Asymmetric Synthesis

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Construction of Enantiomerically Enriched Tertiary α-Hydroxycarboxylic Acid Derivatives by Phase-Transfer-Catalyzed Asymmetric Alkylation of Diaryloxazolidin-2,4-diones**

*Takashi Ooi, Kazuhiro Fukumoto, and Keiji Maruoka**

The direct alkylation of enolates is an important method for the formation of carbon–carbon bonds in synthetic organic chemistry. The concept of diastereoselective alkylation by using chiral auxiliaries has played a dominant role over the past three decades for rigorously controling the stereochemistry. The establishment of systems useful for a broad range of substrates has resulted in chiral auxillaries attaining a preeminent position in the field.[1] On the other hand, complementary catalytic variants have been much less developed despite their practical and fundamental importance.[2] In contrast to the recent emergence of highly efficient transition-metal-catalyzed processes for asymmetric allylations,[2,3] arylations,[2] and vinylations[4] of enolates, reliable protocols for catalytic enantioselective alkylation involving sp^3-hybridized electrophiles, such as alkyl halides, are still restricted.[2,5,6] Although chiral phase-transfer catalysis has made a significant contribution to this area,[2,6] the major drawback of this strategy is that it is only effective for a limited pool of substrates. In particular it has limited applicability in accessing enantioenriched carbonyl compounds of high value which possess quaternary α-carbon stereocenters.[7] Our approach toward this largely unsolved problem utilizes 3,5-diaryloxazolidin-2,4-diones **2** as novel oxygen-containing substrates that undergo highly enantioselective alkylation under mild phase-transfer conditions in the presence of the N-spiro chiral quaternary ammonium bromide **1e** as catalyst (Scheme 1).[8] This substrate–catalyst combination provides a new and practical entry to a wide range of tertiary α-hydroxy-α-aryl carboxylic acid derivatives.[9,10]

The requisite 3,5-diaryloxazolidin-2,4-diones **2** can be readily prepared from racemic α-hydroxy esters by sequential treatment with 1,1′-carbonyldiimidazole (CDI) and an appro-

[*] Dr. T. Ooi, K. Fukumoto, Prof. K. Maruoka
Department of Chemistry
Graduate School of Science
Kyoto University
Sakyo, Kyoto, 606-8502 (Japan)
Fax: (+81) 75-753-4041
E-mail: maruoka@kuchem.kyoto-u.ac.jp

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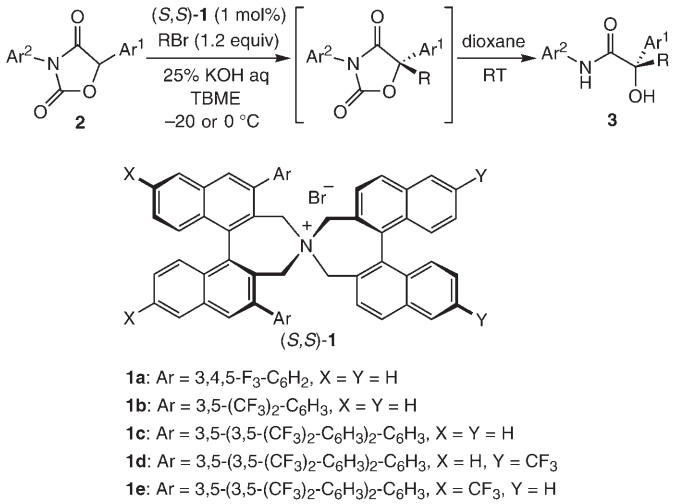


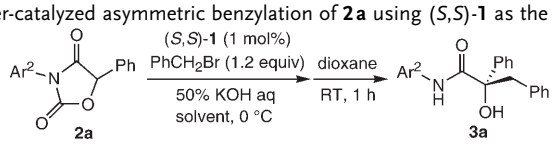
Scheme 1. Enantioselective alkylation of 3,5-diaryloxazolidin-2,4-diones **2** by phase-transfer catalysis of (*S*,*S*)-**1** to afford optically active tertiary α-hydroxy amides **3**.

