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Highly selective glycine phase-transfer catalysis using fluoroanthracenylmethyl cinchonidine catalysts

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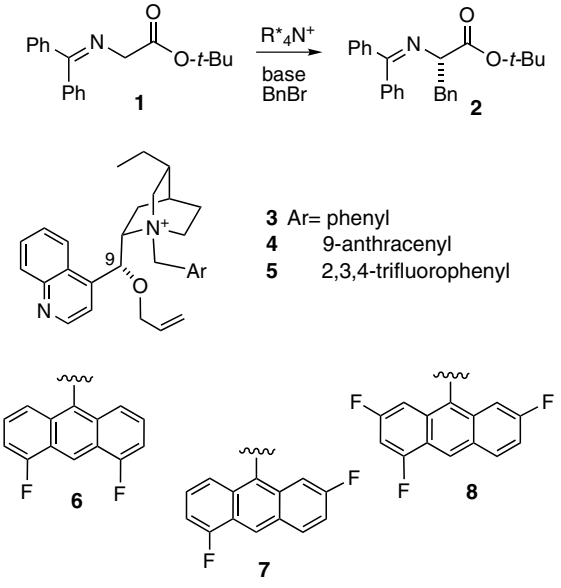
Abstract—Fluoroanthracenylmethyl cinchonidine phase-transfer catalysts have been produced and explored for asymmetric glycine alkylation. The fluoroanthracenylmethyl precursors were made from aryloxazolidinones and aldehydes using an efficient electrophilic substitution with phosphorous pentoxide. The cinchonidine catalysts promote highly selective glycine alkylation under mild conditions. The 1,8-difluoroanthracenyl-10-methyl catalyst **6** (10 mol %) in toluene/THF with 50% aqueous KOH (−20 °C) promoted benzylation of glycine **1** to give **2** in 86% yield, 98% ee. Other electrophiles also gave excellent selectivity and reactivity.

Phase-transfer catalysis (PTC) continues to develop as a practical method for asymmetric synthesis. The process is particularly attractive for glycine alkylation, conjugate addition, and epoxide formation.[1] PTC has numerous attractive features including the use of inexpensive, cinchona alkaloid catalysts, which are readily available in enantiomeric antipodes, simple hydroxide bases for in situ enolate formation, 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.[2] PTC amino acid synthesis is facilitated by the benzophenone imine *tert*-butyl glycine **1** (Scheme 1), pioneered by O'Donnell, due to its extended enolate conjugation and relatively low pK_a value (18.7, DMSO).[3] While there are many successful catalysts for this substrate, the development of generally applicable, readily available catalysts that can operate under mild conditions, remain elusive. We now report a new class of fluorinated anthracenylmethyl cinchonidine derived catalysts that promote glycine alkylation with very high reactivity and selectivity under mild conditions with a wide range of electrophiles.



Scheme 1.

Cinchonidine derived catalysts **3**–**5** (Scheme 1), bases, and reaction condition variations have shown steady improvement in selectivity for the production of *S*-**2**.[3] Non-natural chiral bis-binaphthyl catalysts, that require 12 synthetic steps, have also demonstrated success among others.[3f,4] Asymmetric PTC reactions are reported to follow an interfacial-type mechanism, where

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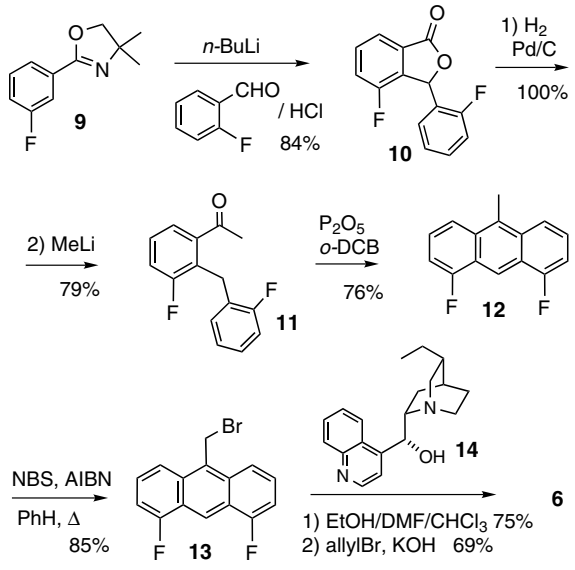
enolate formation occurs at the solvent interface boundary layer and alkylation of the ammonium-enolate ion pair in the organic layer is the rate-limiting step.[5] The placement of a benzyl group on the quinuclidine nitrogen creates a well-defined binding site for the enolate between the quinoline and the ethyl moieties **3**. Benzylation of **1** gives **2** in 75% yield (66% ee) with C9-OH **3**.[3a] The 9-methylanthracene **4**, developed independently by Corey and Lygo accentuates the steric constraints and provides a larger region for non-bonded interaction leading to significant increases in selectivity. In methylene chloride at −78 °C with $CsOH{\cdot}H_2O$ under solid–liquid phase conditions, benzylation of **1** gives 87% yield (94% ee)[3c] with **4** (C9-Oallyl) and at 20 °C in toluene (C9-OH) with 50% aqueous KOH, **2** was produced in 63% yield (89% ee).[3d] The report of Park and Jew using various fluorinated benzyl cinchonidine catalysts, including **5**,[3g] demonstrates an important added benefit to both reactivity and selectivity. Electronegative fluoro substituents can contribute to the overall electron deficiency of the positively charged catalyst enhancing the degree of ion pairing with the enolate. This effect is expected to facilitate both phase-transfer and enhance non-bonded interactions leading to improved selectivity. The steric advantage of the larger anthracenyl functionality is now combined with the beneficial electronic characteristics of fluorine substitution. Catalysts with specific fluoro substituents **6**–**8** were made and tested for glycine alkylation.

