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ARTICLE TYPE

Primary amino acid catalyzed asymmetric intramolecular Mannich reaction for the synthesis of 2-aryl-2,3-dihydro-4-quinolones

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Primary amino acids are found to be good enantioselective catalysts for the direct asymmetric Mannich reaction between 2-amino acetophenone and aldehydes. The 2-aryl-2,3-dihydro-4-quinoline products are obtained in moderate to good yields and good to high enantioselectivities with 10 mol% of primary amino acid catalyst under mild reaction condition.

Quinolones have wide spectrum antibacterial properties and they have been used in pharmaceutical chemistry not only because of their availability orally and parentally but also for their favourable pharmacokinetics.[1] In particular, 2-aryl-2,3-dihydro-4-quinolones have attracted attention because of their activities as anticancer, antimalarial as well as antibiotic agents[2] and as potent cross-species micro RNA inhibitors.[3] These important biological properties have stimulated interest for the synthesis of 2-aryl-2,3-dihydro-4-quinolones from different research groups, particularly in enantioselective fashion as two individual stereoisomers behave in totally different ways.

There are five different routes to access enantiopure 2-aryl/alkyl-2,3-dihydro-4-quinolones (Figure 1).[4-8] The first one is the asymmetric intermolecular 1,4-Michael addition of organometallic reagents to 4-quinolones.[4] Here, handling of air sensitive catalysts and reagents is required. The second method is the kinetic resolution of 2-substituted 2,3-dihydro-4-quinolones by palladium catalyzed allylic alkylation.[5] As this is a kinetic resolution, the starting material was recovered in less than 50% yield. The third strategy is the 6-*endo*-trig cyclization of amino alkylidene β-keto esters.[6] One drawback of this method is the requirement of the ester functionality which makes this approach non atom-economical. The fourth approach is 6-*endo* aza-Michael addition of aminochalcone derivatives.[7] Here also like previous methods, protection of amino group is required and the substrate has to be synthesized in a couple of steps. The fifth and the most direct approach is the asymmetric intramolecular Mannich reaction[8,9] between 2-aminoacetophenone and aldehydes.

Chandrasekhar et al first shown that 2-amino acetophenone could react with arylaldehydes in the presence of proline catalyst to furnish 2-aryl-2,3-dihydro-4-quinolones in good yields; however poor enantioselectivity (<10% ee) was attained.[8a] Pitchumani and Kanagaraj have developed enantioselective synthesis of 2-aryl-2,3-dihydro-4-quinolones using per-6-amino-β-cyclodextrin as chiral base catalyst.[8b] However as cyclodextrins are biological molecules their modification is difficult.

