 h. [g] TMG = tetramethyl guanidine.

Table 2 Substrate scope: substituents on Ar^1 and Ar^2 [a]



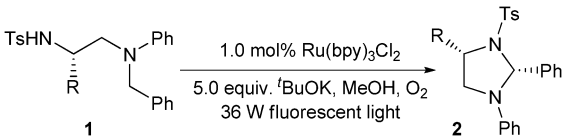
Entry	Ar^1	Ar^2	Product	Time[b]/h	Yield[c] (%)	dr[d]
1	C_6H_5	C_6H_5	**2a**	48	92	10 : 1
2	4-MeC_6H_4	C_6H_5	**2b**	48	93	> 19 : 1
3	4-$MeOC_6H_4$	C_6H_5	**2c**	48	90	> 19 : 1
4	2-$MeOC_6H_4$	C_6H_5	**2d**	48	92	> 19 : 1
5	4-ClC_6H_4	C_6H_5	**2e**	72	92	> 19 : 1
6	4-BrC_6H_4	C_6H_5	**2f**	48	92	8 : 1
7	C_6H_5	4-MeC_6H_4	**2g**	48	94	> 19 : 1
8	C_6H_5	4-$MeOC_6H_4$	**2h**	48	91	> 19 : 1
9	C_6H_5	4-ClC_6H_4	**2i**	72	94	> 19 : 1

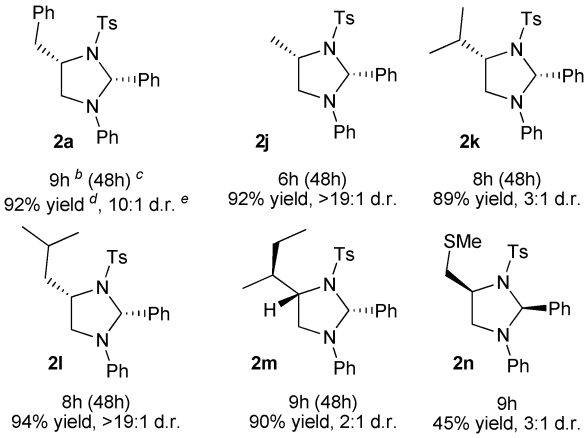
[a] All reactions were carried out with **1a** (0.2 mmol), $Ru(bpy)_3Cl_2$ (1.0 mol%), ^{t}BuOK (5.0 equiv.) and O_2 in MeOH (4 mL) under visible light irradiation at RT. [b] After completion of reaction, DCM (1.0 mL) was added and stirring was continued for the indicated time. [c] Isolated yield. [d] Determined by ^{1}H NMR.

Notably, prolonging the reaction time dramatically increased the diastereoselectivity of the reaction (Table 1, entry 12).

With the optimal reaction conditions in hand, the scope of substrates was explored. This visible light-induced cyclization reaction appeared to be quite tolerant with respect to structural variation of both aryl groups (Table 2). Incorporation of methyl, methoxyl, chloro and bromo substituents at the C(4)-position in Ar^1 or Ar^2 revealed that electronic modification of aromatic rings could be accomplished without a substantial loss of reaction efficiency (Table 2, entries 2–9). As shown in entries 3 and 4, significant latitude in the steric demands of the diamine (**1**) was possible (Ar^1 = 4-$MeOC_6H_4$ and 2-$MeOC_6H_4$, respectively). Attempts to carry out the reaction of the substrate with the alkyl group instead of Ar^1 or Ar^2 failed owing to its lower reactivity. Such problems remain to be further explored.

Table 3 Substrate scope: variation of substituent R[a]

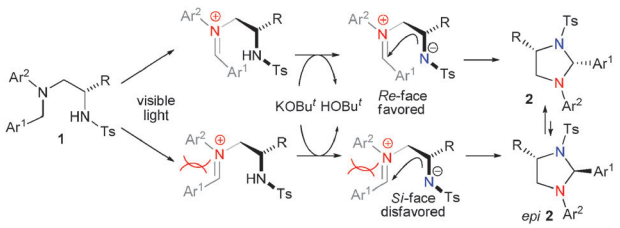




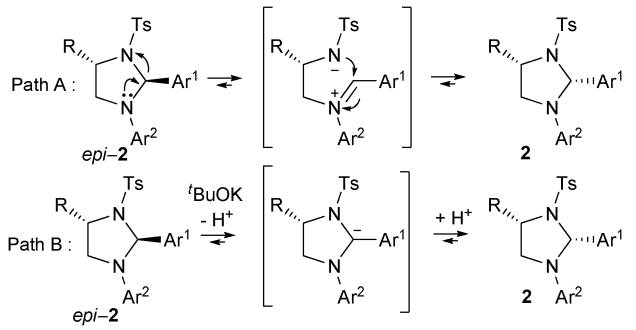
[a] All reactions were carried out with **1** (0.2 mmol), $Ru(bpy)_3Cl_2$ (1.0 mol%), ^{t}BuOK (5.0 equiv.) and O_2 in MeOH (4 mL) under visible light irradiation at RT. [b] Reaction time determined by TLC. [c] DCM (1.0 mL) was added and stirring was continued until 48 h. [d] Isolated yield. [e] Determined by ^{1}H NMR.

