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Phase-transfer catalyzed glycolate conjugate addition

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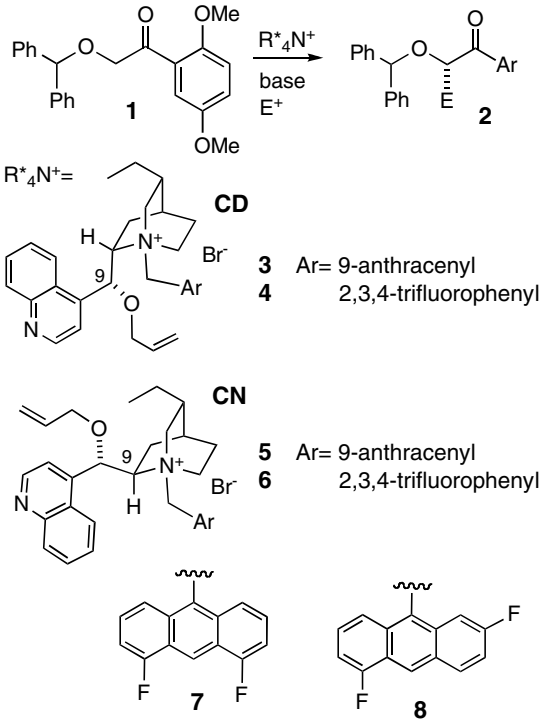
Abstract—Cinchonine based phase-transfer catalysts were developed for enantioselective conjugate additions to electron deficient alkenes, including acylates, acrylonitrile, and chalcone. *N*-Trifulorobenzyl cinchoninium bromide **6** catalyst (20 mol %) in THF at −40 °C promoted the conjugate addition of arylketone glycolate **1** generating *S*-product **2** in good yields and selectivities. Catalyst, solvent, and base variations are presented along with conditions to convert the products to intermediates useful for multistep applications.

Phase-transfer catalysis (PTC) has become a practical method for asymmetric synthesis.[1] The process is particularly attractive using benzophenone protected glycine for alkylation, conjugate addition, and epoxide formation.[2] PTC provides numerous benefits including the use of inexpensive cinchona-derived catalysts, which are readily available in pseudo-enantiomeric antipodes, the use of simple hydroxide bases, and mild conditions performed in either liquid–liquid or liquid–solid mode over an extended temperature range. The formation of C–C bonds through a direct alkylation is a significant synthetic challenge with only a few successes based on catalytic methods.[3] We previously reported PTC conditions for alkylations using diphenylmethyl (DPM) arylketone **1** to give *S*-products **2** with alkyl halides (Scheme 1).[3c,4] Optimal catalysts in this case proved to be the cinchonidine (CD) derived ammonium bromides **3** and **4**, previously developed by Corey, Lygo, and the group of Park and Jew.[5] The protected products **2** in this case are readily transformed to the corresponding hydroxyester intermediate. The new glycolate approach was applied to the synthesis of the diabetes drug ragaglitazar and the farnesyltransferase inhibitor kurasoin A.[4] This substrate has also been developed for asymmetric PTC aldol reactions where the cinchonine (CN) based catalysts **5** and **6** were shown to be most effective to generate protected 1,2-diol products.[6] We now report the development of a novel asymmetric PTC Michael-type conjugate addition with the substrate arylketone **1** to access glutaric acid derivatives, 1,5-dicarbonyl-2-hydroxy substituted products.

Diphenylmethyl (DPM) glycolate 2,5-dimethoxyphenyl ketone **1** was produced as before in three steps beginning with bromoacetic acid.[4] Various catalysts were initially



Scheme 1.

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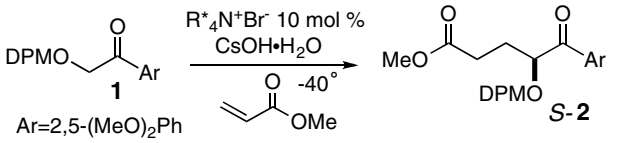
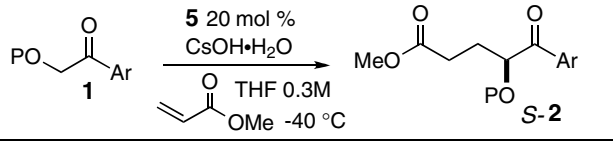
Table 1. Conditions for acrylate conjugate PTC



Entry	Solvent	Cat.	Time (h)	% Yield	% ee
1	THF	**3**	3	61	20
2	THF	**4**	3	60	27
3	THF	**5**	2	58	73
4	THF	**5**	7.5	59	81[a]
5	THF	**5**	1.5	**54**	**82**[b]
6	THF	**6**	2.5	60	63
7	DCM/*n*-hex	**6**	24	53	25
8	Tol	**6**	51	80	60
9	PhCl	**6**	9	71	42
10	THF/tol	**6**	16	77	59

[a] Using 20 mol % catalyst **5**.
[b] With 20 mol % **5** at concentration of 0.3 M.