Following a modified route reported by Newman and Kannan,[6] *m*-fluoro phenyloxazolines **9** was *o*-metallated and reacted with 2-fluorobenzaldehyde (Scheme 2). Treatment of the reaction mixture with HCl gave lactone **10** in 84% isolated yield. Hydrogenation with palladium on carbon catalyst gave the diphenylmethyl intermediate **11** in quantitative yield and treatment with excess methyllithium provided the methyl ketone **12**. Following the reported use of polyphorphoric acid (PPA),[5] the desired 10-methylanthracene **13** was obtained in only low to moderate yield (5–50%). Phosphorous pentoxide (P_2O_5) proved to be a more reliable reagent for this challenging electron-deficient electrophilic aromatic substitution step.[7] When used in *o*-dichlorobenzene (130 °C), 1,8-difluoro-10-methylanthracene **13** was obtained in 74% isolated yield. The corresponding methyl bromide **14** was then generated using NBS (*N*-bromosuccinimide) with AIBN (azo-bis-isobutyronitrile) catalysis in benzene. Dihydrocinchonidine **15** was reacted with **14** to generate the quaternary ammonium bromide and treatment with allyl bromide in the presence of base produced the desired catalyst **6**. Catalysts **7** and **8** were made following the same 7-step route starting with oxazoline **9** and 4-fluorobenzaldehyde and the corresponding 3,5-difluorophenyloxazoline reacted with 4-fluorobenzaldehyde. The intermediates were obtained with comparable yields and the key electrophilic substitution steps using phosphorus pentoxide with the deactivated substrates were equally efficient (69% and 71%, respectively).

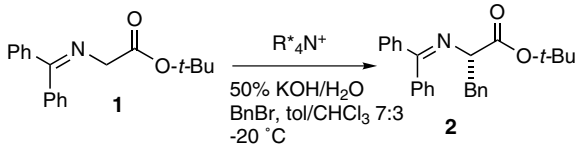


Scheme 2.

Benzylation of glycine **1** was explored using the new catalysts (10 mol %) in toluene–chloroform (7:3) with 50% aqueous KOH initially at −20 °C (Table 1). Reaction with the Corey/Lygo catalyst **4** at −20 °C gave **2** in 88% isolated yield under these conditions (95% ee). With 1,8-difluoro **6**, the selectivity improved to 98% ee. 1,6-difluoro **7** showed improved reactivity, 23 h versus 50 h, however the selectivity dropped to 95% ee. Trifluoro catalyst **8** did not show improved reactivity or selectivity. At lower temperature, −40 °C, **6** gave comparable yield and selectivity with a greatly slowed rate, 120 h. Use of this catalyst **6** at 0 °C gave a similar yield in only 12 h with reduced selectivity (96% ee) and at rt, product was obtained in 92% yield (91% ee) in only 8 h.

The 1,8-difluoro catalyst **6** was explored under more convenient, environmentally benign conditions using toluene–THF mixture with 50% aqueous KOH (Table 2). With a 7:3 ratio of toluene–THF at −20 °C, **2** was produced in 16 h with 82% yield and 97% ee. Using 1:1 toluene–THF, the reaction was completed in 8 h, and the yield and selectivity remained high. 9:1 ratio

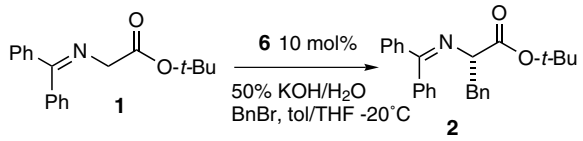
Table 1. Catalyst variation for glycine PTC



Catalyst	Temp (°C)	Time (h)	Yield (%)	Ee[a] (%)
4	−20	44	88	95
6	−20	50	88	98
7	−20	23	92	95
8	−20	54	86	92
6	−40	120	87	98
6	0	12	88	96
6	23	8	92	91

[a] Enantiomeric excess determined by chiral HPLC (Chiracel OJ).

