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DIACETONE-*D*-GLUCOSE-MEDIATED ASYMMETRIC SYNTHESES OF DIHYDROQUINOXALINONES

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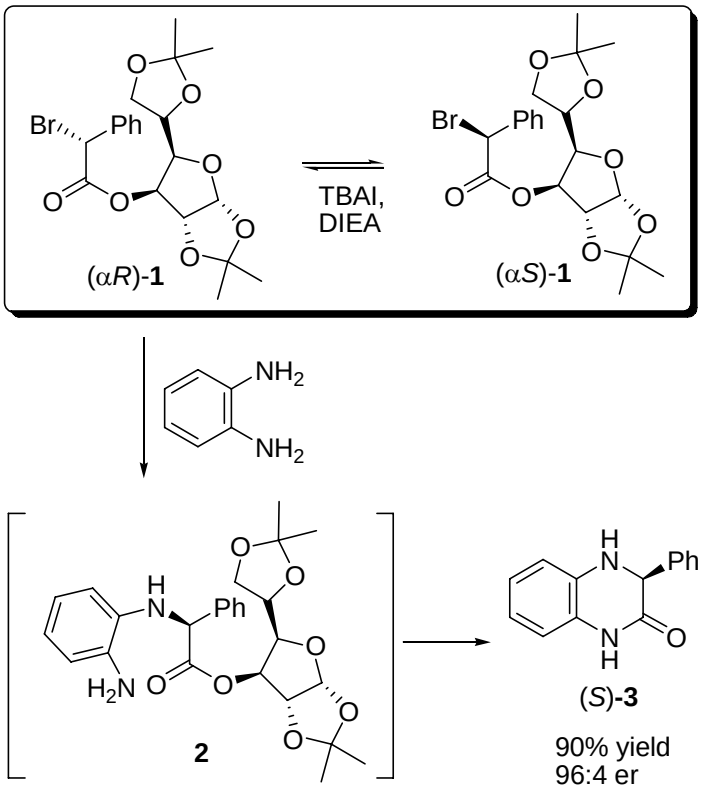
Abstract – Asymmetric syntheses of dihydroquinoxalinones by diacetone-*D*-glucose mediated nucleophilic substitution of α-bromo esters have been investigated. Stereoselective reactions with various 1,2-phenylenediamine nucleophiles in the presence of TBAI and DIEA and following spontaneous removal of the chiral auxiliary can provide dihydroquinoxalinones (**3**-**9**) up to 92% yield and 97:3 er. In addition, we have described the regio- and stereoselective reactions of non-symmetric 1,2-phenylenediamine nucleophiles to provide **10**-**14** up to 90:10 regioisomeric ratio and 98:2 er.

Dihydroquinoxalinone core is of interest as an important pharmacophore in many biologically active compounds.[1a-d] Accordingly, there is growing interest in the preparation of enantioenriched dihydroquinoxalinones and several methods have been developed. Most strategies of previous reports are based on nucleophilic aromatic substitution of *o*-fluoronitrobenzene derivatives with optically pure amino acids in harsh reaction conditions.[1c-h] Consequently, these synthetic routes are limited by the availability of optically pure amino acids and suffer from racemization.[1c,1e] Thus an alternative general strategy has been developed in our laboratory, based on our recent findings of stereoselective nucleophilic substitution mediated by diacetone-*D*-glucose.[2] Herein we wish to report our recent results on asymmetric syntheses of dihydroquinoxalinones by stereoselective nucleophilic substitution of diacetone-*D*-glucofuranosyl α-bromo acetates with various 1,2-phenylenediamine nucleophiles.

