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Neutral Alcohol Nucleophiles for the Substitution of α-Bromo Arylacetates and Applications to Asymmetric Synthesis of Morpholine Derivatives

Wongi Park,[a] Yongtae Kim[a] and Yong Sun Park*[a]

Abstract: Highly stereoselective C-O bond formation in AgOTf-catalyzed substitution of configurationally labile α-bromo arylacetates with neutral alcohol is developed. Also, application of this asymmetric synthetic methodology to the preparation of highly enantioenriched 2-aryl substituted morpholine derivatives is presented.

Introduction

Structural motifs containing oxygen bearing stereocenters are ubiquitous in natural products and important bioactive molecules. Synthetic strategies for stereoselective carbon-oxygen bond formation continue to expand the range of functional groups that could be incorporated.[1] Despite these advances, the subject of stereoselective reactions of configurationally labile α-halo acetates with neutral alcohol nucleophiles has never been explored before.[2] Introduction of alkyloxy group by the substitution of alkyl halide with neutral alcohol under base-free conditions is challenging and offers advantages in mild conditions and easier handling of reagents.[3] As the nucleophilicity of neutral alcohol is not sufficient for a direct attack at α-halo acetates, the activation of the carbon-halogen bond is needed. Lewis acid can complex strongly with a halogen to weaken the carbon-halogen bond.[4] We herein report the first Lewis acid catalyzed stereoselective substitution of α-bromo arylacetates with alcohols to afford α-alkoxy arylacetates. The practical utility of this methodology is also demonstrated by the preparation of highly enantioenriched morpholine derivatives.

In our most recent study on the dynamic resolution of α-bromo arylacetate **1** using *N*-benzoyl-*L*-threonine isopropyl ester, we observed that a diastereomer of **1** showed interesting crystallization behavior. Highly diastereoenriched (*αR*)-**1** was obtained as a solid by crystallization-induced dynamic resolution (CIDR) with up to >99:1 diastereomeric ratio (dr) and efficiently used in nucleophilic substitution.[5] Given the ready availability of optically pure α-bromo arylacetates by CIDR, we recently envisaged that (*αR*)-**1** could be activated by Lewis acid for the reaction with neutral alcohol nucleophiles as shown in Figure 1. This process could be extremely useful for the asymmetric synthesis of α-alkoxy arylacetates using a wide variety of easily available alcohol nucleophiles.

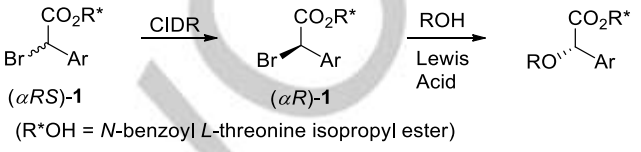

Figure 1. Asymmetric synthesis of α-alkoxy arylacetates.

Results and Discussion

Initial studies on the substitution of α-bromo phenylacetate **1a** were carried out with methanol as a nucleophile as shown in Table 1. When α-bromo phenylacetate **1a** of 50:50 dr was treated with methanol (3.0 equiv) in $CHCl_3$ without Lewis acid catalyst, no conversion occurred as expected (entry 1). We next attempted the same reaction in the presence of some selected Lewis acids. When $AlCl_3$, $FeCl_3$, or Ag_2O was used as a Lewis acid, the reaction barely proceeded to give α-methoxy phenylacetate **2** as shown in entries 2-4. With strongly halophilic silver salts, AgOTf and AgO_2CCF_3, the reactions with **1a** of 50:50 dr were completed within 20 h and produced **2** without a noticeable stereoselectivity (entries 5 and 6), which indicates that the dynamic kinetic resolution of α-bromo phenylacetate (α*RS*)-**1a** is not functioning in this Lewis acid catalyzed substitution. The reaction of α-chloro phenylacetate gave **2** with a much lower conversion (26%) and a little stereoselectivity of 67:33 dr (entry 7). When α-bromo acetate **1a** of 86:14 dr or 99:1 dr was treated with methanol under the same conditions, α-methoxy phenylacetate **2** was obtained with somewhat decreased stereoselectivities of 74:26 dr and 91:9 dr, respectively, as shown in entries 8 and 9. The observed conversions and drs of **2** indicate that the α-bromo stereogenic center is configurationally labile under the reaction conditions and the rate of substitution is not sufficiently fast with respect to the epimerization promoted by AgOTf.[6]

