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Cumyl Ester as the C-Terminal Protecting Group in the Enantioselective Alkylation of Glycine Benzophenone Imine

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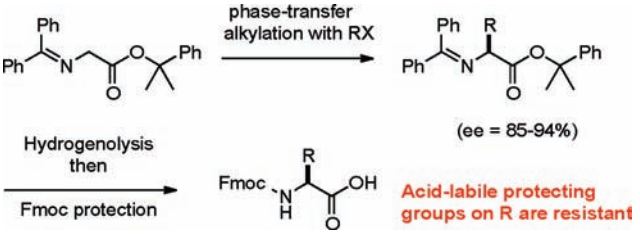
ABSTRACT



Cumyl ester is an optimal C-terminal protecting group for glycine benzophenone imine in asymmetric alkylation reactions catalyzed by *Cinchona* chiral phase-transfer catalysts. High levels of enantioselectivity have been obtained (up to 94% ee) with this substrate, which provides an attractive alternative to the analogous *tert*-butyl ester. N-terminal imines and the C-terminal esters can be cleaved from alkylation products by hydrogenolysis, while maintaining acid-labile side chain protecting groups.

Unnatural amino acids are important starting materials for the synthesis of peptides and natural products. Controlling the absolute configuration of the α-center is a key challenge in producing these materials. Due to their significance, numerous methods have been developed to access α-amino acids enantioselectively.

The asymmetric alkylation reaction of glycine imine esters catalyzed by chiral phase-transfer catalysts is now a leading method for the synthesis of enantioenriched α-amino acids (Figure 1).[1−4] After its initial discovery in 1989,[5] this method has now been optimized to the point where high yields and levels of enantioselectivity are commonly observed. Most efforts were directed toward identifying ideal catalysts, rather than the ideal glycine substrates.[6] In terms of catalyst optimization, chiral phase-transfer catalysts derived from the *Cinchona* alkaloids have been widely used, due to their low cost and easy access from natural sources. Initial studies showed enantioselectivities ranging from 42 to 66% with *N*-benzyl cinchonidine and substrate **1a**, whereas lower ee's were obtained with the benzyl ester **1b**.[7] Later studies proved that *O*- and *N*-alkylated *Cinchona* catalysts such as **3** provided higher ee's with substrate **1a** (up to 99%).[8−10] Other studies reported higher order oligomers (dimers or trimers of *Cinchona*),[11−13] as well as methods that could be applied directly to solid-phase.[14] In parallel efforts, chiral catalysts based on biphenyl or binapthyl motifs such as **4** were developed that afforded high levels of

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enantioselectivity with a broader range of substrates than the *Cinchona*-based catalysts, including substrates such as **1b**.[15,16] However, these catalysts required multistep sequences, which is a disadvantage with respect to the *Cinchona*-based catalysts that can be obtained in 1−2 steps from low-cost, easy to access commercially available starting materials. Therefore we sought a substrate that would combine the high levels of enantioselectivity observed with the *Cinchona*-based catalysts along with an easy and mild route to deprotection. Despite major advancements in this field, we recognized that acid-labile protecting groups present on the side chains are not easily carried through a sequence from asymmetric alkylation products **2** to provide Fmoc protected derivatives, which is unfortunate because acid-labile protecting groups are routinely used in Fmoc solid-phase synthesis. To address this issue, we report a new glycine benzophenone imine substrate for the asymmetric alkylation reaction that incorporates a cumyl ester **1c** in place of the most common protecting group, *tert*-butyl ester **1a**. Like **1a**, **1c** affords high enantioselectivities in the asymmetric alkylation reaction. However **1c** holds the advantage over **1a** that both the *N*- and *C*-terminal protecting groups can be cleaved simultaneously under mild conditions by hydrogenolysis while maintaining acid-labile, side chain protecting groups.

