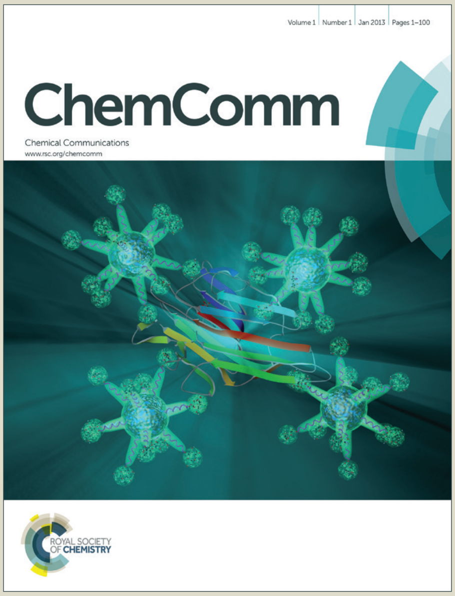
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name RSCPublishing

COMMUNICATION

Cite this: DOI: 10.1039/x0xx00000x

Efficient Synthesis of Chiral Cyclic Acetals by Metal and Brønsted Acid Co-Catalyzed Entioselective Four-component Cascade Reactions

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

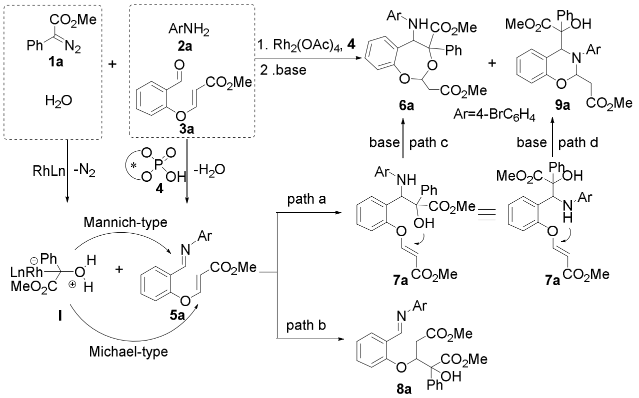
Lin Qiu, Xin Guo, Chaoqun Ma, Huang Qiu, Shunying Liu*, Liping Yang and Wenhao Hu*

Four-component Mannich reactions subsequently followed by an intramolecular oxo-Michael addition were developed to efficiently produce chiral cyclic acetals with high diastereoselectivity and enantioselectivity.

Multicomponent reactions (MCRs)[1] and cascade reactions[2] are highly attractive to efficiently construct structurally complex organic molecules with formation of multiple chemical bonds in one step. The combination of a multicomponent reaction and a cascade process in one system would maxmize the synthetic efficiency of complex molecules from simple starting materials in an atom- and step-economic fashion.[3] However, due to the great challenges of the control of stereoselectivity and the order of bond formation, only a few successful examples of enantioselective cascade multicomponent reactions have been developed.[4]

Stereogenic acetals are important structure in various natural products and biologically active agents, ranging from simple carbohydrates to complex spiroketal polyketides.[5] They are also known as versatile intermediates for asymmetric synthesis.[6] A number of useful strategies have been devised for their preparations, such as synthesis from chiral starting materials or by the use of stoichiometric chiral reagents,[7] and catalytical methods for the enantioselective synthesis.[8-9] These motivate us to seek for an efficient reaction to install optically active acetals in a mild, rapid and step-economic approach.

In recent years, our group has reported several highly selective multi-component reactions by trapping in-situ-generated active intermediates (including oxonium ylides, ammonium ylides and ziwwtterions) with electrophiles.[10-12] The trapping process presents an extremely fast reaction rate under mild conditions to construct *β*-amino-α-hydroxy acid derivatives from simple starting materials in one step. [10] Inspired by these results, we intended to use a bifunctional component (**3a**) containing a carbonyl group and a Michael acceptor functionlity in the multicomponent reaction (Scheme 1). The protic oxonium ylide **I** generated from diazo compound and water was designed to be trapped by a bifunctional electrophile **5a**, containing an imine group and Michael acceptor with an oxygen atom in the contiguous position. The electrophilic trapping process of oxonium ylide **I** by imines followed an intramolecular addition by Micheal acceptor will possibly offer optical acetal drivatives (Scheme 1). The bifunctional electrophile **5a** can be easily *in situ* generated from aniline **2a** and methyl 3-(2-formylphenoxy)propenoate **3a**[13] in one pot.