In order for α-bromo phenylacetate (*αR*)-**1a** to be advantageously utilized in the reaction with alcohol, the substitution should be much faster than the epimerization of (*αR*)-**1a** on exposure to Lewis acid. As a simple way of increasing the rate of substitution with respect to the epimerization, we used more excess amounts of methanol as shown in entries 10-15. The nucleophilic substitution (S_N2) of (*αR*)-**1a** of 99:1 dr with 10 equiv. of methanol produced (*αS*)-**2** with 96:4 dr (entry 10).[7] Our attempt to improve the dr of **2** using other solvents such as *n*-hexane, DMF, THF and CH_3CN didn't succeed to give higher yield and dr as shown in entries 11-14. We next explored the utility of neat conditions with 10 equiv. of methanol nucleophile. Pleasingly, as shown in entry 15, the neat

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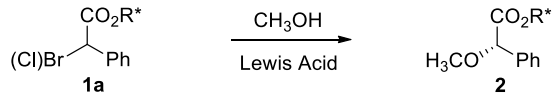
reaction of (*αR*)-**1a** with methanol in the presence of AgOTf are completed faster than the solution reactions to afford (*αS*)-**2** with 99:1 dr.[8]

Table 1. Optimization of the substitution conditions



(R*OH = *N*-benzoyl *L*-threonine isopropyl ester)

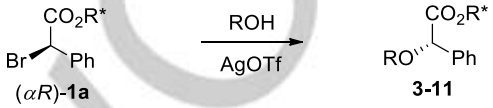
Entry[a]	Dr of **1a**	Lewis Acid	Equiv of Nuc (Solvent)	Conv.[b]	Dr[b]
1	50:50	none	3.0 ($CHCl_3$)	0	-
2	50:50	$AlCl_3$	3.0 ($CHCl_3$)	0	-
3	50:50	$FeCl_3$	3.0 ($CHCl_3$)	7	51:49
4	50:50	Ag_2O	3.0 ($CHCl_3$)	0	-
5	50:50	AgOTf,	3.0 ($CHCl_3$)	99	53:47
6	50:50	AgO_2CCF_3	3.0 ($CHCl_3$)	99	51:49
7	50:50 (Cl)	AgOTf,	3.0 ($CHCl_3$)	26	67:33
8	86:14	AgOTf,	3.0 ($CHCl_3$)	99	74:26
9	99:1	AgOTf	3.0 ($CHCl_3$)	99	91:9
10	99:1	AgOTf	10 ($CHCl_3$)	99	96:4
11	99:1	AgOTf	10 (*n*-hexane)	74	96;4
12	99;1	AgOTf	10 (DMF)	13	93:7
13	99:1	AgOTf	10 (THF)	47	96:4
14	99:1	AgOTf	10 (CH_3CN)	5	95:5
15	99:1	AgOTf	10 (neat)	99	99:1

[a] The reactions were carried out with Lewis acid (1.2 equiv) in solvent (0.5 M) at rt for 20 h. [b] The conversions and drs were determined by ^{1}H NMR of the reaction mixture.