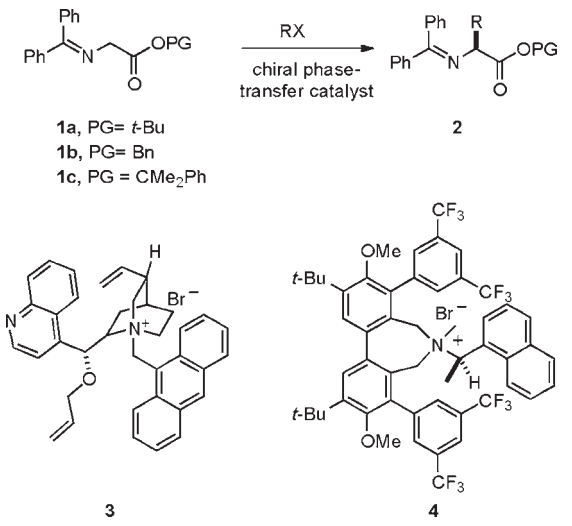
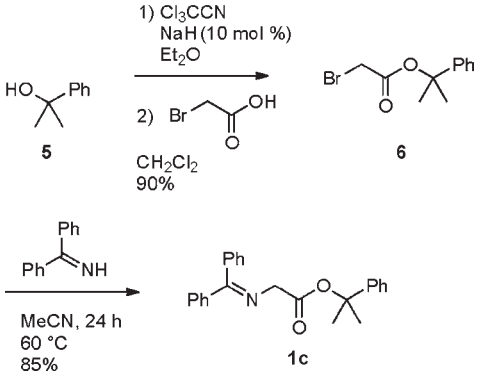


Figure 1. Asymmetric alkylation of *tert*-butyl and benzyl ester glycine imine by chiral phase transfer catalysts.

Synthesis of the cumyl ester substrate **1c** started from commercially available 2-phenyl-2-propanol (**5**, Scheme 1). Treatment of **5** with Cl_3CCN and a catalytic amount of NaH furnished a known trichloracetimidate[17] that was reacted with bromoacetic acid, giving **6** in 90% yield over the two steps. Using a method from the literature,[18] alkylation of diphenyl ketimine[19] with **6** in MeCN at 60 °C gave the alkylation substrate **1c** in 85% yield, making **1c** available in three steps and 77% overall yield from 2-phenyl-2-propanol.

Scheme 1. Synthesis of Cumyl Ester Protected Glycine Benzophenone Imine



With the glycine-derived substrate **1c** in hand, optimal conditions for the asymmetric alkylation reaction were developed using BnBr as the electrophile (Table 1). Alkylation of **1c** with CsOH as the base and chiral phase-transfer catalyst **3** in CH_2Cl_2, or a mixture of toluene and CH_2Cl_2 (7:3), at low temperatures (−78 or −50 °C) furnished the product **2a** in good ee (87−91%), but in low to moderate yield (48−62%, entries 1−3). Using $CHCl_3$ in place of CH_2Cl_2 raised the ee slightly to 94% when the reaction was carried out at −50 °C (entry 4). Lowering the temperature to −78 °C slowed the reaction considerably, giving **2a** in only 42% yield, and did not enhance enantioselectivity (entry 5). Following these reactions over time indicated that the starting material **1c** was often consumed before BnBr. Therefore using a slight excess of **1c** with respect to BnBr (1.4 equiv) was deemed optimal, providing **2a** in higher yield (86%) and 94% ee (entry 6).