We have previously reported that reactions of diacetone-*D*-glucofuranosyl α-halo acetates with various amine nucleophiles in the presence of tetrabutylammonium iodide (TBAI) and diisopropylethylamine (DIEA) provided the substitution products with high stereoselectivities.[2] The chiral information of *D*-glucose is transferred to the substitution at α-halo carbon center via dynamic kinetic resolution in the nucleophilic substitution with amine nucleophiles. For example, the α-bromo stereogenic center of α-bromo-α-phenylacetate (**1**) undergoes rapid epimerization in the presence of DIEA and TBAI, and (α*R*)-**1** reacts with a nucleophile preferentially.[3] We envisaged that the stereoselective nucleophilic

substitution of **1** with 1,2-phenylenediamine and subsequent intramolecular amide formation could lead to highly enantioenriched 3-substituted dihydroquinoxalinones. As shown in scheme 1, initial studies were carried out with two diastereomeric mixture (1:1) of α-bromo-α-phenylacetate (**1**) and 1,2-phenylenediamine (1.5 equiv) in the presence of TBAI (1.0 equiv) and DIEA (1.0 equiv) in CH_2Cl_2 at room temperature.[4] To our delight (*S*)-3-phenyldihydroquinoxalinone (**3**) was obtained in 90% yield with 96:4 er (enantiomeric ratio) in the one-pot reaction for 18 h.[5] The observed er and yield of the product (**3**) suggest that the α-bromo stereogenic center is configurationally labile with respect to the rate of substitution and two diastereomers of **1** are dynamically resolved under the reaction condition. It is noteworthy that mono-alkylated product (**2**) is not prone to react with another equivalent of electrophile and no trace of bis-alkylation product was detected. The exclusive formation of mono-alkylated product is attributed to the steric hindrance of the bulky *ortho*-substituent for the second substitution. Instead, spontaneous intramolecular amide formation of the amino group took place to remove chiral auxiliary and furnished 3-phenyl dihydroquinoxalinone (**3)**.

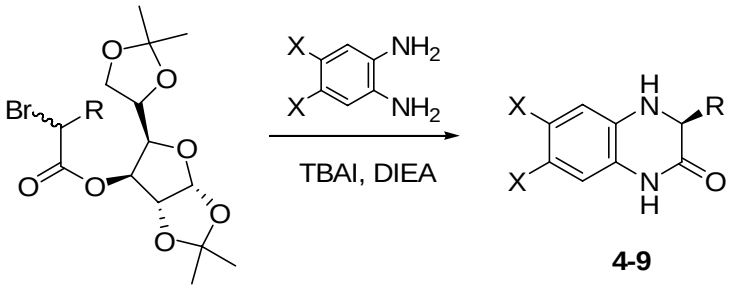


Scheme 1. Dynamic kinetic resolution of α-bromo-α-phenylacetate (**1**).

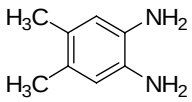
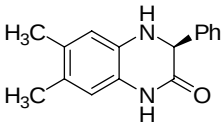
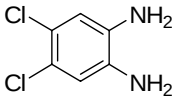
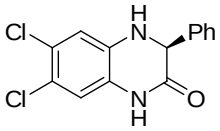
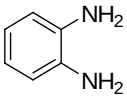
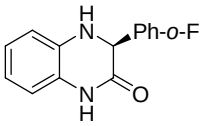
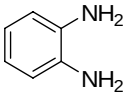
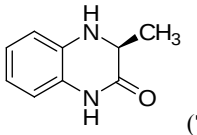
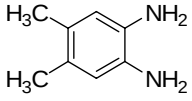
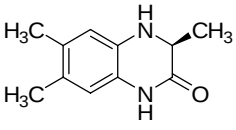
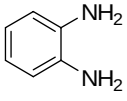
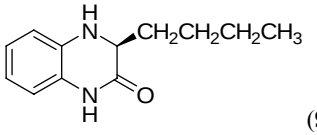
With the identification of diacetone-*D*-glucose as an effective and convenient stereocontrolling element for asymmetric syntheses of dihydroquinoxalinones, we set out to examine the scope of this methodology with various 1,2-phenylenediamine nucleophiles and α-bromo acetates as shown in Table 1. Treatment

of **1** with 4,5-dimethyl-*o*-phenylenediamine, TBAI and DIEA for 18 h at room temperature gave 3-phenyldihydroquinoxalinone (**4**) in 92% yield with 95:5 er (entry 1). This methodology is also efficient for the asymmetric preparation of dihydroquinoxalinone (**5**) with 4,5-dichloro-*o*-phenylenediamine nucleophile (entry 2). In addition, reaction of α-bromo-α-(*o*-fluorophenyl)acetate with 1,2-phenylenediamine under the same condition provided 3-(*o*-fluorophenyl)dihydroquinoxalinone (**6**) in 63% yield with 97:3 er (entry 3).