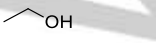
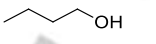
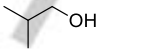
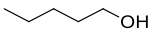
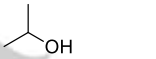
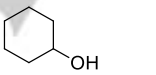
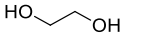
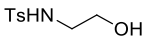
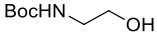
A range of alcohols was then investigated as nucleophiles in the substitution reaction with α-bromo phenylacetate (*αR*)-**1a** under neat conditions. All the tested aliphatic alcohols underwent the substitution reaction smoothly to afford the corresponding α-alkoxy acetates **3**-**11** with excellent yields (85–95%) and high drs. The steric demand of the alkyl group of alcohol nucleophile did not play an important role, with most of selected primary and secondary alcohols furnishing the best results described in entries 1-6. However, no substitution product was obtained in the reaction with highly sterically hindered *tert*-butyl alcohol. In the reaction with ethylene glycol, the mono substituted hydroxyethyl ether **9** was isolated in a much lower yield of 38% with the same high dr (entry 7). In addition, coupling of (*αR*)-**1a** with protected amino alcohols such as *N*-tosyl-2-aminoethanol and *N*-Boc-2-aminoethanol successfully yielded α-(2-aminoethoxy) phenylacetates **10** and **11** with 99:1 dr in 87% and 91% yields, respectively, as shown in entries 8 and 9.

The substitutions with phenol derivatives showed interesting results as depicted in Scheme 1. Our first examination with phenol and *p*-chlorophenol showed that they do not have appropriate reactivity with **1a** to give substitution products under the same conditions and most of **1a** was recovered. When phenol was activated with an electron donating methoxy group, the reactions provided the substitution products and showed interesting regioselectivity, which is markedly dependent on the structure of methoxyphenol nucleophiles. With *para*-methoxyphenol nucleophile, the substitution of (*αR*)-**1a** provided α-aryloxy substituted acetate exclusively and following reduction with $LiAlH_4$ afforded phenoxyethanol **12** with 97:3 enantiomeric ratio (er) in 58% overall yield. In contrast, in the reaction with *ortho*-methoxyphenol, *C*-alkylation is favored over *O*-alkylation. The substitution of (*αR*)-**1a** with *ortho*-methoxyphenol and following reduction provided diarylethanol **13** and phenoxyethanol **14** in a ratio of 3:1. The AgOTf-catalyzed Friedel-Crafts alkylation product **13** was isolated in 51% overall yield with 98:2 er and the *O*-alkylation product **14** was isolated in 20% overall yield with 97:3 er.[9]

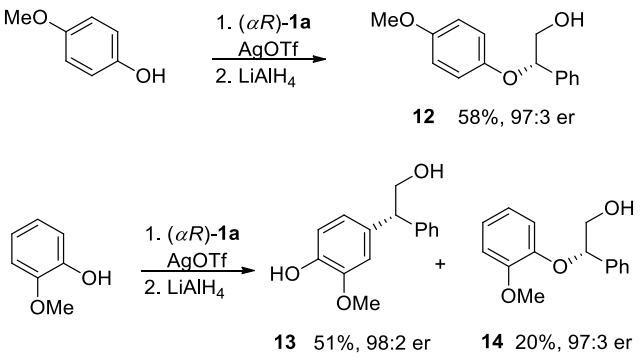
Table 2. Nucleophilic substitutions with alcohols



(R*OH = *N*-benzoyl *L*-threonine isopropyl ester)

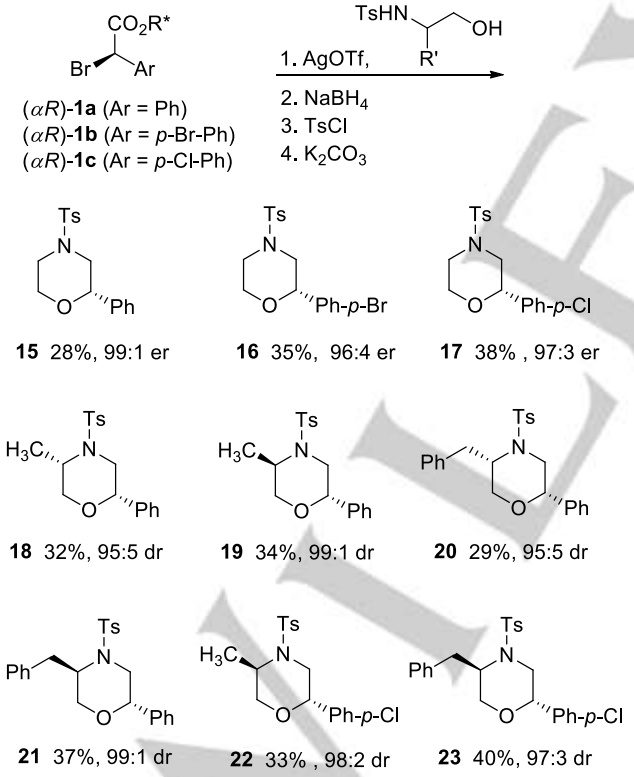
Entry [a]	ROH	Product	Yield (%)	Dr[b]
1		**3**	92	99:1
2		**4**	98	98:2
3		**5**	84	99:1
4		**6**	91	99:1
5		**7**	88	99:1
6		**8**	83	99:1
7		**9**	38	99:1
8		**10**	87	99:1
9		**11**	90	99:1