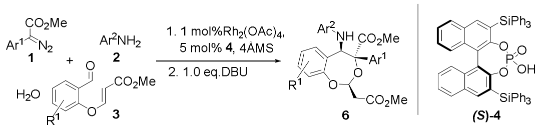


Scheme 1. Designed reaction pathway for the four-component cascade reactions of aryl diazoesters **1a** with water, anilines **2a** and methyl 3-(2-formylphenoxy)propenoates **3a**.

For this designed four-component cascade reaction, one particular challenge is how to achieve an excerllent stereoselectivitive control in both the multi-component and the cascade processes. Another challenge is that how to control the order of multiple bond formaiton, mainly including the competition of nucleophilic Mannich addition *vs*. Michael addition (Scheme 1, path a ***vs*.** path b) as well as that of intramolecular oxy-Michael additon[14] *vs*. aza-Michael addtion[15] (Scheme 1, path c *vs*. path d). Addtionally, for the multi-component process, the aniline will competitively attack diazo compound to form the undesired ammonium ylides, which will deteriorate the generation of the important intermediate oxonium ylide **I**.

We began our investigation with the $Rh_2(OAc)_4$ (1 mol%) catalyzed four-component coupling reaction of aryl diazoesters **1a**, water, anilines **2a**, and methyl 3-(2-formylphenoxy)propenoates **3a** in DCM at 25°C. To suppress the side reaction pathway and achieve enantioselective control of the desired process, we chosen the ratio of **1a**: H_2O: **2a**: **3a** as 1.5:0.5:1.2:1.0. By extensive reaction condition optimization (see ESI, Table S1), we found that the best result was achieved with 5 mol% of **4** as the co-catalyst and one equivalents of DBU as base in the presence of 4 Å molecular sieve (MS) in DCM at 25°C and gave the desired product **6a** in 45% yield with >95:5 dr and 91% ee value.

Table 1. Enantioselective four-component cascade reactions of aryldiazoacetates **1** with water, anilines **2** and methyl 3-(2-formylphenoxy)propenoates **3**.[a]

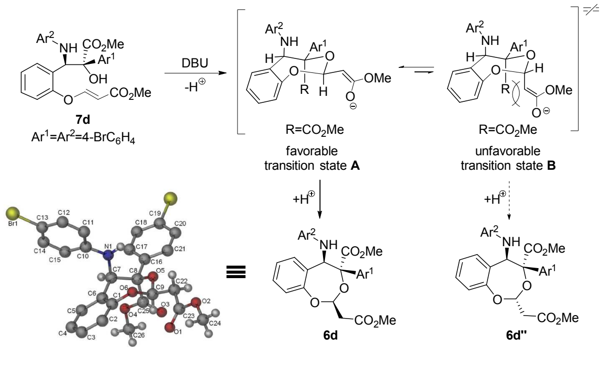


Entry	**1**/Ar^1	**2**/Ar^2	**3**/R^1	6/ yield(%)[b,c]	ee (%)[d]
1	**1a**/Ph	**2a**/4-BrC_6H_4	**3a**/H	**6a**/45	91
2	**1b**/4-MeC_6H_4	**2a**/4-BrC_6H_4	**3a**/H	**6b**/43	95
3	**1c**/4-ClC_6H_4	**2a**/4-BrC_6H_4	**3a**/H	**6c**/51	99
4	**1d**/4-BrC_6H_4	**2a**/4-BrC_6H_4	**3a**/H	**6d**/47	96
5	**1e**/3-BrC_6H_4	**2a**/4-BrC_6H_4	**3a**/H	**6e**/46	98
6	**1f**/2-$MeOC_6H_4$	**2a**/4-BrC_6H_4	**3a**/H	**6f**/38	95
7	**1a**/Ph	**2b**/4-ClC_6H_4	**3a**/H	**6g**/46	90
8	**1a**/Ph	**2c**/3-ClC_6H_4	**3a**/H	**6h**/42	90
9	**1a**/Ph	**2d**/3,4-$Cl_2C_6H_3$	**3a**/H	**6i**/52	92
10	**1a**/Ph	**2e**/3,4-$F_2C_6H_3$	**3a**/H	**6j**/53	94
11	**1a**/Ph	**2f**/3,5-$F_2C_6H_3$	**3a**/H	**6k**/43	93
12	**1a**/Ph	**2g**/3-F,4-BrC_6H_3	**3a**/H	**6l**/41	88
13	**1a**/Ph	**2a**/4-BrC_6H_4	**3b**/4-MeO	**6m**/47	76
14	**1a**/Ph	**2a**/4-BrC_6H_4	**3c**/6-MeO	**6n**/45	98
15	**1a**/Ph	**2a**/4-BrC_6H_4	**3d**/4-Cl	**6o**/51	98
16	**1a**/Ph	**2a**/4-BrC_6H_4	**3e**/4-Br	**6p**/53	97
17	**1a**/Ph	**2a**/4-BrC_6H_4	**3f**/4-^{t}Bu	**6q**/42	97

[a] Reaction conditions: **1**/H_2O/**2**/**3** was 1.5/0.5/1.2/1.0. [b] Isolated yield of **6.** [c] only single diastereoisomer. [d] Determined by chiral HPLC with IC or OD-H column.