Table 1. Asymmetric syntheses of dihydroquinoxalinones (**4-9**).



4-9

Entry[a]	Nucleophile	R	Product	Yield (%)[b]	Er (*S*:*R*)[c]
1		Ph	 (**4**)	92	95:5
2		Ph	 (**5**)	81	97:3
3		*o*-F-Ph	 (**6**)	63	97:3
4		CH_3	 (**7**)	88	90:10
5		CH_3	 (**8**)	85	86:14
6		n-Butyl	 (**9**)	73	93:7

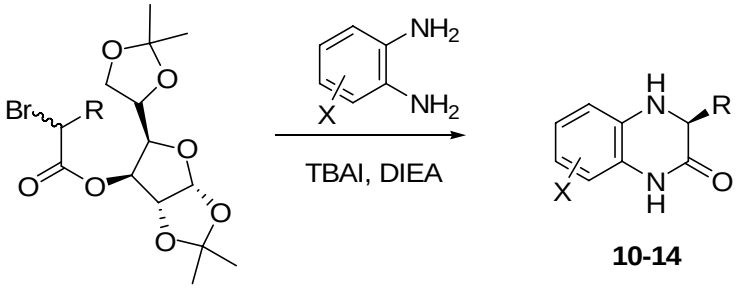
(a) All reactions were carried out in CH_2Cl_2. (b) Isolated yields. (c) The ers are determined by CSP-HPLC (Chiralcel OJ-H column).

Encouraged by the observation of high enantioselectivities in the reactions of α-aryl-α-bromoacetates, we examined the dynamic kinetic resolution of α-alkyl-α-bromoacetates for asymmetric syntheses of

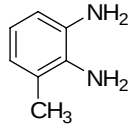
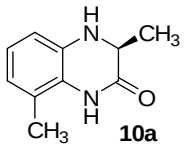
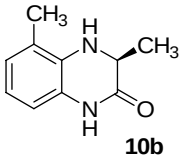
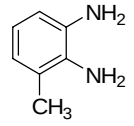
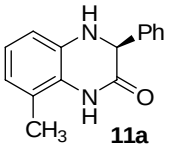
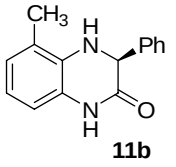
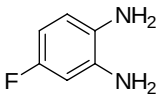
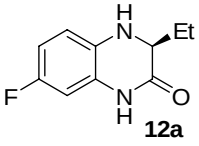
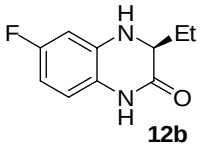
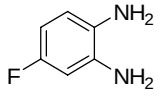
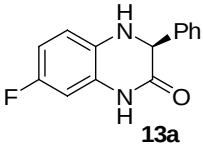
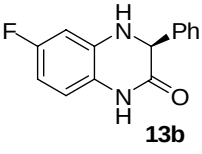
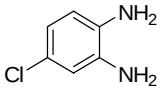
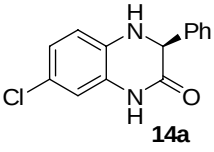
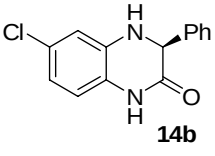
3-alkyldihydroquinoxalinones as shown (entries 4-6). The reaction of α-bromo-α-methylacetate with 1,2-phenylenediamine afforded 3-methyldihydroquinoxalinone (**7**) with slightly lower stereoselectivity (90:10 er, entry 4). As with 4,5-dimethyl-*o*-phenylenediamine nucleophile, the reaction in CH_2Cl_2 successfully took place to afford dihydroquinoxalinone (**8**) in 85% yield with 86:14 er (entry 5). When α-bromo-α-butyl acetate was treated with TBAI and DIEA for 48 h, 3-butyldihydroquinoxalinone (**9**) was obtained in 73% yield with 93:7 er (entry 6). The higher reaction temperature (50 °C) increases the rate of cyclization but has no effect on stereoselectivity. Considering the important role of solvent for the appropriate DKR conditions of α-bromoacetates, we have examined various solvents in the asymmetric syntheses of **8** and **9**.[3] In both cases, however, solvent appeared to have little influence on the stereoselectivity. 3-Methyldihydroquinoxalinone (**8**) was obtained with 84:16 er in THF, 83:17 er in CH_3CN, 87:14 er in ether, 83:17 er in chloroform and 86:14 er in toluene. Also, 3-butyldihydroquinoxalinone (**9)** was obtained with 93:7 er in chloroform and 92:8 er in toluene.