[a] All the reactions were carried out with 1.2 equiv of AgOTf at rt for 10 h under neat conditions (if needed for solubility reason, we used least possible amount of solvent, $CHCl_3$). [b] The dr values were determined by ^{1}H NMR of the reaction mixture.



Scheme 1. Substitutions of (*αR*)-**1a** with methoxyphenols.

Morpholines are common structural cores of a broad range of biological and pharmacological natural or synthetically important organic molecules.[10] Given the prevalence and importance of this class of compounds, we applied the synthetic methodology to the asymmetric preparation of morpholine analogues starting from (*αR*)-**1a-c** and *N*-tosyl 2-aminoethanols as building blocks. The four-step synthetic sequences afforded morpholine derivatives **15-23** in 28-40% overall yields with high stereoselectivities up to 99:1 er or dr. The substitution of (*αR*)-**1a-c** with *N*-tosyl 2-aminoethanol, reduction by $NaBH_4$, tosylation of the alcohol and ring closure with K_2CO_3 afforded *N*-tosyl 2-aryl substituted morpholines **15**, **16** and **17** with 99:1 er, 96:4 er, and 97:3 er, respectively as shown in Scheme 2. Also, 2,5-disubstituted morpholine derivatives **18-23** were successfully prepared using 2-alkyl substituted 2-aminoethanols. In the reactions of (*αR*)-**1a** with *N*-tosyl *L*- and *D*-alaninol nucleophiles, no stereo-differentiation with the chiral alcohols was observed in the substitution step and the substitution products were obtained with 99:1 dr in both reactions. After the four-step transformation sequence, however, *cis*-morpholine **18** was obtained with a lower dr of 95:5 than that of *trans*-morpholine **19**. Similar results were found with *N*-tosyl *L*- and *D*-phenylalaninol nucleophiles to produce *cis*-morpholine **20** with 95:5 dr and *trans*-morpholine **21** with 99:1 dr.[11] In addition, the same reactions of (*αR*)-**1c** with *D*-alaninol and *D*-phenylalaninol produced *trans*-morpholines **22** with 98:2 dr and **23** with 97:3 dr, respectively.



Scheme 2. Asymmetric synthesis of *N*-tosyl-2-aryl-morpholines.

Conclusions

We have developed an efficient synthetic method for the highly stereoselective carbon–oxygen bond formation by AgOTf-catalyzed substitution of α-bromo arylacetates with alcohol nucleophiles. At the best of our knowledge, no previous studies have investigated the stereoselective substitution of α-halo acetates with neutral alcohols under mild acidic conditions. The capacity to install oxygen bearing stereocenters in direct proximity to ester groups allows for a diverse range of synthetic elaboration. The evidence for the synthetic efficiency of this method was demonstrated by a concise asymmetric synthesis of *N*-tosyl 2-aryl-morpholine derivatives.

Experimental Section

Supporting Information (see footnote on the first page of this article): Experimental details and copies of NMR spectra and HPLC chromatograms are provided in supporting information

Acknowledgments

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Keywords: Asymmetric synthesis • Nucleophilic Substitution • Crystallization • Lewis acid • Alcohol

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[3] The reactions of α-halo acetates with metal alcoholates gave complex mixtures or predominantly led to cleavage of the ester before the substitution at α-position.