Table 2. Substrate variations for conjugate PTC



Entry	P	Ar	Time (h)	% Yield	% ee
1	DPM	Ph	0.5	56	48
2	DPM	4-MeOPh	4.5	60	69
3	DPM	2-MeOPh	1.5	65	72
4	DPM	2,4-$(MeO)_2$Ph	6	51	65
5	DPM	2,5-$(MeO)_2$Ph	1.5	**54**	**82**
6	DPM	2,5-$(MeO)_2$Ph	0.25	70	64[a]
7	DPM	2,5-$(MeO)_2$Ph	0.75	62	78[b]
8	Bn	2,5-$(MeO)_2$Ph	5.5	**52**	**81**

[a] Performed at 0 °C.
[b] At −20 °C.

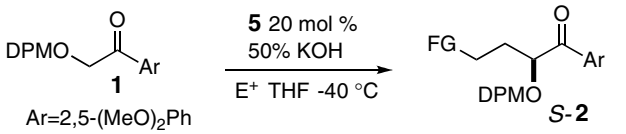
screened for reactivity using methacrylate (3.5 equiv) at −40 °C with cesium hydroxide hydrate (5 equiv) as base (0.2 M, Table 1). Cinchonidine (CD) derived catalysts **3**, **4** proved to be highly reactive; however the selectivities obtained were low at 20–27% ee (chiral HPLC, entries 1 and 2). THF was found to be the optimal solvent, providing for short reaction times. Cinchonine (CN) catalysts **5** and **6** were found to give high selectivities, again for *S*-isomer **2**, used in THF. When the catalyst load was increased to 20 mol %, *N*-anthracenylmethyl-**5** gave product with 82% ee and moderate yield of 54% after only 1.5 h (entry 5). This combination of catalyst **5** proved to be optimal in this case. Other catalysts investigated included C9-hydroxy and benzylated ethers, in the place of the *O*-allyl substituent, in both the CD and CN series. All were found to be inferior to CN-**5** showing very low (0–10% ee) selectivities. The Maruoka di-2-naphthylbisbinaphthyl ammonium bromide also gave **2** with low (10% ee) selectivity.[7] The more common, less-polar PTC solvents, dichloromethane, toluene, chlorobenzene, and various solvent combinations required much longer reaction times and gave product with lower selectivities (entries 7–10). In some cases, however, higher isolated yields of **2** were obtained.

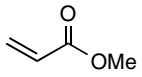
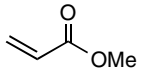
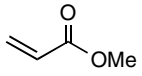
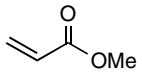
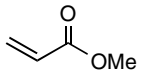
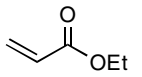
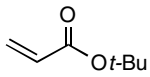
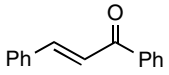
Catalyst **5** in THF was further explored with substrate variations (Table 2). While 2,5-dimethoxyphenyl DPM protected ketone **1** was the initial substrate, as optimized previously for PTC alkylation, we needed to access the effect of substrate variations on the new conjugate addition reaction. As seen previously,[4] the simple phenyl ketone **1** (entry 1) gave lower selectivity, 48% ee. The addition of electron rich methoxy groups showed improved yield and selectivity (entries 2–4). The more electron rich enolate will form a tighter ion-pair with the catalyst with accentuated van der Waals contacts generating improved selectivity. The position of the methoxyls in this case is also critical, as seen comparing 2,4-dimethoxy **1** (entry 4) at 65% ee for 6 h and 2,5-dimethoxy **1** (entry 5) at 82% ee after only 1.5 h as before shown in Table 1. Improved isolated yields were obtained, at the expense of selectivity, when the reaction was performed at higher temperatures. When performed at 0 °C, a yield of 70% (entry 6, 64% ee) was obtained. After only 15 min, the starting material **1** was consumed. At −20 °C, the reaction was complete in 45 min and a yield of 62% (entry 7, 78% ee) was found. The influence of the glycolate O-protecting groups was also explored. Previous PTC alkylations with **1** showed that the common benzyl group (Bn) at this position lowered the selectivity to 71% ee.[4] In this case for conjugate addition, **1** with a Bn group in the place of DPM also gave excellent selectivity at 81% ee (5.5 h, entry 8). Shorter reaction times (1.5 h) prompted continued investigation of the DPM substrate **1**.