Under the optimized reaction conditions, the generality of this enantioselective cascade protocol for preparation of seven-membered-ring *O*, *O*-acetals was investigated, and the results are shown in Table 1. Several subtituted aromatic diazoesters afforded the corresponding *O*, *O*-acetals 6 in moderate yields and execllect steroselectivity (entries 1-6). The daizo substrate 1b bearing 4-methyl substituent also gave the desired product with a high diastereoselectivity (>99:1) and enantioselectivity (entry 2). It is worthy to mention that 2-MeO-phenyldiazoacetate 1f with large steric hindrance was equally effective, providing the desired product **6f** in 38% yield with 95% ee (entry 6). Moderate yields with high dr and ee values were obtained for the substrates bearing halogen groups in 3- or 4-position of the aryl rings of anilines (entries 7-11). However, when 3-fuloro-4-bromo phenylamine were used, the ee value slightly decreased to 88% (entry 12). A number of substituted methyl 3-(2-formylphenoxy)propenoates were also employed in this reaction (entries 13-17), and varying substitution patterns were found to be tolerated except 4-MeO substrate **3b**, which reacted in a moderate yield (47%) with high diasteroselectivity but relatively lower enantioselectivity (76% ee, entry 13).

To probe the reaction mechanism, Mannich additional products **7i** and **7i'**, [10g] the potential intermediate, were successfully isolated in 65% yield with 90:10 dr, and gave the major intermediate **7i** with 92% ee and the minor **7i'** with no enatioselectivity (see ESI, Scheme S1). Furthermore, **7i** can offer the corresponding product **6i** under the standard DBU-catalyzed conditions in 90% isolated yield with a good steroselectivity (dr >99:1 and ee 91%). While the minor intermediate **7i'** cannot be transferred into **6i'** under the same conditions even the reaction time was extended to 48 hours. These results indicated that Mannich additional products **7i** from the ylide trapping process were the possible intermediates in this four-component cascade transformation. The similar dr and ee values of intermediate **7i** to the resulting product **6i** also imply that the first and second chiral carbon centers in **6** are catalytically introduced by chiral phosphoric acid **4**, and the third chiral carbon center is well controlled by the first and second chiral carbon centers.



Scheme 2. The possible transition state for the specified stereoselectivity of oxy-Michael additon.

On the basis of these preliminary results, this multi-component transformation was possible promoted as expectation (see ESI, Scheme S2). The *in situ* formed protic oxonium ylide (**I**) [10] was immediately trapped by Brønsted acid-activated bifunctional electrophile **II** [16] that generated from aniline **2** and methyl 3-(2-formylphenoxy) propenoate

3, leading to the optically active intermediate **7**. A possible transition state of oxy-Michael addition for the excellent diastereoselectivity had been proposed and illustrated in Scheme 2. The observed product **6d** (favorable product) arised from the intermediate **7d** *via* the transition state **A** in which the enol group maintained in an equatorial position. The possible minor product **6d''** was not observed in this reaction, which was possibly attributed to the more steric hindrance between the ester group and the enol group in the unfavorable transition **B**. The absolute structure of major product **6d** was confirmed by X-ray crystal structures (see ESI).

Conclusions

We have developed a four-component cascade transformation based on $Rh_2(OAc)_4$ and chiral Brønsted acids-co-catalyzed Mannich/base-catalyzed oxy-Michael additional reaction. The transformation features a mild, rapid and efficient method to synthesize densely substituted seven-membered-ring O,O-acetals bearing a quaternary stereogenic carbon center from simple starting precursors in moderate yields with high diastereoselectivity and enantioselectivity. Further expansion of substrates is being pursued in our lab.