A variety of substituted 1,2-diamine derivatives can be successfully employed in this photoredox-initiated reaction (Table 3). For example, 1,2-diamines **1j** and **1l** prepared from L-alanine and L-leucine could afford the corresponding products **2j** and **2l** in high yields (92 and 94% yields, respectively) and excellent diastereoselectivities (> 19 : 1). The substrates **1k** and **1m** derived from L-valine and L-isoleucine generated products **2k** and **2m** in 89 and 90% isolated yields, respectively, but with relatively lower diastereoselectivities. Moreover, the heteroatom-substituted diamine **1n** was also tolerated in this process and it gave the corresponding tetrahydroimidazole **2n** in 45% yield with 3 : 1 dr.

The structures and the absolute (2*R*,4*S*)-configuration of **2a** have been unambiguously established by X-ray diffraction studies.[12] Based on our experimental results, a stereochemical course of this reaction was proposed as depicted in Scheme 2. The addition of the nitrogen anion to the iminium ion from



Scheme 2 Proposed stereochemical pathways.

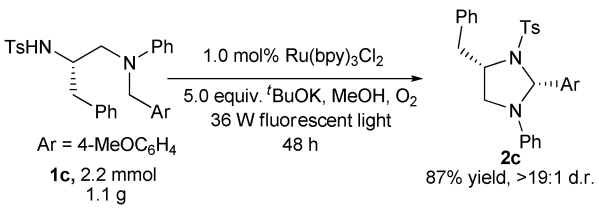


Scheme 3 Two pathways of the epimerization of the product.

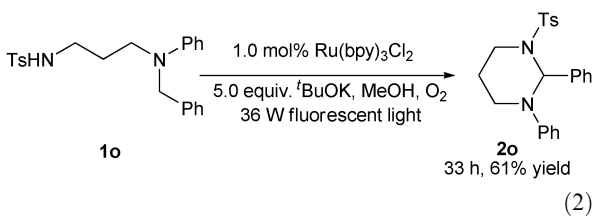
its *Re* is much more favorable than that to its *Si* face due to the steric repulsion. When the reaction time was prolonged, product *epi*-**2** could be converted into the thermodynamically more stable *cis* form under the reaction conditions.

Two pathways were proposed to explain the epimerization. In path A, *epi*-**2** could isomerize to **2** through the iminium ion intermediate with the assistance of MeOH or the ruthenium catalyst (Scheme 3). Alternatively, excess ^{t}BuOK in the reaction system might promote the epimerization through a deprotonation/diastereoselective protonation sequence (path B). To gain some insights into this process, a few control experiments were carried out. Treatment of **2c** (dr = 3 : 1) with MeOH/CH_2Cl_2 and $Ru(bpy)_3Cl_2$, respectively, for 48 h increased the dr to 9 : 1 in both cases, while the dr was dramatically improved to 13 : 1 in the presence of ^{t}BuOK (5 equiv.).[12] These results indicated that path B was more favorable although we could not rule out path A at the current stage.

To demonstrate the preparative utility of this methodology, the reaction of **1c** (1.1 g) was performed on a 2.2 mmol scale in the presence of 1 mol% of $Ru(bpy)_3Cl_2$ under our standard conditions, affording *cis*-**2c** in 87% yield with >19 : 1 dr (eqn (1)). Significantly, this method can be extended to the synthesis of biologically important hexahydropyrimidine derivatives in 61% yield (eqn (2)).[13]



(1)



(2)

In summary, we have developed an efficient synthesis of highly substituted tetrahydroimidazole derivatives by means of intramolecular cyclizations of diamines through a photoredox catalysis strategy. The reaction itself features simple experimental procedures under benign conditions and is completely atom-economic in character.

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Notes and references

1 For selected reviews of visible light photoexcition of an organometallic complex to initiate organic reactions, see: (*a*) T. P. Yoon, M. A. Ischay and J. Du, *Nat. Chem.*, 2010, **2**, 527; (*b*) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102.

2 For a recent review of chemistry using visible light, see: X. Sala, I. Romero, M. Rodriguze, E. Lluis and A. Llobet, *Angew. Chem., Int. Ed.*, 2009, **48**, 2842.