Further improvements were found when conditions were explored using 50% aqueous KOH as base mixed with THF (Table 3). This combination allowed for sub-zero temperatures, at −40 °C with improved yield and selectivity. A 72% isolated yield was obtained with 83% ee with methacrylate (entry 1). Use of toluene or THF/toluene (7:3) as solvent further improved the selectivity to 86% ee (entries 2 and 3). Fluorinated anthracenylmethyl-CN catalysts **7** and **8**[8] were also shown under these conditions to give high selectivities at 83% and 79% ee (entries 4 and 5). Ethyl and *t*-butyl acrylate (entries 6 and 7) gave high selectivities, 82% and 78% ee, for conjugate addition using the THF/toluene mixture. Acrylonitrile proved to be a problematic electrophile giving low yields and high selectivity, as with CsOH·H_2O and using 50% KOH, 90% ee (entry 8). Chalcone, with a β-phenyl substituent, also reacted to give PTC conjugate addition products (entry 9). In this case a 2:3 mixture of *syn*:*anti* diastereomers was obtained with 73% and 27% ee, respectively. An X-ray crystal structure was obtained in this case for the purified major *anti* isomer.[9]

The *S*-stereochemistry of the addition products **2** was established by direct comparison to known material (Scheme 2). The labile DPM group was removed and a benzoate was attached to generate **9**. Baeyer–Villiger type oxidation conditions of Shibasaki,[10] as employed

Table 3. Conjugate PTC with other electrophiles

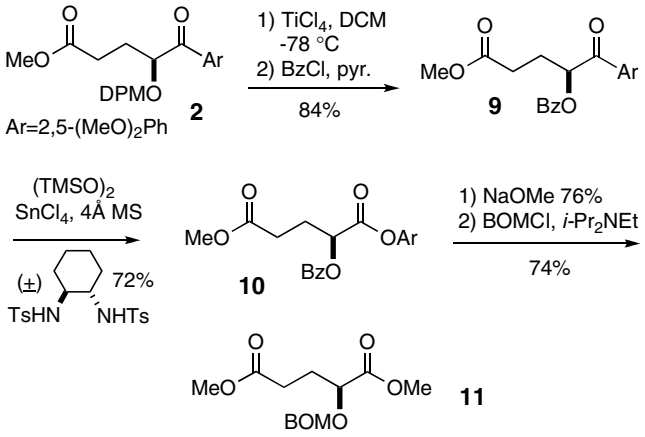


Entry	E^+	FG	Time	% Yield	% ee
1		CO_2Me	5	72	83
2		CO_2Me	3	52	86[a]
3		CO_2Me	7	75	86[b]
4		CO_2Me	10	59	83[c]
5		CO_2Me	7	68	79[d]
6		CO_2Et	6	68	82[b]
7		CO_2t-Bu	24	63	78[b]
8		CN	6	25	90[e]
9		PhCO, 3-Ph	19	63[f]	73[g]

[a] Using toluene as solvent.
[b] With THF/tol, 7:3.
[c] Using **7** as catalyst.
[d] With **8** as catalyst.
[e] Using $CsOHH_2O$.
[f] 2:3 ratio of *syn*, *anti* isomers.
[g] *syn* isomer, 27% ee for *anti*.

previously using bis-trimethylsilylperoxide with catalytic tin chloride and (±)-di-*p*-toluene sulfonamide cyclohexane,[3c] gave the aryl ester **10**. Treatment with sodium methoxide in methanol allowed for the formation of the methyl glutamate ester and protection with benzyloxymethyl chloride gave the known (−)-diester **11** without epimerization.[11]

Asymmetric conjugate addition has been demonstrated using a glycolate substrate for the production of α-alkoxy substituted products. A variety of acrylate substrates react with good yield and selectivity using cinchonine-derived catalysts using either cesium hydroxide under liquid–solid condition or 50% aqueous KOH with added THF.



Scheme 2.

Acknowledgments

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Supplementary data

Supplementary data (NMR, HPLC, and optical rotation data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.071.

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