Notes and references

Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, East China Normal University, 3663 North Zhongshan Rd., Shanghai, China. Fax: 86-21-62221237; Tel: 86-21-62221235; E-mail: syliu@sist.ecnu.edu.cn; whu@chem.ecnu.edu.cn

† Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 For reviews of multicomponent reaction, see: (a) I. Ugi, *Pure Appl. Chem.* 2001, **73**, 187; (b)V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen and L. Balagopal, *Acc. Chem. Res.*, 2003, **36**, 899; (c) A. Dömling, *Chem. Rev.*, 2005, **106**, 17; (d)B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463; (e) J. Yu, F. Shi and L.-Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156; (f) C. de Graaff, E. Ruijter and R. V. A. Orru, *Chem. Soc. Rev.*, 2012, **41**, 3969.

2 For reviews of cascade reaction, see: (a) R. Kazem Shiroodi and V. Gevorgyan, *Chem. Soc. Rev.*, 2013, **42**, 4991; (b) X. Zeng, *Chem. Rev.*, 2013, **113**, 6864; (c) U. Wille, *Chem. Rev.*, 2012, **113**, 813; (d) C. J. Ball and M. C. Willis, *Eur. J. Org. Chem.*, 2013, **2013**, 425.

3 For selected examples of multicomponent cascade reactions: (a) Y. Chi, S. T. Scroggins and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2008, **130**, 6322; (b) W. Shu, G. Jia and S. Ma, *Angew. Chem. Int. Ed.*, 2009, **48**, 2788; (c) J. Jiang, X. Guan, S. Liu, B. Ren, X. Ma, X. Guo, F. Lv, X. Wu and W. Hu, *Angew. Chem. Int. Ed.*, 2012, **52**, 1539; (d) R. Y. Nimje, M. V. Leskinen and P. M. Pihko, *Angew. Chem. Int. Ed.*, 2013, **52**, 4818.

4 (a) Y. Chi, S. T. Scroggins and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2008, **130**, 6322; (b) A. Dondoni and A. Massi *Acc. Chem. Res.* 2006, **39**, 451; (c) J. Yu, F. Shi and L. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156.

5 J. E. Aho, P. M. Pihko and T. K. Rissa, *Chem. Rev.*, 2005, **105**, 4406.

6 (a)N. Rehnberg, A. Sundin and G. Magnusson, *J. Org. Chem.*, 1990, **55**, 5477; (b)H.-G. Schmalz, E. Heßler, J. W. Bats and G. Dürner, *Tetrahedron Lett.*, 1994, **35**, 4543; (c)D. Seebach, A. R. Sting and M. Hoffmann, *Angewandte Chemie International Edition in English*, 1996, **35**, 2708; (d)C. Mavragani and H. Moutsopoulos, *Clinical Reviews in Allergy & Immunology*, 2007, **32**, 284; (e) E.M. Carreira, L. Kvaerno, *Classics in Stereoselective Synthesis*; Wiley-VCH: 2009.

7 (a)S. G. Davies and L. M. A. R. B. Correia, *Chem. Commun.*, 1996, **0**, 1803; (b)H. Matsutani, S. Ichikawa, J. Yaruva, T. Kusumoto and T. Hiyama, *J. Am. Chem. Soc.*, 1997, **119**, 4541; (c)S. D. Rychnovsky and B. M. Bax, *Tetrahedron Lett.*, 2000, **41**, 3593; (d)M. Uchiyama, M. Oka, S. Harai and A. Ohta, *Tetrahedron Lett.*, 2001, **42**, 1931; (e)M. D. Spantulescu, M. A. Boudreau and J. C. Vederas, *Org. Lett.*, 2008, **11**, 645.

8 For selected examples of organocatalytic asymmetric synthsis stereogenic acetals: (a)I. Čorić, S. Müller and B. List, *J. Am. Chem. Soc.*, 2010, **132**, 17370; (b)I. Čorić, S. Vellalath and B. List, *J. Am. Chem. Soc.*, 2010, **132**, 8536; (c)S. Vellalath, I. Čorić and B. List, *Angew. Chem. Int. Ed.*, 2010, **49**, 9749; (d)K. Asano and S. Matsubara, *Org. Lett.*, 2012, **14**, 1620; (e)T. Okamura, K. Asano and S. Matsubara, *Chem. Commun.*, 2012, **48**, 5076; (f)J. H. Kim, I. Čorić, S. Vellalath and B. List, *Angew. Chem. Int. Ed.*, 2013, **52**, 4474.

9 For selected examples of metal catalytic asymmetric synthsis stereogenic acetals: (a)H. Nagano and T. Katsuki, *Chem. Lett.*, 2002, **31**, 782; (b)Y. Kawamura, Y. Kawano, T. Matsuda, Y. t. Ishitobi and T. Hosokawa, *J. Org. Chem.*, 2009, **74**, 3048; (c)S. Handa and L. M. Slaughter, *Angew. Chem. Int. Ed.*, 2012, **51**, 2912; (d) X. Wang, Z. Han, Z. Wang and K. Ding, *Angew. Chem. Int. Ed.*, 2012, **51**, 936.