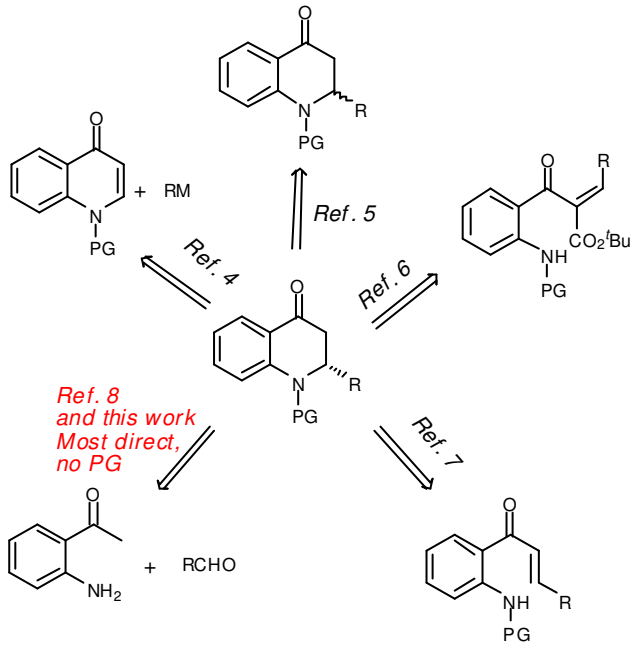

Figure 1 Synthetic approaches to 2-aryl-2,3-dihdro-4-quinolones

Recently, Yang, Luo and co-workers reported amino acid derived sulfonamide catalyzed asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones; though the products were obtained in moderate enantioselectivities (maximum 74% ee).[8c] Taking all these facts into account and realizing the importance of 2-aryl-2,3-dihydro-4-quinolones we thought that a high enantioselective synthesis by intramolecular Mannich reaction using simple organocatalysts is well desirable. Herein, we describe primary amino acid[10] catalyzed one pot asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones and also employ a variety of 2-aminoacetophenones for the first time.

We started our investigation by screening different primary amino acids **I-VIII** for the reaction between 2-aminoacetophenone (**1a**) and benzaldehyde (**2a**). The reactions were performed in the presence of 10 mol% of catalyst in methanol solvent at room temperature. After stirring for 4 days with valine (**I**) catalyst, the product **3a** was obtained in 40% yield with 77:23 er (Table 1, entry 1).

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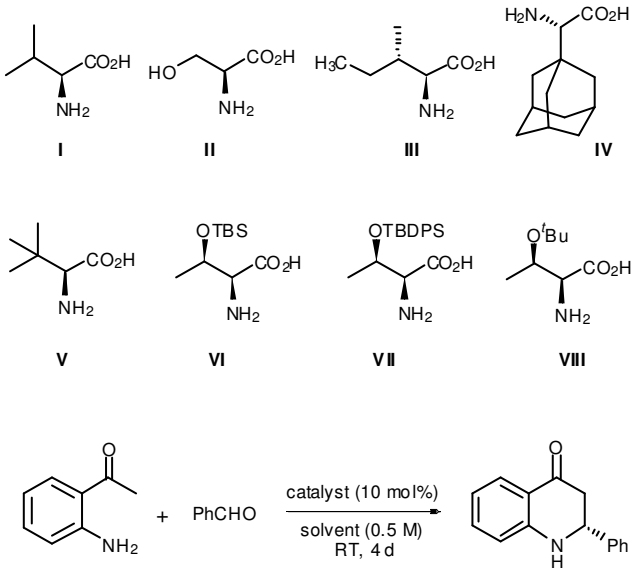
Table 1 Catalyst screening and optimization of reaction condition

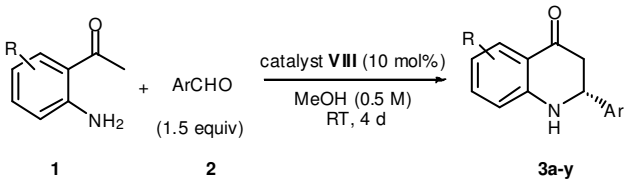


entry[a]	catalyst	solvent	yield[b]	er[c]
1	**I**	MeOH	40	77:23
2	**II**	MeOH	46	67:33
3	**III**	MeOH	44	76:24
4	**IV**	MeOH	35	85:15
5	**V**	MeOH	50	85:15
6	**VI**	MeOH	45	81.5:18.5
7	**VII**	MeOH	42	79:21
8	**VIII**	MeOH	55	87:13
9	**VIII**	TFE	50	85:15
10	**V**	TFE	51	90.5:9.5

[a]Reaction condition: 0.2 mmol of **1a** with 0.3 mmol of **2a** in 0.4 mL solvent using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