Reactions of non-symmetric 1,2-phenylenediamine nucleophiles can produce two regioisomeric dihydroquinoxalinones. In an effort to understand how two different amino groups affect the regiochemistry of the substitution, we initially examined 2,3-diaminotoluene as a nucleophile as shown in Table 2 (entry 1). Treatment of α-bromo-α-methyl acetate with the nucleophile, TBAI and DIEA for 48 h gave 3-methyl-8-methyldihydroquinoxalinone (**10a)** as a major product with 90:10 er and 3-methyl-5-methyldihydroquinoxalinone (**10b)** as a minor product with 89:11 er (entry 1). The regioselectivity of 90:10 suggests significantly different reactivities of two amino groups. The sterically less hindered amino group of the nucleophile is more reactive than the amino group with two *ortho*-substituents. The regiochemistry of **10a** was assigned by comparison to the ^{1}H-NMR of authentic material individually prepared.[6] Also, the reaction of α-bromo-α-phenylacetate with 2,3-diaminotoluene gave 8-methyl-3-phenyldihydroquinoxalinone (**11a)** as a major product with 97:3 er and 5-methyl-3-phenyldihydroquinoxalinone (**11b)** as a minor product with 90:10 er in a regioisomeric ratio of 90:10. The regiochemistry of **11** was assigned by analogy to the regiochemistry of **10**. Furthermore, we attempted the substitution reactions with 4-fluoro- and 4-chloro-1,2-phenylenediamine nucleophiles as shown in Table 2 (entries 3-5). Treatment of α-bromo-α-ethylacetate with 4-fluoro-1,2-phenyl-enediamine, TBAI and DIEA in CH_3CN gave 3-ethyl-7-fluorodihydroquinoxalinone (**12a)** as a major product with 83:17 er and 3-ethyl-6-fluorodihydroquinoxalinone (**12b)** as a minor product with 81:19 er in a regioisomeric ratio of 87:13 (entry 3). The amino group *para* to the fluoro group reacted faster than the amino group *meta* to the fluoro group. Two regioisomers of **12** were produced in 65% yield after 96 h stirring at room temperature and non-cyclized product is also isolated in 23% yield. The higher reaction temperature (80 °C) increases the rate of cyclization but has no effect on stereoselectivity. The regiochemistry of **12** was assigned by comparison to the ^{1}H NMR of authentic material reported

Table 2. Regioselective asymmetric syntheses of dihydroquinoxalinones (**10-14)**.