10 For selected examples of oxonium ylides trapping reactions: (a) C. D. Lu, H. Liu, Z. Y. Chen, W. H. Hu and A. Q. Mi, *Org. Lett.*, 2005, **7**, 83; (b) H. X. Huang, X. Guo and W. H. Hu, *Angew. Chem. Int. Ed.*, 2007, **46**, 1337; (c)W. H. Hu, X. F. Xu, J. Zhou, W. J. Liu, H. X. Huang, J. Hu, L. P. Yang and L. Z. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 7782; (d)X. F. Xu, J. Zhou, L. P. Yang and W. H. Hu, *Chem. Commun.*, 2008, **44**, 6564; (e)X. Zhang, H. X. Huang, X. Guo, X. Y. Guan, L. P. Yang and W. Hu, *Angew. Chem. Int. Ed.*, 2008, **47**, 6647; (f) X. Y. Guan, L. P. Yang and W. H. Hu, *Angew. Chem. Int. Ed.*, 2010, **49**, 2190; (g)Y. Qian, C. Jing, T. Shi, J. Ji, M. Tang, J. Zhou, C. Zhai and W. Hu, *ChemCatChem.*, 2011, **3**, 653; (h)X. Xu, Y. Qian, L. Yang and W. Hu, *Chem. Commun.*, 2011, **47**, 797; (i)Y. Qian, C. Jing, S. Liu and W. Hu, *Chem. Commun.*, 2013, **49**, 2700.

11 For selected examples of ammonium ylides trapping reactions: (a)Y. H. Wang, Y. X. Zhu, Z. Y. Chen, A. Q. Mi, W. H. Hu and M. P. Doyle, *Org. Lett.*, 2003, **5**, 3923; (b)J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang and W.-H. Hu, *J. Am. Chem. Soc.*, 2011, **133**, 8428; (c) C.-Y. Zhou,

J.-C. Wang, J. Wei, Z.-J. Xu, Z. Guo, K.-H. Low and C.-M. Che, *Angew. Chem. Int. Ed.*, 2012, **51**, 11376.

12 For selected examples of ziwwtterions trapping reactions: (a) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle and W.-H. Hu, *Nat. Chem.*, 2012, **4**, 733; (b) W. Hu, M. Li, L. Zan, D. Prajapati, *Org. Biomol. Chem.,* 2012, **10**, 8808; (c) Xing, C. Jing, X. Li, H. Qiu, W. Hu, *Org. Lett.,* 2013, **15**, 3578.

13 For selected reactions of 3-(2-formylphenoxy)propenoates: (a)M. S. Kerr, J. Read de Alaniz and T. Rovis, *J. Am. Chem. Soc.*, 2002, **124**, 10298; (b)S.-L. Cui, J. Wang, X.-F. Lin and Y.-G. Wang, *J. Org. Chem.*, 2007, **72**, 7779; (c)I. Kim, H.-K. Na, K. R. Kim, S. G. Kim and G. H. Lee, *Synlett*, 2008, **2008**, 2069.

14 For examples of diastereoselective cyclic acetal syntheses by intramolecular oxy-Michael addition via hemiacetal formation, see: a) D. A. Evans and J. A. Gauchet-Prunet, *J. Org. Chem.*, 1993, **58**, 2446; (b) H. Watanabe, K. Machida, D. Itoh, H. Nagatsuka and T. Kitahara, *Chirality*, 2001, **13**, 379; (c) P. A. Evans, A. Grisin and M. J. Lawler, *J. Am. Chem. Soc.*, 2012, **134**, 2856.

15 For examples of diastereoselective intramolecular aza-Michael reactions see: (a)D. Enders, C. Wang and J. X. Liebich, *Chem. Eur. J.*, 2009, **15**, 11058; (b)H. Pellissier, *Chem. Rev.*, 2012, **113**, 442.

(a) A. E. Allen and D. W. C. MacMillan, *Chem. Sci.*, 2012, **3**, 633; (b) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744; (c) A.G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713; (d) D. Uraguchi and M. Terada. *J. Am. Chem. Soc.*, 2004, **126**, 5356; (e) Z. Han, H. Xiao, X. Chen and L. Gong, *J. Am. Chem. Soc.,* 2009, **131**, 9182.Citations here in the format A. Name, B. Name and C. Name, *Journal Title*, 2000, **35**, 3523; A. Name, B. Name and C. Name, *Journal Title*, 2000, **35**, 3523.