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Phase-Transfer-Catalyzed Asymmetric Acylimidazole Alkylation

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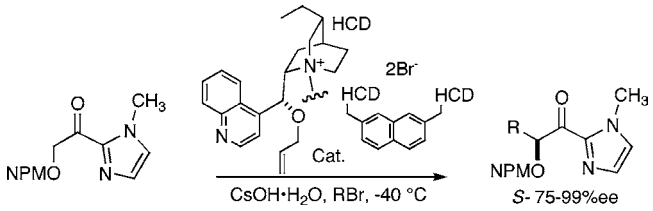
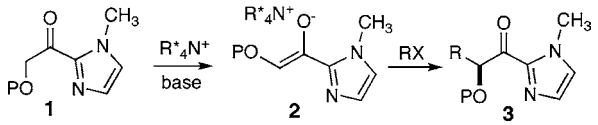
ABSTRACT



2-Acylimidazoles are alkylated under phase-transfer conditions with cinchonidinium catalysts at −40 °C with allyl and benzyl electrophiles in high yield with excellent enantioselectivity (79 to >99% ee). The acylimidazole substrates are made in three steps from bromoacetic acid via the *N*-acylmorpholine adduct. The catalyst is made in high purity allowing for *S*-product formation (6−20 h) under mild conditions, consistent with an ion-pair mechanism. The products are readily converted to useful ester products using methyltriflate and sodium methoxide, via a dimethylacylimidazolium intermediate without racemization. The process is efficient, direct, and amenable to other electrophiles and transformations that proceed through an enolate intermediate.

Asymmetric alkylation is a powerful transformation for carbon−carbon bond formation, accommodating various electrophilic coupling partners. While the transformation is strategic for a wide range of targets, it yet remains limited to auxiliaries for synthetic applications.[1] In an effort to improve efficiency with a broader scope for sp^3-electrophiles, catalytic versions have been extensively explored. Enolate alkylations with chiral amine catalysts by Koga employ cyclic silylenol ethers,[2] and more recently, stannylenol ethers have been developed using chromium−salen catalysts by Jacobsen.[3] Intramolecular proline-catalyzed alkylation is successful for five- and six-ring formations using iodo-aldehyde bisesters according to List.[4] We now report an efficient, broadly applicable approach to asymmetric enolate alkylation using acylimidazoles reacted under mild phase-transfer conditions with cinchonidine-derived catalysts. This approach produces a range of products with high selectivity and is suitable for multistep applications (Scheme 1).

Scheme 1. Phase-Transfer Acylimidazole Alkylation



Phase-transfer-catalyzed (PTC) glycine alkylation, using either liquid−liquid or solid−liquid conditions, has become a practical approach to amino acid synthesis.[5] The highly

(1) Eames, J.; Suggate, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 186−189.

(2) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829−8830.

(3) (a) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62−63. (b) Doyle, A. G.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 3701−3705.

(4) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450−451.

(5) (a) Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526−533. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518−525. (c) Patterson, D. E.; Xie, S.; Jones, L. A.; Osterhout, M. H.; Henry, C. G.; Roper, T. D. *Org. Process Res. Dev.* **2007**, *11*, 624−627.

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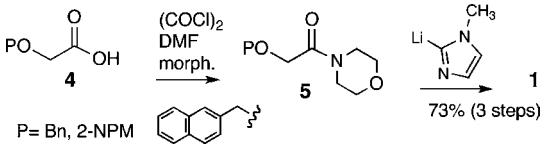
unsaturated diphenylimine *tert*-butyl ester substrate of O'Donnell is well suited for enolate formation and alkylation.[6] We recently reported PTC alkylation of aryl ketones to provide α-hydroxy products with good selectivity, together with applications for the syntheses of ragaglitazar and kurasoin A.[7] The selectivities were high with a range of electrophiles, yet a problematic Baeyer−Villiger transformation was required to convert the PTC product to esters needed for synthetic applications. 2-Acylimidazoles **1** are now shown to be suitable for PTC alkylation, possessing an α-hydrogen sufficiently acidic for low-temperature reactivity through the ion-paired enolate **2**, and the product **3** can be readily transformed for applications (Scheme 1). Evans recently reported the use of α,*β*-unsaturated acylimidazoles for Lewis acid catalyzed additions.[8] 2-Acylimidazoles are readily N-methylated to give an imidazolium intermediate, which can undergo nucleophilic displacement.[9]

Acylimidazole **1** was produced in three steps using inexpensive, convenient reagents (Scheme 2). Bromoacetic