priate aromatic amine (Ar^2NH_2) in CH_2Cl_2.[11] The feasibility of the stereoselective alkylation of **2** was examined under typical liquid–liquid phase-transfer conditions with 3,5-diphenyloxazolidin-2,4-dione (**2a**, $Ar^2 = Ph$) as a representative substrate and chiral quaternary ammonium bromide (*S*,*S*)-**1a**[12a,b] as the catalyst. The reaction of **2a** ($Ar^2 = Ph$) with benzyl bromide (1.2 equiv) in the presence of **1a** (1 mol%) in toluene/50% aqueous solution of KOH was found to proceed at 0°C, and TLC analysis confirmed the consumption of all the substrate **2a** after 18 h. Subsequent addition of dioxane and continuous stirring of the reaction mixture at room temperature for 1 h facilitated the one-pot partial hydrolysis to directly afford the corresponding tertiary α-hydroxy amide **3a** ($Ar^2 = Ph$) in 79% yield, albeit with low enantiomeric excess (19% *ee*; Table 1, entry 1). Switching the 3,3′-aromatic substituent (Ar) to a 3,5-bis(trifluoromethyl)phenyl group (**1b**)[12c] resulted in a diminished yield with a similar degree of enantioselectivity (entry 2). To our surprise, however, a dramatic improvement in the selectivity was attained in the reaction with **1c** (which has radially disposed 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl moieties) as a catalyst,[12d,e] and furnished **3a** ($Ar^2 = Ph$) in 85% yield and with 91% *ee* (entry 3).

We then focused on modifying the catalyst further by introducing an electron-withdrawing trifluoromethyl group at the 6,6′-positions of each binaphthyl subunit. Evaluation of the performance of the new chiral ammonium bromides **1d** and **1e** revealed the superiority of **1e** (entries 4 and 5); the phase-transfer-catalyzed benzylation of **2a** ($Ar^2 = Ph$) in the presence of **1e** gave the desired **3a** ($Ar^2 = Ph$) with 96% *ee*. Although the electronic nature of the aryl group (Ar^2) on the nitrogen atom of **2a** subtly affected the enantioselectivity and reaction efficiency (entries 6 and 7), we observed a beneficial effect of using ethereal solvents such as cyclopentyl methyl ether (CPME) and *tert*-butyl methyl ether (TBME). Substantial rate acceleration and virtually complete stereochemical control were achieved by using TBME (entries 8 and 9). It should be noted that the decreased chemical yield stems from hydrolysis prior to the alkylation because of the increased polarity of the solvent, which was overcome by reducing the concentration of the base to an aqueous solution of 25% KOH (entry 10).

With optimized conditions in hand, the scope of this new asymmetric enolate alkylation protocol was thoroughly investigated, and the representative results are summarized in Table 2.[13] In general, 1 mol% of **1e** with 1.2 equivalents of alkyl halide was sufficient for smooth alkylation, and in some cases the reaction was performed at lower temperature to enable the catalyst to achieve its full stereocontrol. A series of benzylic bromides of different steric and electronic properties were tolerated, thus allowing the preparation of structurally diverse, enantioenriched α-alkyl mandelic acid derivatives (entries 1–5). Construction of stereogenic quaternary carbon centers bearing allylic and propargylic substituents on **2** can also be achieved in a similar manner (entries 6–8). Both

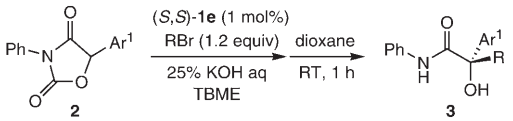
Table 1: Optimization of the phase-transfer-catalyzed asymmetric benzylation of **2a** using (*S*,*S*)-**1** as the catalyst.[a]

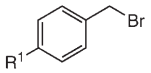
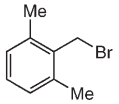
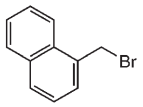


Entry	Catalyst	**2a** (Ar^2)	Solvent	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	**1a**	Ph	PhMe	18	79	19
2	**1b**	Ph	PhMe	20	65	19
3	**1c**	Ph	PhMe	19	85	91
4	**1d**	Ph	PhMe	20	83	92
5	**1e**	Ph	PhMe	19	87	96
6	**1e**	*p*-F-C_6H_4	PhMe	18	84	87
7	**1e**	*p*-MeO-C_6H_4	PhMe	17	81	94
8	**1e**	Ph	CPME	3	69	92
9	**1e**	Ph	TBME	5	75	99
10[d]	**1e**	Ph	TBME	7	82	99

[a] Unless otherwise specified, the reaction was carried out with 1.2 equiv of benzyl bromide in the presence of (*S*,*S*)-**1** (1 mol%) in a mixture of organic solvent and a 50% aqueous solution of KOH at 0°C for the given reaction time, after which dioxane was added and stirring was continued at room temperature for 1 h. [b] Yield of isolated product. [c] The enantiopurity of α-hydroxy amide **3a** was determined by HPLC analysis on a chiral stationary phase (DAICEL Chiralpak AS-H) with hexane/2-propanol as the solvent. The absolute configuration was deduced from that of **3g**. [d] Aqueous 25% KOH solution was used as a base.