After the optimized conditions for the asymmetric alkylation reaction with **1c** were developed, the scope of the method was explored using different electrophiles (Table 2). First, alkylation of the benzyl ester substrate **1b**[7] with 5-(bromomethyl)-2-((((*tert*-butyldimethylsilyl)oxy)methyl)-pyridine[20] was performed (entry 1) under the optimized conditions to provide a point of comparison for the cumyl ester **1c**, because both C-terminal protecting groups can be removed by hydrogenation.[20] The product **2b** was obtained in reasonable yield but only 80% ee under these conditions. In contrast, alkylation of the cumyl ester **1c** with the same electrophile under the same conditions furnished the product **2c** in good yield (79%) and excellent ee (94%), illustrating that optimization of the subst-

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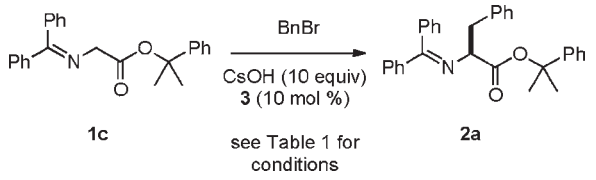
Table 1. Optimization of the Asymmetric Alkylation Conditions with the Cumyl Ester **1c**



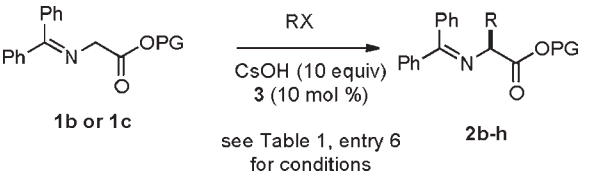
1c 2a

entry	equiv of **1c**	solvent	temp (°C)	yield (%)	ee (%)
1	1.0	CH_2Cl_2	−50	67	87
2	1.0	CH_2Cl_2	−78	52	91
3	1.0	Toluene/CH_2Cl_2 (7:3)	−78	48	90
4	1.0	Toluene/$CHCl_3$ (7:3)	−50	62	94
5	1.0	Toluene/$CHCl_3$ (7:3)	−78	42	89
6	1.4	Toluene/$CHCl_3$ (7:3)	−50	86	94

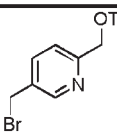
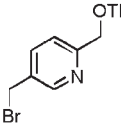
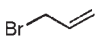
rate structure provided a significant enhancement in the enantioselectivity of the reaction. Previous optimization of the same reaction with the *tert*-butyl protected glycine benzophenone imine **1a** gave the corresponding product in 80% yield and 93% ee demonstrating no loss of enantioselectivity with the cumyl ester substrate **1c**.[20] Next, a series of alkyl, alkenyl, and alkynyl electrophiles were employed under the optimized conditions (entries 3−7) in reactions with **1c**. With the exception of EtI as the electrophile (entry 4, 85% ee), all reactions proceeded in >90% ee.

Alkylation product **2c** was carried forward to Fmoc-protected derivative **7** to develop conditions for the simultaneous *C*-and *N*-deprotection reaction (Scheme 2). Hydrogenolysis of substrate **2c** using H_2 (75 psi) and $Pd(OH)_2/C$ as the catalyst afforded the *C*- and *N*-deprotected amino acid that could be isolated along with diphenylmethane, a benzophenone imine byproduct, following removal of the catalyst by filtration. Isopropyl benzene, derived from the cumyl ester, is volatile and was removed during concentration of the reaction mixture. The crude reaction mixture was taken forward without additional purification into the Fmoc protection step. Under standard conditions employing Fmoc-(OSu) and aqueous $NaHCO_3$ as the base, the known amino acid **7**[20] was obtained in 77% yield using this sequence over the two steps. This method represents a significant improvement for the synthesis of **7** with respect to the previous method starting from the *tert*-butyl ester **1a**, which should translate to other syntheses where acid-labile protecting groups on side chains are desired. Starting from **1a**, global deprotection with

Table 2. Reaction Scope



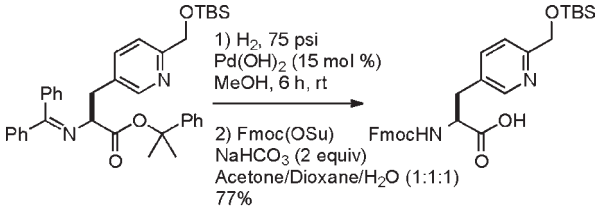
1b or 1c 2b-h

entry	PG	RX	product	yield (%)	ee (%)
1	Bn		**2b**	70	80
2	Cumyl		**2c**	79	94[a]
3	Cumyl	MeI	**2d**	56	92
4	Cumyl	EtI	**2e**	77	85
6	Cumyl		**2f**	85	91
7	Cumyl		**2g**	91	92

[a] Alkylation of the *tert*-butyl ester **1a** gave the corresponding product in 80% yield and 93% ee under the same conditions.