A little less enantioselectivity was observed with L-serine (**II**) (entry 2). L-isoleucine (**III**) could not change the enantioselectivity much and the product was obtained in similar yield (entry 3). A higher enantioselectivity was achieved with 1-adamantyl(amino)acetic acid (**IV**) albeit in less yield (entry 4). L-*tert*-leucine (**V**) provided the product in similar enantioselectivity but a higher yield of 50% was obtained (entry 5). Then we found that O-protected L-threonine derivatives (**VI-VIII**)[11] are quite effective for our reaction. Though TBS protected L-threonine (**VI**) and TBDPS protected L-threonine (**VII**) could not change much the enantioselectivity of the reaction (entries 6-7), a higher enantioselectivity was attained with O^{t}Bu-L-threonine catalyst (**VIII**) (entry 8). A change of the solvent from methanol to trifluoroethanol did not alter the enantioselectivity with catalyst **VIII**, but surprisingly higher enantioselectivity was attained with catalyst **V** (entry 10). Future experiments were carried out either with catalyst **V** in trifluoroethanol (condition A) or with catalyst **VIII** in methanol (condition B). A sluggish reaction was observed after lowering the reaction temperature to 0 ^{o}C and increasing the catalyst loading did not enhance the enantioselectivity or yield of the product.

Table 2 Substrate scope of the catalytic enantioselective intramolecular Mannich reaction



entry	R	Ar	3	yield[b]	er[c]
1[a]	H	Ph	**3a**	51	90.5:9.5
2	H	4-OMeC$_6$H$_4$	**3b**	75	93:7
3	H	4-MeC$_6$H$_4$	**3c**	61	89.5:10.5
4	H	4-*t*BuC$_6$H$_4$	**3d**	45	89:11
5	H	4-FC$_6$H$_4$	**3e**	62	89:11
6	H	4-ClC$_6$H$_4$	**3f**	60	90:10
7	H	4-BrC$_6$H$_4$	**3g**	69	87:13
8	H	4-OHC$_6$H$_4$	**3h**	70	92:8
9	H	4-OEtC$_6$H$_4$	**3i**	52	92:8
10	H	4-O*n*PrC$_6$H$_4$	**3j**	49	92:8
11	H	4-O*i*BuC$_6$H$_4$	**3k**	58	93:7
12	H	4-OAllC$_6$H$_4$	**3l**	55	91:9
13	H	4-O*n*OctC$_6$H$_4$	**3m**	32	92:8
14	H	4-OAcC$_6$H$_4$	**3n**	46	90:10
15	H	3-OMeC$_6$H$_4$	**3o**	67	90:10
16	H	3-ClC$_6$H$_4$	**3p**	38	82:18
17	H	3-BrC$_6$H$_4$	**3q**	35	83:17
18	H	4-OH-3-OMeC$_6$H$_3$	**3r**	73	96:4
19	H	3,4-(OMe)$_2$C$_6$H$_3$	**3s**	61	92:8
20	H	3,4,5-(OMe)$_3$C$_6$H$_2$	**3t**	61	89:11
21	H	2-furyl	**3u**	23	82:18
22	H	2-pyrrolyl	**3v**	28	86.5:13.5
23	5-Cl	4-OMeC$_6$H$_4$	**3w**	43	92:8
24	5-Me	4-OMeC$_6$H$_4$	**3x**	71	91:9
25	3,5-(Me)$_2$	4-OMeC$_6$H$_4$	**3y**	33	84.5:15.5

[a]Reaction was carried out with catalyst **V** in TFE solvent (condition A). [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiralcolumn.

With the optimized reaction condition in hand we ventured in the scope of the reaction. Except for benzaldehyde (**2a**), condition B was followed for all substituted benzaldehydes as we failed to achieve similar enantioselectivities for other aldehydes using condition A. Gratifyingly, condition B was suitable for substituted benzaldehydes and good to high enantioselectivities were obtained (Table 2). As can be seen, a variety of 4-substituted benzaldehydes can be employed in our reaction and incorporation of electron withdrawing or electron rich groups did not affect the outcome of the reaction (entries 1-14). *p*-Anisaldehyde provided the product **3b** in 75% yield with 93:7 er