3 For reviews of the photochemistry and photophysics of $Ru(bpy)_3^{2+}$ and related complexes, see: (*a*) K. Kalyanasundaram, *Coord. Chem. Rev.*, 1982, **46**, 159; (*b*) A. Juris, V. Balzani, F. Barigelletti, S. Campagna, P. Belser and A. V. Zelewsky, *Coord. Chem. Rev.*, 1988, **84**, 85.

4 (*a*) M. A. Ischay, M. E. Anzovino, J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2008, **130**, 12886; (*b*) J. Du and T. P. Yoon, *J. Am. Chem. Soc.*, 2009, **131**, 14604; (*c*) M. A. Ischay, Z. Lu and T. P. Yoon, *J. Am. Chem. Soc.*, 2010, **132**, 8572; (*d*) Z. Lu, M. Shen and T. P. Yoon, *J. Am. Chem. Soc.*, 2011, **133**, 1162.

5 (*a*) J. M. R. Narayanam, J. W. Tucker and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2009, **131**, 8756; (*b*) L. Furst, B. S. Matsuura, J. M. R. Narayanam, J. W. Tucker and C. R. J. Stephenson, *Org. Lett.*, 2010, **12**, 3104; (*c*) J. W. Tucker, J. M. R. Narayanam, S. W. Krabbe and C. R. J. Stephenson, *Org. Lett.*, 2010, **12**, 368; (*d*) J. W. Tucker, J. D. Nguyen, J. M. R. Narayanam, S. W. Krabbe and C. R. J. Stephenson, *Chem. Commun.*, 2010, **46**, 4985.

6 (*a*) A. G. Condie, J. C. Gonzalez-Gomze and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2010, **132**, 1464; (*b*) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharyny and D. C. Fabry, *Chem. Commun.*, 2011, **47**, 2360.

7 (*a*) D. A. Nicewicz and D. W. C. MacMillan, *Science*, 2008, **322**, 77; (*b*) D. A. Nagib, M. E. Scott and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 10875; (*c*) H. W. Shih, M. N. V. Wal, R. L. Grange and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 13600.

8 (*a*) R. G. Kallen and W. P. Jencks, *J. Biol. Chem.*, 1966, **241**, 5851; (*b*) S. J. Benkovic, P. H. Benkovic and R. Chrzanowski, *J. Am. Chem. Soc.*, 1970, **92**, 523; (*c*) A. R. Katritzky, H.-Y. He and A. K. Verma, *Tetrahedron: Asymmetry*, 2002, **13**, 933; (*d*) A. R. Katritzky, H.-Y. He and J. Wang, *J. Org. Chem.*, 2002, **67**, 4951; (*e*) R. Sakai, K. Suzuki, K. Shimamoto and H. Kamiya, *J. Org. Chem.*, 2004, **69**, 1180; (*f*) D. R. Ijzendoorn, P. N. M. Botman and R. H. Blaauw, *Org. Lett.*, 2005, **8**, 239; (*g*) R.-H. Jiao, S. Xu, J.-Y. Liu, H.-M. Ge, H. Ding, C. Xu, H.-L. Zhu and R.-X. Tan, *Org. Lett.*, 2006, **8**, 5709.

9 (*a*) S. V. Liebermann, *J. Am. Chem. Soc.*, 1955, **77**, 1114; (*b*) M. Kerfanto, A. Brault, F. Venien, J. M. Morvan and A. Le Rouzic, *Bull. Soc. Chim. Fr.*, 1975, 196; (*c*) M. Sekiya and H. Sakai, *Chem. Pharm. Bull.*, 1969, **17**, 32; (*d*) A. T. Stewart and C. R. Hauser, *J. Am. Chem. Soc.*, 1955, **77**, 1098.

10 H.-B. Xie, J.-T. Zhu, Z.-X. Chen, S. Li and Y.-M. Wu, *J. Org. Chem.*, 2010, **75**, 7468.

11 (*a*) L.-Q. Lu, Y.-J. Cao, X.-P. Liu, J. An, C.-J. Yao, Z.-H. Ming and W.-J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 6946; (*b*) L.-Q. Lu, F. Li, J. An, J.-J. Zhang, X.-L. An, Q.-L. Hua and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 9542; (*c*) X.-F. Wang, Q.-L. Hua, Y. Cheng, X.-L. An, Q.-Q. Yang, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 8379.

12 See ESI† for details.

13 (*a*) S. Groszkowki, L. Korzycka and W. Bialasiewicz, *Pol. J. Pharmacol. Pharm.*, 1973, **25**, 573 (*Chem. Abstr.*, 1974, **80**, 116181r); (*b*) K. Drandarov, A. Guggisberg and M. Hesse, *Helv. Chim. Acta*, 1999, **82**, 229.