6 N HCl was required to observe full cleavage of the *tert*-butyl ester, which resulted in concominant deprotection of the TBS group. In the following step, the same group was reattached using a large excess of TBSCl. Therefore, the mild deprotection conditions and ability to carry an acid-labile protecting group through the entire sequence make the cumyl ester **1c** attractive over the *tert*-butyl ester **1a**, with respect to sequence length and overall atom economy.

Scheme 2. Transformation of Alkylation Product **2c** to Fmoc Derivative **7**



2c **7**

The scope of the substrate **1c** was extended further by transforming alkylation product **2g** to amino acid **9** (Scheme 3). Sonogashira coupling of **2g** with the known

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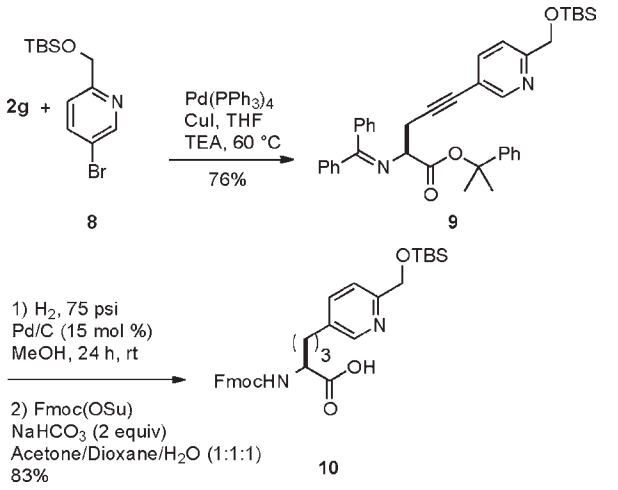
Scheme 3. Transformation of Alkylation Product **2g** to Fmoc Derivative **10**



bromopyridine derivative **8**,[21] using catalytic amounts of $Pd(PPh_3)_4$ (10 mol %) and CuI (20 mol %),[20] furnished the product **9** in 76% yield, showing that the cumyl ester is stable to these reaction conditions. Next, three transformations on **9** were carried out in one step by catalytic hydrogenation. Full reduction of the alkyne group of **9**, along with hydrogenolysis of the *C*- and *N*-protecting groups, gave the free amino acid derivative with a saturated side chain, all while maintaining the TBS group. After filtration and concentration, protection of this intermediate with Fmoc(OSu) in the same manner as in the synthesis of **7** gave the Fmoc amino acid **10**[20] in 83% yield over the two steps. The sequence from **2g** to **9** not only illustrates how additional functional groups can be transformed during the *C*- and *N*-deprotection step but also represents a significant improvement toward the synthesis of amino acid **10**, which previously took six steps from **8**, including a step to replace the acid-labile TBS group.[20]

In conclusion, a new glycine-derived substrate for the asymmetric alkylation is presented. Using a *Cinchona*-based catalyst, the cumyl ester substrate **1c** affords alkylation products in high enantiomeric excess that can be transformed under mild conditions to free amino acids. This research is expected to facilitate the asymmetric syntheses of Fmoc amino acids that contain acid-labile protecting groups on their side chains.

Acknowledgment. We thank Wayne State University, including the Honors College for a grant to E.C., for its generous funding of this research.

Supporting Information Available. Experimental procedures for synthesis of **1c**, **2a**–**g**, **6**, **7**, **9**, and **10**, including characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.