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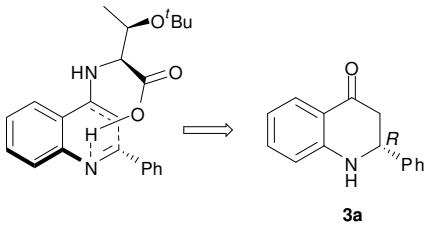
(entry 2). 4-Alkylsubstituted benzaldehydes delivered the products with fairly good level of enantioselectivities (entries 3-4). Different halo-substitutions at the 4-position of benzaldehyde were also tolerated and the products were obtained in similar enantioselectivities (entries 5-7). 4-Hydroxybenzaldehyde can also be employed and product **3h** was observed in satisfactory yield with 92:8 er (entry 8). Encouraged by this result and that of entry 2, we screened different 4-alkoxybenzaldydes for our reaction and acceptable yields with high enantioselectivities (>90:10 er) were attained in all cases (entries 9-13). Good enantioselectivity was also achieved with 4-acetoxybezaldehyde (entry 14). Then different 3-substituted benzaldehydes were screened (entries 15-17). Though, *m*-anisaldehyde afforded product **3o** in good enantioselectivity (entry 15), diminished yields and enantioselectivities were observed for products **3p** and **3q** (entries 16-17). Pleasingly, our reaction condition is suitable for the employment of different di and tri-substituted benzaldehydes (entries 18-20) and vanillin proved to be the best aldehyde with 96:4 er (entry 18). Different heteroaromatic aldehydes can also be engaged in our reaction albeit poor yields were observed (entries 21-22). Additionally, different substituted 2-amino acetophenones were also employed for the first time in this reaction (entries 23-25). 5-Chloro-2-aminoacetophenone (**1b**) provided product **3w** in moderate yield with 92:8 er but a higher yield was attained for product **3x** in similar enantioselectivity.

A proposed transition state model has been shown in Figure 2 and it dictates that the primary amino group of the catalyst generates an enamine intermediate. Also only *Si* face of the newly generated imine double bond is exposed for enamine addition. We also assume that the carboxylic acid group of catalyst simultaneously activates the imine from the *Re* face for the addition. The absolute configuration of the product could be envisaged as "*R*" by this model and it was also confirmed by the comparison of the optical rotation with literature value (see supporting information for details).



3a

Figure 2 Proposed transition state

Conclusions

In summary, we have developed primary α-amino acid catalyzed asymmetric intramolecular Mannich reaction between 2-aminoacetophenones and aryl aldehydes. This report shows that primary α-amino acids are better catalysts than secondary α-amino acid such as proline for this particular reaction. Future applications of primary amino acids in related reactions are in progress in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental procedures and ^{1}H, ^{13}C NMR and HPLC data of all products]. See DOI: 10.1039/b000000x/

1 *a*) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. Dipardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235; *b*) J. Nilsson, E. Ø. Nielsen, T. Liljefors, M. Nielsen, O. Sterner, *Bioorg. Med. Chem. Lett*., 2008, **18**, 5713; *c*) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347; *d*) A. Ahmed, M. Daneshtala, *J. Pharmaceutical Sci.*, 2012, **15**, 52.

2 *a*) Y. Xia, Z. –Y. Yang, P. Xia, K. F. Bastow, Y. Tachibana, S. –C. Kuo, E. Hamel, T. Hackle, K. –H. Lee, *J. Med. Chem.*, 1998, **41**, 1155.; *b*) S. –X. Zhang, J. Feng, S. –C. Kuo, A. Brossi, E. Hamel, A. Tropsha, K. –H. Lee, *J. Med. Chem.*, 2000, **43**, 167; *c*) A. E. Nibbs, K. A. Scheidt, *Eur. J.Org. Chem*., 2012, 449; *d*) A. Patti, S. Pedotti, T. Grassi, A. Ido lo, M. Guido, A. De Donno, *J. Organomet. Chem.*, 2012, **716**, 216.

3 S. Chandrasekhar, S. N. C. V. L. Pushpavalli, S. Chatla, D. Mukhopadyay, B. Ganganna, K. Vijeender, P. Srihari, C. R. Reddy, M. J. Ramaiah, U. Bhadra, *Bioorg. Med. Chem. Lett*., 2012, **22**, 645.

