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Phase-transfer catalyzed asymmetric arylacetate alkylation

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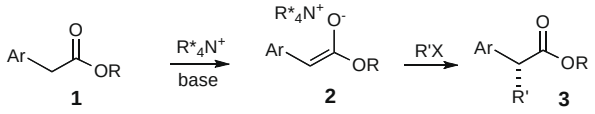
ABSTRACT

Phenethyl arylacetates are alkylated under phase-transfer conditions with cinchona catalysts with alkyl halides in high yield with excellent enantioselectivity (84–99% ee) following recrystallization. Cinchonidine (CD) derived catalyst gave the (*R*)-product and cinchonine (CN) catalyst produced the (*S*)-product. The phenethyl (PE) ester group is removed, using ammonium formate and catalytic Pd/C, to give alkylated carboxylic acid products in high selectivity. The utility of the approach is demonstrated by a direct synthesis of (*S*)-naproxen™.

Asymmetric alkylation is a key transformation for carbon–carbon bond formation, typically performed using chiral auxiliaries.[1] Recent developments are focused on the development of chiral catalysts with simple achiral substrates. While there have been some advances, successful examples remain limited. Koga pioneered catalytic enolate alkylation with chiral amine catalysts and cyclic silylenol ethers.[2] Jacobsen and Doyle recently reported selective stannylenol ether alkylation using chromium-salen catalysis.[3] A metal-free organocatalytic approach for intramolecular alkylation was reported using iodo-aldehyde bis-esters by List with methylproline catalysis.[4] SOMO activation of enamine adducts has been reported by MacMillan for enantioselective alkylation with allylsilanes.[5] We now report an approach to asymmetric arylacetate alkylation using phenethyl esters **1** under mild phase-transfer conditions with cinchona alkaloid-derived catalysts. Reversible enolate formation provides non-covalent catalyst interaction via electrostatic ion-pairing **2**. This approach produces a range of products **3** with good selectivity which can be enhanced through simple recrystallization and is suitable for multi-step applications (Scheme 1). Following alkylation, the phenethyl moiety can be converted to various products, including the corresponding carboxylic acid in high yield upon hydrogenolysis.

Phase-transfer catalyzed (PTC) alkylation, performed under liquid–liquid or solid–liquid conditions,[6] has become a practical approach to amino acid synthesis using the well-known diphenylimine *t*-butyl glycine ester of O'Donnell.[7] We recently reported a PTC alkylation method with aryl ketones to provide α-hydroxy products with good selectivity, including applications to the syntheses of ragaglitazar and kurasoin A.[8] 2-Acylimidazoles were subsequently developed as more efficient PTC substrates for asymmetric glycolate alkylations.[9] We now report an approach to arylacetate alkylation performed under simple PTC conditions to access both (*R*)- and (*S*)-products. α-Alkylated arylacetates comprise a wide range of compounds, many of which possess important biological activity.[10] Common approaches for enantioselective arylacetate alkylation rely primarily on chiral auxiliaries.[11] The utility of the new PTC route focusing on naphthyl acetates is further demonstrated by a synthesis of the nonsteroidal anti-inflammatory agent (*S*)-naproxen™.[12]



Scheme 1.

Cinchona-derived PTC catalysts were initially screened for reactivity and selectivity including *N*-arylmethyl cinchonidines **4** and **5**, developed previously for PTC glycine alkylation (Scheme 2).[6,7] The *N*-trifluorobenzyl hydrocinchonidine (HCD) catalyst **4** and the HCD dimer catalyst **5**, based on a 2,7-dimethylnaphthalene linker, proved to be most efficient as previously found with aryl ketone and acyl imidazoles.[7f,9] These catalysts are available in three steps from inexpensive cinchonidine and the complementary pseudo-enantiomeric cinchonine (CN). The route to **5** reported by Park and Jew was modified to insure high catalyst purity and to avoid the production of non-selective ammonium salts formed by incomplete quinuclidine N-arylmethylation and 2,7-bis-bromo-

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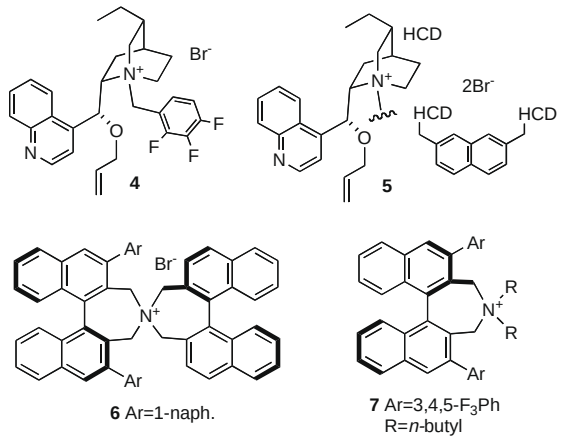


Scheme 2.

methyl naphthalene.[7e,f,9] Bis-binaphthyl ammonium bromide **6** and the *N,N*-di-*n*-butyl catalyst **7**, developed by Maruoka and coworkers,[7d,13] were also screened for PTC arylacetate alkylation.