10-14

Entry[a]	Nucleophile	R	Product major	Product minor	Yield (%)[b] (major:minor)[c]	Er (*S*:*R*)[d] major	Er (*S*:*R*)[d] minor
1		Me	 **10a**	 **10b**	63 (90:10)	90:10	89:11
2		Ph	 **11a**	 **11b**	73 (90:10)	97:3	90:10
3		Et	 **12a**	 **12b**	65 (87:13)	83:17	81:19
4		Ph	 **13a**	 **13b**	75 (90:10)	94:6	96:4
5		Ph	 **14a**	 **14b**	82 (71:29)	98:2	96:4

(a) All reactions were carried out in CH_2Cl_2, except for the reaction in CH_3CN of entry 3. (b) Isolated yields of two regioisomers. (c) The regioisomeric ratios were determined by ^{1}H-NMR and confirmed by HPLC. (d) The ers were determined by CSP-HPLC (Chiralcel OJ-H for **10**, **11**, **13, 14** and Chiralcel OB-H for **12**)).

previously.[1d] The reactions of α-bromo-α-phenylacetate with 4-fluoro-1,2-phenylenediamine and 4-chloro-1,2-phenylenediamine provided **13** and**14** in 75% and 85% yields, respectively, with higher enantioselectivities than those of **12**. The regiochemistry of **13** and **14** was assigned by analogy to the regiochemistry of **12**. The regiochemical aspects of the results showed that regioselectivity depends critically on the steric effect of *ortho*- and *meta*-substituents on 1,2- phenylenediamine nucleophile.

We conclude that readily available diacetone-D-glucose is an effective and convenient chiral auxiliary for asymmetric syntheses of dihydroquinoxalinones. Since various α-bromo acetates can be easily obtained in racemic form and configurational lability of them is readily induced, the process is quite general and does not rely on the availability of optically pure amino acids. To the best of our knowledge, there is no previous report of the general strategy for regio- and enantioselective syntheses of dihydroquinoxalinones. Spontaneous removal of chiral auxiliary and simple protocol with mild conditions suggest further development of this DKR approach. Application of this methodology to the asymmetric syntheses of various kinds of heterocyclic compounds is underway.

ACKNOWLEDGEMENTS

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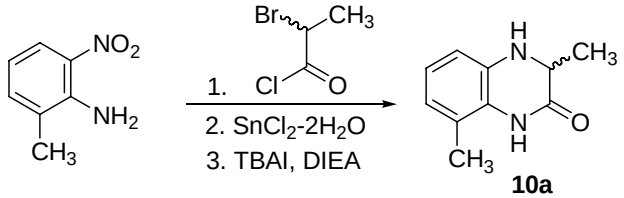
REFERENCES AND NOTES