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[6] When (*αR*)-**1a** of >99:1 dr was allowed to epimerize in the presence of AgOTf (1.2 equiv) in $CDCl_3$ (0.5M), (*αR*)-**1a** was recovered with 98:2 dr after 0.5 h, 96:4 dr after 1 h, 93:7 dr after 2 h, and 80:20 dr after 5 h.

[7] The absolute configuration of (*αS*)-**2** is determined after reductive cleavage of the chiral auxiliary to give (*S*)-2-methoxy-2-phenylethan-1-ol, by comparing the optical rotation and the chiral HPLC analysis of previously reported compound.[1e] Also, the absolute configurations of morpholine derivatives **15**, **18**, **19** and **21** are confirmed by comparison of the optical rotation and/or the chiral HPLC analysis of reported values.[12c-g] The complete inversion of stereochemistry and the rate dependency on alcohol concentration indicate the occurrence of S_N2-type reaction.

[8] Under neat conditions, conversions of 50% or more were reached in a relatively short time (0.5 h), while completion of the reaction requires a much longer time (up to 10 h).

[9] The regioisomeric structure of **13** was confirmed after the conversion to methyl 2-(4-benzyloxy-3-methoxyphenyl)-2-phenylacetate by comparing the NMR spectra with those of previously reported. K. Taniguchi, Y. Miyao, K. Yamano, T. Yamamoto, T. Terai, T. Kusunoki, K. Tsubaki, Y. Shiokawa, *Chem. Pharm. Bull.* **1996**, *44*, 1188-1195.

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[11] We reasoned that the epimerization occurred during the cyclization step to convert *cis*-morpholines **18** and **20** into thermodynamically more stable *trans*-morpholines **19** and **21** under the basic conditions. When a solution of **18** (95:5 dr) in CH_3CN was stirred with K_2CO_3 for 2 days under the same cyclization conditions, **18** was recovered with a dr of 92:8.

[12] a) K. Seth, S. R. Roy, B. V. Pipaliya, A. K. Chakraborti, *Chem. Commun.,* **2013**, *49*, 5886–5888; b) P. N. Devine, R. M. Heid Jr., D. M. Tschaen, *Tetrahedron* **1997**, *53*, 6739-6746; c) M. K. Ghorai, D. Shukla, A. Bhattacharyya *J. Org. Chem.* **2012**, *77*, 3740−3753; d) H. Sun, B. Huang, R. Lin, C. Yang, W. Xia, *Beilstein J. Org. Chem.* **2015,** *11,* 524–529; e) J. V. Matlock, T. D. Svejstrup, P. Songara, S. Overington, E. M. McGarrigle, V. K. Aggarwal, *Org. Lett.* **2015**, *17*, 5044−5047; f) S. J. Gharpure, J. V. K. Prasad, *J. Org. Chem.* **2011**, *76*, 10325-10331; g) B. Ritzen, S. Hoekman, E. D. Verdasco, F. L. van Delft, F. P. J. T. Rutjes, *J. Org. Chem.* **2010**, *75*, 3461–3464.

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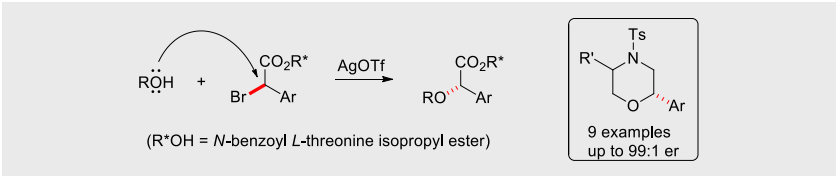

Highly stereoselective C-O bond formation in AgOTf-catalyzed substitution of α-bromo arylacetates with neutral alcohol nucleophiles is developed and applied to the preparation of highly enantioenriched 2-aryl-morpholine derivatives.

*nucleophilic substitution

Stereoselective C–O bond formation*

*W. Park, Y. Kim, Y. S. Park**

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