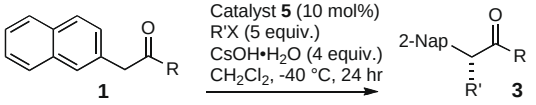
PTC reactions were performed under various conditions for naphthyl acetate alkylation using 2-naphthyl **1** variations and catalyst CD-**5** (Table 1). Solid–liquid conditions were found to be superior using insoluble cesium hydroxide hydrate as base in dichloromethane (DCM) at −40 °C (24 h). Liquid–liquid PTC conditions with aqueous KOH-toluene were unproductive in this case. With acylimidazole **1** (entry 1), product **3** was produced in moderate yield (73%) and no selectivity (0% ee, chiral HPLC) using either catalyst **4** or **5** (10 mol %) with benzyl bromide. In contrast, the previously investigated glycolate acylimidazoles were found to react with excellent selectivity under these conditions.[9] Esters were also explored and good reactivity in most cases was obtained (entries 2, 3, and 5), however the selectivity was low using benzyl bromide, allyl bromide, or methyl iodide. The *t*-butyl ester variant (entry 4) gave no reaction even after extended reaction times (48 h).[14] Acyl oxazolidinone (entry 6) showed poor reactivity while the phenethyl amide (entry 7) showed excellent reactivity (92%) and low selectivity (34% ee). The related 2-naphthyl acetyl phenethyl ester (entry 8) showed excellent reactivity (99%) with improved selectivity (56% ee) for the *R*-product. Extension of the ester chain lowered the selectivity and reactivity (entry 9). Extended aromatic functionality with the 1-naphthyl homolog (entry 10) and the addition of a second phenyl (entry 11) produced product with comparable selectivities and lower yields. The 6-methoxynaphthyl acetyl ester (entry 12) also showed excellent reactivity with moderate selectivity.

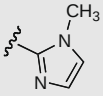
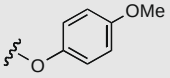
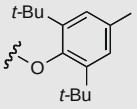
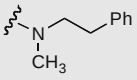
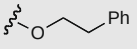
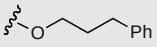
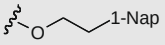
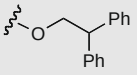
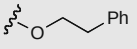
The phenylacetyl phenethyl (PE) ester **1** was also investigated under the solid–liquid PTC conditions (Scheme 3). With allyl bromide as electrophile the *R*-product **3** was obtained in 77% yield with high selectivity, 93% ee using CD-dimer **5**. In contrast to previous arylketone and acylimidazole substrates, which highly favor *Z*-enolate intermediates, phenylacetate esters give *E* and *Z* enolates **2** with comparable energies.[8a]

Additional catalysts and conditions were explored to further improve the selectivity with naphthyl acetyl ester **1** (Table 2). Other catalysts, trifluorobenzyl **4**, and the binaphthyl ammonium bromides **6** and **7** were found to produce lower yields and selectivities using allyl bromide.

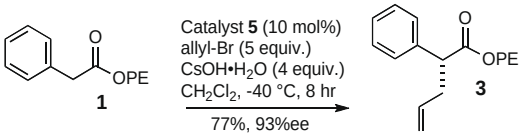
While the naphthyl acetates are limited with only modest selectivities, the crystalline nature of the phenethyl ester products **3** allowed for subsequent recrystallization to provide improved selectivity in most cases. The naphthyl acetyl phenethyl ester **1** substrate was reacted with various electrophiles under the optimal conditions using CD-catalyst **5** (Table 3). Allyl bromides reacted with moderate initial selectivity (entries 1–3). Following recrystallization from warm ether/hexanes, selectivities were shown to be greatly improved (70–93% ee) and overall yields were modest for this two-step operation, involving chromatography and recrystallization (63–68%). Benzyl bromides (entries 4–7) produced products that were obtained in excellent selectivity (92–99% ee) and good

Table 1



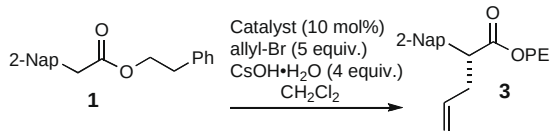
Entry	R =	R'X	%Yield	% ee
1		BnBr	73	0[a]
2		BnBr	86	0
3	O-4-PMB	BnBr	98	24
4	O-*t*-Bu	MeI	0	0[a]
5		Allyl-Br	54	8
6		Allyl-Br	48	8
7		Allyl-Br	92	34
8		Allyl-Br	**99**	**56**
9		Allyl-Br	67	28
10		Allyl-Br	78	59
11		Allyl-Br	78	54
12		Allyl-Br	82	43[a]

[a] 6-MeO-naphthyl acetate as substrate **1**.



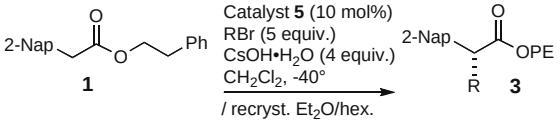
Scheme 3.