1. (a) S. N. Ha, P. J. Hey, R. W. Ransom, M. Harrell, K. L. Murphy, R. Chang, T.-B. Chen, D.-S. Su, M. K. Markowitz, M. G. Bock, R. M. Freidinger, and F. J. Hess, *Biochem. Biophys. Res. Commun.*, 2005, **331**, 159. (b) D. Gupta, N. N. Ghosh, and R. Chandra, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1019. (c) D.-S. Su, M. K. Markowitz, R. M. Dipardo, K. L. Murphy, C. M. Harrell, S. S. O'Malley, R. W. Ransom, R. S. L. Chang, S. Ha, F. J. Hess, D. J. Pettibone, G. S. Mason, S. Boyce, R. M. Freidinger, and M. G. Bock, *J. Am. Chem. Soc*., 2003, **125**, 7516. (d) P. E. Mahaney, M. B. Webb, F. Ye, J. P. Sabatucci, R. J. Steffan, C. C. Chadwick, D. C. Harnish, and E. J. Trybulski, *Bioorg. Med. Chem.*, 2006, **14**, 3455. (e) C.-L. Tung and C.-M. Sun, *Tetrahedron Lett.*, 2004, **45**, 1159. (f) C. Jamieson, M. S. Congreve, D. F. Emiabata-Smith, S. V. Ley, J. J. Scicinski, *Org. Process. Res. Dev.*, 2002, **6**, 823. (g) R. J. Holland, I. R. Hardcastle, and M. Jarman, *Tetrahedron Lett*., 2002, **43**, 6435. (h) E. Laborde, B. T. Peterson, and L. Robinson, *J. Comb. Chem.*, 2001, **3**, 572.
2. (a) H. J. Kim, Y. Kim, E. T. Choi, M. H. Lee, E. S. No, and Y. S. Park, *Tetrahedron*, 2006, **62**, 6303. (b) H. J. Kim, E.-k. Shin, J.-y. Chang, Y. Kim, and Y. S. Park, *Tetrahedron Lett.*, 2005, **46**, 4115.
3. It has been proposed by several examples that the epimerization promoted by TBAI (or TBAB) via nucleophilic displacement of the halide ion and/or base via keto-enol tautomerization. (a) N. R. Treweeke, P. B. Hitchcock, D. A. Pardoe, and S. Caddick, *Chem. Commun*., 2005, 1868. (b) J.-y. Chang, E.-k. Shin, H. J. Kim, Y. Kim, and Y. S. Park, *Tetrahedron*, 2005, **61**, 2743. (c) Y. Valenrod, J. Myung, and R. N. Ben, *Tetrahedron Lett*., 2004, **45**, 2545. (d) J. Nam, S.-k. Lee, and Y. S. Park, *Tetrahedron*, 2003, **59**, 2397. (e) P. N. Devine, B. S. Foster, E. J. J. Grabowski, and P. J. Reider, *Heterocycles*, 2002, **58**, 119. (f) S. Caddick, C. A. M. Afonso, S. X. Candeias, P. B. Hitchcock, K. Jenkins, L. Murtagh, D. Pardoe, A. G. Santos, N. R. Treweeke, and R. Weaving, *Tetrahedron*, 2001, **57**, 6589. (g) S.-k. Lee, S. Y. Lee, and Y. S. Park, *Synlett*, 2001, 1941. (h) R. N. Ben and T. Durst, *J.*

Org. Chem., 1999, **64**, 7700.

4. General procedure for the preparation of dihydroquinoxalinones (**3-14)**: To a solution of diacetone glucofuranosyl α-bromoacetate (1.0 mmol) in CH_2Cl_2 (*ca.* 0.1 M) at rt were added DIEA (1.0 equiv), TBAI (1.0 equiv) and 1,2-phenylenediamine (1.5 equiv). After the resulting reaction mixture was stirred at rt for 18 h, the mixture was quenched with *aq.* 5%-HCl solution (10mL). The resulting mixture was extracted with CH_2Cl_2 (10 mL × 2) and the combined extracts were washed with brine. The solvent was removed under reduced pressure and the crude material was purified by column chromatography to give a dihydroquinoxalinone.
5. In references 2a and 2b, we have established that (*S*)-products were provided in the substitution of diacetone-D-glucofuranosyl α-haloacetates with various aliphatic and aromatic amine nucleophiles. We proposed that (α*R*)-**1** is the faster reacting diastereomer due to the formation of an intermolecular hydrogen bond that facilitates delivery of the nucleophile.[2a] The absolute configurations of dihydroquinoxalinones (**3-14)** are provisionally assigned by analogy. The specific rotation of **12a {**$[\alpha]_D^{20}$ = +10.6° (c = 0.19, DMSO)} compared with the data in literature allowed us to confirm the (*S*)-configuration.[1d]
6. The regiochemistry of **10** was assigned by comparison of ^{1}H-NMR with authentic material individually prepared from the procedure shown below. ^{1}H NMR ($CDCl_3$, 400 MHz) **10a**, 8.11 (br, 1H), 6.80-6.56 (m, 3H), 3.98 (q, *J* = 6.6 Hz, 1H), 3,83 (br, 1H), 2.25 (s, 3H), 1.46 (d, *J* = 7.2 Hz, 3H); **10b**, 8.69 (br, 1H), 6.80-6.56 (m, 3H), 4.04 (q, *J* = 6.6 Hz, 1H), 3,71 (br, 1H), 2.17 (s, 3H), 1.49 (d, *J* = 6.8 Hz, 3H).



10a