4 *a*) R. Shintani, T. Yamagami, T. Kimura, T. Hayashi, *Org. Lett*. 2005, **7**, 5317; *b*) X. Zhang, J. Chen, F. Han, L. Cun, J. Liao, *Eur. J. Org. Chem.*, 2011, 1443.

5 B. –L. Lei, C. –H. Ding, X. –F. Yang, X. –L. Wan, X. –L. Hou, *J. Am. Chem. Soc*., 2009, **131**, 18250.

6 *a*) Z. Feng, Q. L. Xu, L. X. Dai, S. L. You, *Heterocycles* 2010, **80**, 765; *b*) X. Liu, Y. Lu, *Org. Lett.*, 2010, **12**, 5592; *c*) X. Xiao, X. Liu, S. Dong, Y. Cai, L. Lin, X. Feng, *Chem. Eur., J*. 2012, **18**, 15922.

7 *a*) M. Rueping, S. A. Moreth, M. Z. Bolte, *Z. Naturforsch B* 2012, **67b**, 1021; *b*) S. Cheng, L. Zhao, S. Yu, *Adv. Synth. Catal.*, 2014, **356**, 982.

8 *a*) S. Chandrasekhar, K. Vijeender, C. Sridhar, *Tetrahedron Lett*., 2007, **48**, 4935; *b*) K. Kanagaraj, K. Pitchumani, *J. Org Chem.* 2013, **78**, 744; *c*) H. Zheng, Q. Liu, S. Wen, H. Yang, Y. Luo, *Tetrahedron: Asymmetry* 2013, **24**, 875. For a recent report on copper (II) catalyzed asymmetric [1,6]-aza-electrocyclization of 1,3 dicarbonyl compounds having related structures, see: P. C. Knipe, M. D. Smith, *Org. Biomol. Chem*., 2014, **12**, 5094.

9 For reviews on organocatalytic asymmetric Mannich reactions, see: *a*) A. Córdova, *Acc. Chem. Res*. 2004, **37**, 102; *b*) A.Ting, S. E. Schaus, *Eur. J. Org. Chem*., 2007, 5797; *c*) M. M. B. Marques, *Angew. Chem. Int. Ed.*, 2006, **45**, 348; *d*) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Rutjes, *Chem. Soc. Rev*., 2008, **37**, 29; *e*) M. Benohoud, Y. Hayashi, In *Asymmetric Organocatalysis 1: Lewis base and acid catalysis*, B. List, Ed. Thieme Verlag: Stuttgart, 2012, pp 73-134; *f*) X. –H. Cai, B. Xie, *ARKIVOC* 2013, 264.

10 For a review on primary amino acids as privileged catalysts in enantioselective organocatalysis, see: L. –W. Xu, Y. Lu, *Org. Biomol. Chem*., 2008, **6**, 2047.

11 For selected recent reports on O-protected-L-threonine catalyzed asymmetric transformations, see: *a*) S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc*., 2007, **129**, 288; *b*) S. S. V. Ramasastry, K. Albertshofer, N. Utsumi, F.Tanaka, C. F. Barbas III, *Angew. Chem. Int. Ed*., 2007, **46**, 5572; *c*) N. Utsumi, M. Imai, F.Tanaka, S. S. V. Ramasastry, C. F. Barbas III, *Org. Lett*., 2007, **9**, 3445; *d*) H. Zhang, S. S. V. Ramasastry, F.Tanaka, C. F. Barbas III, *Adv. Synth. Catal*., 2008, **350**, 791; *e*) X. Wu, Z. Jiang, H. –M. Shen, Y. Lu, *Adv. Synth. Catal*., 2007, **349**, 812; *f*) L. Cheng, X. Han, H. Huang, M. W. Wong, Y. Lu, *Chem. Commun*., 2007, 4143; *g*) T. C. Nugent, M. Shoaib, A. Shoaib, *Org. Biomol. Chem*., 2011, **9**, 52; *h*) T. C. Nugent, A. Sadiq, A. Bibi, T. Heine, L. L. Zeonjuk, N. Vankova, B. S. Bassil, *Chem. Eur. J*., 2012, **18**, 4088.