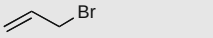
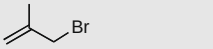
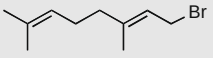
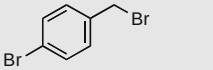
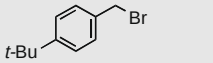
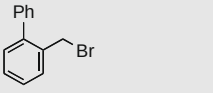
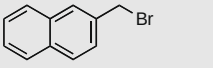
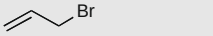
Table 2



Entry	Cat.	Temp (°C)	Time (h)	%Yield	% ee
1	**4**	−40	8	72	48
2	**5**	−40	8	**99**	**56**
3	**6**	−40	8	81	44
4	**7**	−40	8	52	46
5	**5**	−20	4	84	22
6	**5**	−60	50	76	49

Table 3



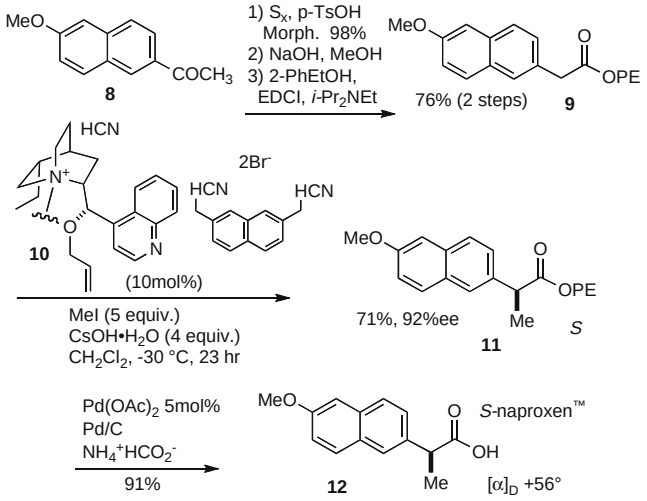
Entry	RBr	Time (h)	Crude % ee	% Yield[a]	% ee
1		47	46	63	93
2		26	57	68	86
3		28	59	68	70
4		28	48	81	97
5		23	71	72	99
6		28	89	81	92
7		27	63	73	94
8	MeI	18	55	71	92
9		19	43	62	85[b]

[a] Yields shown are for products purified by short-path silica gel chromatography and recrystallized from ether/hexanes.

[b] 6-MeO-naphthyl acetate as substrate **1**.

overall yields (72–81%). Reaction with methyl iodide (entry 8) also gave high selectivity (92% ee) with modest overall yield (71%) for the *R*-product **3**. The 6-methoxynaphthyl acetyl PE ester (entry 9) showed good reactivity and selectivity (85% ee).

A short, five-step synthesis of the well-known anti-inflammatory agent (*S*)-naproxen™ was performed to demonstrate utility of aryl acetate PTC (Scheme 4).[12] The requisite aryl acetyl PE ester was generated from 2-acetyl-6-methoxynaphthalene **8**. Willgerodt–Kindler reaction with precipitated sulfur, *p*-TsOH, and morpholine gave the acetylthioamide, which was hydrolyzed to the corresponding acid.[15] Esterification generated phenethyl **9** in



Scheme 4.

excellent overall yield. The pseudo-enantiomeric cinchonine (CN) dimer catalyst **10** was produced using the optimized route developed for CD-**5**. PTC methylation now using **10** under the solid–liquid conditions with methyl iodide (23 h) gave product (*S*)-**11**, initially in 99% yield (64% ee, 230 mg scale). Recrystallization (Et_2O/hex.) gave **11** in 71% overall yield with 92% ee. Notably this methylated product **11** is produced with high selectivity using the CN catalyst to give the complementary *S*-product. The PE ester was converted to the carboxylic acid **12** using the reported conditions of Carpino ($Pd(OAc)_2$, Pd/C 5 mol %) with ammonium formate, 91% yield, $[\alpha]_D$ +56.[16]

Commercially obtained *S*-naproxen **12** was independently converted to the PE ester **11** and the optical rotation and the chiral HPLC trace were compared with the PTC-derived product ($[\alpha]_D$ +27.5 to +29 for PTC-derived **11**). The comparable selectivity, (*R*)-product from CD and (*S*)-product from CN catalyst, suggests a complementary mode of interaction for the enolate **2** and the pseudoenantiomeric catalysts. Selectivities for previous glycolate substrates were not complementary, where CD catalysts gave (*S*)-products and the CN catalyst also produced (*S*)-products but with much lower selectivity.[8] A kinetic effect with preferential enolate-catalyst pairing and alkylation, via *E* or *Z*-**2**, may also be operative in this case.

Arylacetate PTC alkylation is a general approach to enantioenriched α-alkylated products using simple substrates and catalysts. Complementary enantiomeric products are produced from either CD or CN catalysts in high selectivities following recrystallization. The phenethyl ester products are readily converted to useful products.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, characterization, and NMR and HPLC data for all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.090.

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