Scheme 2. Synthesis of Acylimidazoles



acid was reacted with benzyloxy nucleophiles corresponding to the alkoxy group incorporated at the 2-position to give **4**. Intermediate **4** was converted to the *N*-acyl product **5** using oxalyl chloride in DMF, and finally, lithiated *N*-methylimidazole was added to give **1** (P = 2-naphthylmethyl, 2-NPM) in 73% overall isolated yield. The benzyloxy substrate (P = Bn) was also efficiently produced using this sequence. A variety of cinchona-derived PTC catalysts were screened for reactivity and selectivity, including *N*-arylmethyl cinchonidine as used previously for glycine alkylation (Figure 1).[6] The *N*-trifluorobenzyl hydrocinchonidine (HCD) catalyst **6** and the HCD dimer catalyst **7**, based on 2,7-dimethylnaphthalene, proved to be most efficient.[6g] These catalysts are available in three simple steps from inexpensive cinchonidine. The original Park−Jew synthesis of **7** was modified to ensure high catalyst purity and to avoid the production of nonselective ammonium salts due to incom-

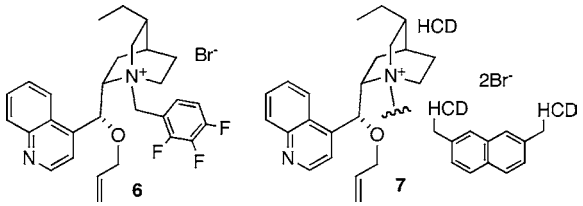
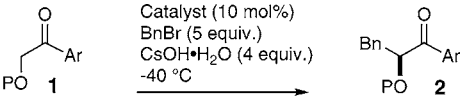


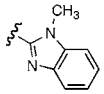
Figure 1. PTC catalysts.

plete quinuclidine N-arylmethylation with 2,7-bisbromomethyl naphthalene.[10]

PTC reactions were performed to identify the optimal substrate−catalyst combination and reaction conditions (Table 1). Solid−liquid conditions were found to be optimal

Table 1. Acylimidazole PTC Benzylation



entry	Ar=	P=	cat.	sol.	%yield	%ee
1		Bn	**6**	DCM	86	74
2	"	Bn	**7**	tol.	86	74
3	"	2-NPM	**6**	DCM	82	86
4	"	"	**7**	DCM	83	91[a]
5	"	"	**7**	hex.-DCM	85	91
6		2-NPM	**7**	DMC	76	93
7		"	**7**	"	31	0
8		"	**7**	"	99	69

[a] RbOH used as base.

using insoluble cesium hydroxide hydrate as base in dichoromethane (DCM) at −40 °C. Use of liquid−liquid conditions with aqueous KOH−toluene proved to be unproductive. With benzyl acylimidazole **1** (*N*-methyl, P = Bn), *S*-product was produced in high yield (86%) with good selectivity (74% ee, chiral HPLC) using either catalyst **6** or **7** (10 mol %) with benzyl bromide (entries 1 and 2). Under these conditions, no N-alkylation or acylimidazole cleavage was observed, and the reactions were remarkably fast, being complete in 6−8 h. The 2-naphthylmethyloxy (2-NPM) acylimidazole substrate **1** was then explored (entries 3−5). Use of catalyst **6** for PTC benzylation showed improved selectivity (86% ee), and the cinchonidinium dimer catalyst

(6) (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353−2354. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415. (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595−8598. (d) Ooi, T.; Kameda, K.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519−6520. (e) Jew, S.; Yoo, M.; Jeong, B.; Park, I. Y.; Park, H. *Org. Lett.* **2002**, *4*, 4245−4248. (f) Park, H.; Jeong, B.; Yoo, M.; Lee, J.; Park, M.; Lee, Y.; Kim, M.; Jew, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036−3038. (g) O'Donnell, M. J.; Delgado, F.; Hostettler, C.; Schwesinger, R. *Tetrahedron Lett.* **1998**, *39*, 8775−8778.

(7) (a) Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2005**, *70*, 9470−9479. (b) Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2006**, *71*, 8651−8654.

(8) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943.

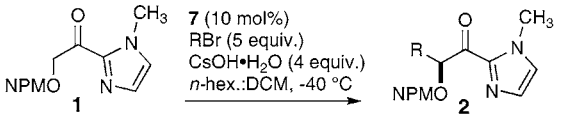
(9) Miyashita, A.; Suzuki, Y.; Nagasaki, I.; Ishiguro, C.; Iwamoto, K.-I.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 1254−1258.

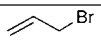
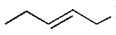
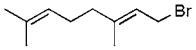
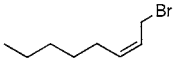
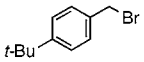
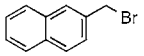
(10) See refs 6f,g. See Supporting Information for details.