Table 2: Catalytic asymmetric alkylation of 3-phenyl-5-aryloxazolidin-2,4-dione (**2**) under phase-transfer conditions.[a]



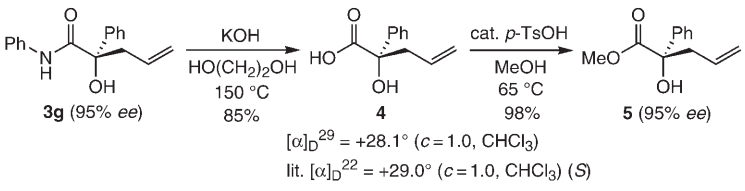
Entry	**2** (Ar^1)	RBr	T [°C]	t [h]	Yield[b] [%]	*ee*[c,d] [%]	Product
							
1	Ph (**2a**)	R^1 = Me	0	9	83	94	**3b**
2	Ph (**2a**)	R^1 = F	−20	23	81	97	**3c**
3	Ph (**2a**)	R^1 = Ph	0	8	80	94	**3d**
4	Ph (**2a**)		0	10	76	94	**3e**
5	Ph (**2a**)		−20	22	80	96	**3f**
6	Ph (**2a**)	$CH_2{=}CHCH_2Br$	0	7	83	95	**3g**
7	Ph (**2a**)	$CH_2{=}C(Me)CH_2Br$	−20	24	80	97	**3h**
8	Ph (**2a**)	$CH{\equiv}CCH_2Br$	0	9	81	86	**3i**
9	*p*-F-C_6H_4	$PhCH_2Br$	0	6	76	90	**3j**
10	*p*-MeO-C_6H_4	$PhCH_2Br$	−20	23	87	90	**3k**
11	2-furyl	$PhCH_2Br$	0	7	81	94	**3l**
12	2-thienyl	$PhCH_2Br$	−20	24	81	99	**3m**

[a] The reaction was carried out with 1.2 equiv of alkyl halide and 1 mol% of **1e** in a mixture of TBME and an aqueous 25% KOH solution under the given reaction conditions. [b] Yield of isolated product. [c] The enantiomeric excess of **3** was determined by HPLC analysis on a chiral stationary phase. [d] The absolute configuration of **3g** was assigned to be *S* by comparison of the optical rotation with the reported value after amide hydrolysis[13] (see Scheme 2).

electron-withdrawing and electron-donating substituents on **2** were also tolerated (entries 9 and 10). Moreover, the catalytic asymmetric quaternization of **2** possessing a heteroaromatic group as Ar^1 was feasible, and excellent enantioselectivity was observed (entries 11 and 12).

The tertiary α-hydroxy amide **3** thus obtained can be cleanly converted into the corresponding α-hydroxycarboxylic acid by simple treatment with KOH in ethylene glycol at 150 °C as shown in Scheme 2, and no loss in the enantiomeric excess of **4** was confirmed by HPLC analysis after further derivatization to its methyl ester **5**. The absolute configuration of **4** was assigned to be *S* by comparison of the optical rotation with the literature value.[14]

In conclusion, we have successfully introduced a new catalyst **1e** for realizing catalytic, highly enantioselective alkylation of substrates **2** under mild phase-transfer conditions. This system represents the first example of the catalytic asymmetric alkylation of glycolates that establishes stereogenic quaternary carbon centers, and offers direct access to various optically active tertiary α-hydroxy acids and their derivatives. These compounds are an important class of chiral building blocks, in particular for the preparation of complex biologically active substances.[15] Further investigations on expanding the scope of our approach in terms of both the nucleophiles and electrophiles are currently underway.



Scheme 2. Conversion of tertiary α-hydroxy amide **3g** into the corresponding α-hydroxy acid **4** and ester **5**.

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[13] Unfortunately, the present system was not effective for less reactive electrophiles; for example, the attempted methylation of **2a** with methyl iodide (10 equiv) under otherwise similar conditions afforded **3** ($Ar^1 = Ph$, $R = Me$) in 45% yield with 36% *ee*. In addition, alkylation with alkyl halides such as ethyl iodide and butyl iodide gave only O-alkylation product.

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