Table 2. Solvent variations for PTC alkylation



Tol/THF ratio	Time (h)	Yield (%)	Ee (%)
7:3	16	82	97
1:1	8	83	96
9:1	24	95	96
1:9	7	81	95
1:0			
0:1			
7:3	26	86	98[a]
7:3	55	81	98[b]

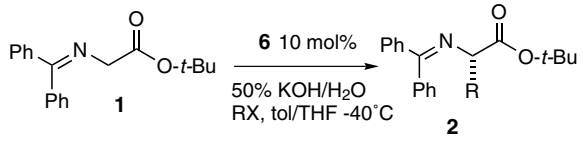
[a] Performed at −40 °C.
[b] 5 mol % of catalyst was used.

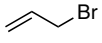
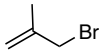
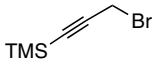
affected the rate, 24 h, but not the yield or selectivity. Lower temperature, −40 °C, required 26 h for completion and the selectivity was again excellent (98% ee). Use of 5 mol % **6** greatly slowed the reaction rate to 55 h.

The new 1,8-difluoro catalyst **6** was applied to various allylic, propargyl, and alkyl electrophiles at −40 °C (Table 3). Allyl bromide reacted with excellent yield and selectivity, 98% ee in 11 h. Methallyl bromide reacted at a slower rate, but also gave **2** with 98% ee. Methyl iodide also gave **2** with high selectivity, however the yield was reduced to 66%. TMS propargyl bromide reacted in 11 h, again with excellent yield and selectivity.

The tight-ion pair model of Corey can be used to rationalize the stereoinduction (Fig. 1).[3e] The quinoline and the ethyl group form a defined binding region for the glycine enolate where the enolate oxygen points directly at the less hindered face of the ammonium ion. The extended π-conjugation of the enolate and the imine adopt a face to face π-interaction with the quinoline and the *tert*-butyl group of the ester is placed over the anthracene moiety in the favored pathway **A**. Alkylation, opposite from the isoquinoline, generates the observed

Table 3. PTC alkylation with electrophiles



RX	Time (h)	Yield (%)	Ee (%)
	11	87	98
	28	90	98
CH_3I	21	66	97
	11	92	98

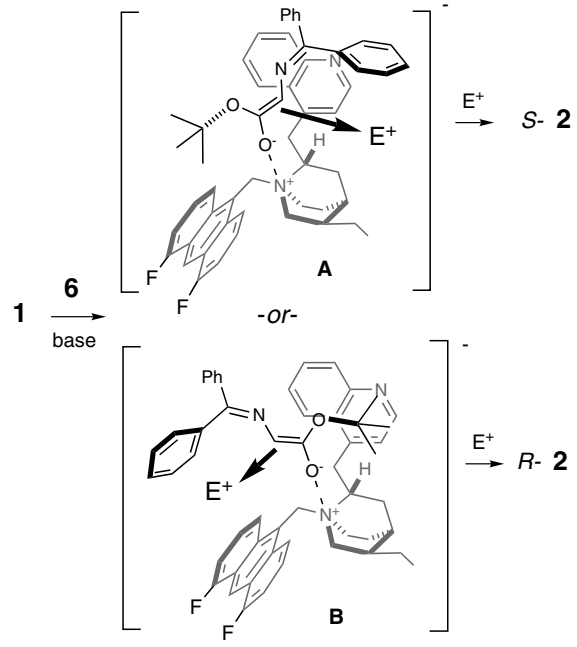


Figure 1. Transition state of the *E*-enolate from **1**.

S-**2** product as indicated. The other face of the enolate is exposed in pathway **B** leading to the minor enantiomer *R*-**2**. In this case, the π-interaction is lost and the electrophile trajectory is occluded by the anthracenyl group of the catalyst. The presence of the fluoro substituents accentuates the electron deficiency of the ammonium ion. This effect shortens the distance between the enolate oxygen and the ammonium ion of the catalyst in the tight ion pair, enhancing non-bonded interactions leading to improved selectivity.

New fluoroanthracenyl cinchonidinium catalysts were produced that demonstrate enhanced reactivity and selectivity for PTC glycine alkylation. Phosphorous pentoxide mediates intramolecular electrophilic substitution with the deactivated intermediates allowing for specific placement of fluoro groups. Convenient liquid–liquid conditions with aqueous KOH in toluene–THF are used at moderate temperatures to achieve high reactivity and selectivity with a wide range of electrophiles. These favorable results bode well for the use of these catalysts with other substrates under PTC conditions.

Acknowledgements

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Supplementary data

^{1}H NMR and optical rotation data for all compounds are provided. Supplementary data associated with this

article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.185.

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