7 was most effective, generating product **2** with 91% ee. Other imidazoles were also synthesized and investigated as PTC substrates (entries 6−8). *N*-Methylbenzoimidazole (entry 6) showed good reactivity (76%) with excellent selectivity (93% ee), while *N*-phenylimidazole (entry 7) gave low yields of racemic product. In contrast, *N*-benzylimidazole (entry 8) produced a quantitative yield with moderate selectivity (69% ee). The *N*-methylbenzoimidazole substrate was not found to be general when reacted with other electrophiles. PTC reactions with this substrate were accompanied by N-alkylation, and the conversion to ester products was also found to be problematic.

Other electrophiles were also found to be useful for PTC alkylation with *N*-methyl-2-acylimidazole-2-NPM-**1** (Table 2). Reactions were performed with 10 mol % of catalyst **7**

Table 2. PTC Alkylation with Various Electrophiles



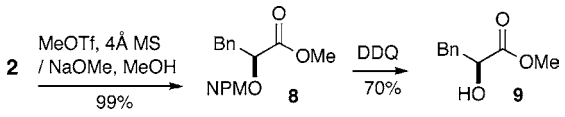
entry	RBr	time (hr)	%yield[a]	%ee[b]
1		8	90	88
2		6	84	86
3		7	80	91
4		6	75	75
5		8	77	79
6		5	85	91
7		22	88	>99
8		20	92	>99
9		22	88	>99

[a] Yields represent isolated, purified products. [b] Chiral HPLC.

with 5 equiv of electrophile and CsOH•H_2O in a 1:1 mixture of hexanes and dichloromethane (−40 °C). In some cases, the order of reagent addition was shown to affect the outcome. With base added last, slightly higher reaction rates and selectivities were noted. This effect is in accord with large-scale investigations recently reported for glycine PTC.[5c] With acylimidazole **1**, this effect is not as pronounced. Addition of electrophile or base as the last reagent to the cold reaction mixture produced comparable results. The catalyst load in some cases was lowered to 5 mol % without significant reduction in either yield or selectivity, yet 1 mol % of catalyst produced very slow reaction rates. Use of allyl and methallyl bromides (entries 1 and 2) gave products in high yields and very good selectivities (88 and 86% ee). Other allylic electrophiles included (*E*)-2-pentenyl, geranyl, and (*Z*)-2-octenyl bromides (entries 3−5), which reacted with good to excellent results to give novel products. Substituted benzyl bromides (entries 7−9) required longer reactions times (20 h), and in all cases, excellent yields and near complete selectivities (>99% ee) were obtained.

The stereoinduction was established by conversion to the methyl ester **9** (Scheme 3). Treatment with methyltriflate

Scheme 3. Elaboration to Methyl Ester



provided the *N*,*N*-dimethylimidazolium intermediate which was displaced with sodium methoxide to give 2-NPM ester **8** in quantitative yield with no racemization detected (chiral HPLC). Previous procedures employing methanol and DBU (diazabicyclo[5,4]undecene) or other bases proved to be less effective in this case.[8,9] Removal of the 2-NPM group with DDQ (dichlorodicyanoquinone) gave the known (*S*)-methyl ester **9** ([α]$_D$ −6.25, lit. [α]$_D$ −6.8).[11]

The *S*-stereoinduction is consistent with the model proposed for "pocket" binding mode with the (*Z*)-enolate located between the quinoline and quinuclidine groups on the catalyst and the enolate oxygen being ion paired with the least hindered face of the catalyst ammonium nitrogen, as depicted in Figure 2 for transition state **A** (Figure 2). In this

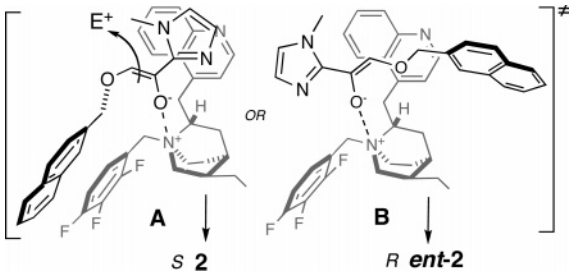


Figure 2. Stereoinduction for PTC alkylation.

arrangement, the extended π-system of the enolate and the imidazole interact with the quinoline of the catalyst, and the 2-NPM group of the substrate is also aligned with the aryl moiety attached to the quinuclidine nitrogen, leading to the observed *S*-product **2**. A (*Z*)-enolate geometry is predicted to be lower in energy for the acylimidazole, consistent with trapping experiments made with arylketones reacted under PTC conditions.[7a] In contrast, the corresponding *E*-geometry is favored for the *tert*-butyl glycine enolate.[6] Arrangement **B** lacks the extended π-interactions with only minimal contact with the enolate and the imidazole, leading to the minor *R*-isomer of **2**.

(11) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, *120*, 4345−4353.

Acylimidazole PTC alkylation is shown to be a general approach to enantioenriched α-hydroxy products with broad utility using simple, readily available substrates and catalysts. Applications to other transformations and target directed synthesis can now follow.

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Supporting Information Available: Experimental procedures, characterization, and data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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