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Catalytic Asymmetric Alkylation of Substituted Isoflavanones

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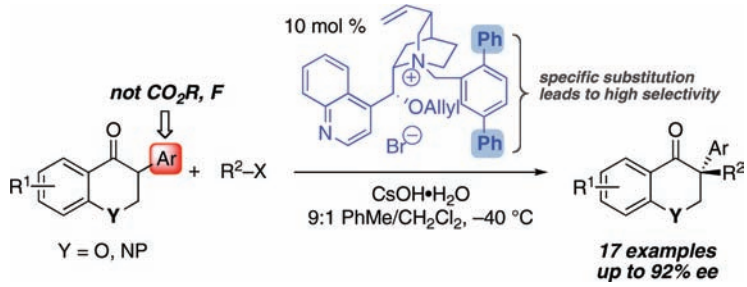
ABSTRACT



The asymmetric alkylation of isoflavanones (3-aryl-chroman-4-ones) and protected 3-phenyl-2,3-dihydroquinolin-4(1*H*)-ones catalyzed by a novel cinchonidine-derived phase transfer catalyst E is reported. This functionalization occurs at the unactivated C3 methine to afford novel products that can easily be functionalized to generate more complex fused ring systems. The process accommodates a variety of isoflavanones and activated electrophiles and installs a stereogenic quaternary center in high yield and with good-to-excellent selectivity. Isoflavanones are a privileged class of natural products with a broad spectrum of biological activities including insecticidal, antimicrobial, antibacterial, estrogenic, antitumor, and anti-HIV activity.[1] Isoflavanones are also precursors for more complex natural products such as pterocarpans and rotenones.[1] Given their therapeutic promise, selective strategies to access new classes of isoflavanones and related structures has high value.[2] The functionalization of the C3 position could promote beneficial interactions with biological targets of interest. Specifically, an alkylation at C3 can rapidly access new members of the general class of biologically active homoisoflavanones.[3]

The installation of stereodefined quaternary centers[4] in aryl-substituted indanones has been reported[5] but the corresponding methodology for the related isoflavanones has not been developed to the same extent. The larger core structure of isoflavanones (six carbons versus five for indanones) and potential scission of the C−O bond via elimination under basic conditions make modifications at C3 with established approaches a challenging endeavor. The palladium-catalyzed asymmetric alkylations of enol carbonates developed independently by Stoltz and Trost is restricted to allyl electrophiles and related structures by virtue of the reaction mechanism.[6] Alkylations of aryl ketones with a strongly electron-withdrawing group (F, CO_2R, CN) in the α-position

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have recently been reported separately by Deng, Dixon and Jorgensen using phase transfer catalysis (PTC).[7] Transition metal-catalyzed enantioselective α-arylations of tetralones and indanones have also been reported, but surprisingly, these reactions have focused predominately on α-methyl substituted substrates.[8] To date, a general solution to produce C3-substituted isoflavanones efficiently with high enantiomeric excess for the newly formed quaternary stereogenic center has not emerged. We report herein the direct asymmetric alkylation of isoflavanones (**1**, Y = O) and protected 3-phenyl-2,3-dihydroquinolinones (**1**, Y = NP) catalyzed by a new cinchonidine-derived quaternary ammonium salt to afford alkylated heterocycles (**2**, Figure 1).

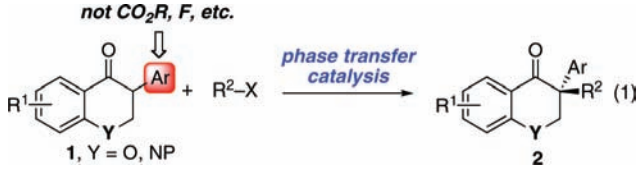
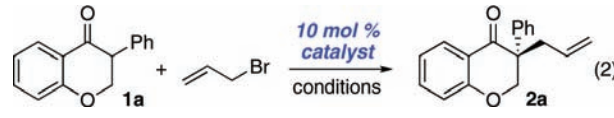


Figure 1. Phase transfer alkylation of unactivated benzocyclic ketones (this work).

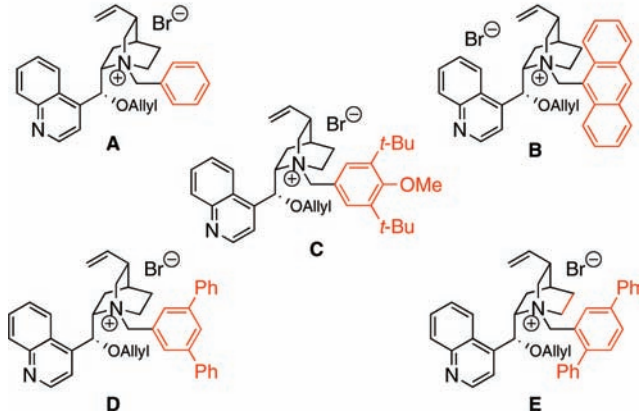
Our studies began by treating isoflavanone (**1a**) with allyl bromide and surveying various cinchonidine-derived quaternary ammonium salts and reaction conditions (Table 1). Initial problems of low conversion were circumvented by using excess base and alkyl halide to consume **1a**, which allowed us to focus our attention on obtaining optimal selectivities. Employing catalyst **A** and 50% aqueous KOH as the base at ambient temperature provided encouraging results (15% ee, entry 1). Cooling the reaction to 0 °C resulted in a minor increase in enantioselectivity (21% ee, entry 2). Vigorous stirring of the reaction increased the reaction rate, as did increasing the catalyst loading from 5 to 10 mol %, but neither modification dramatically improved the stereoselectivity of the reaction.

We hypothesized that a larger nitrogen substituent appended to the quinuclidine core might improve the stereoselectivity, which led us to employ well-known phase-transfer catalyst **B**.[9] This modulation and changing the base from aqueous KOH to solid $CsOH{\cdot}H_2O$ provided a moderate increase in enantiomeric excess (entry 3), which improved

Table 1. Optimization of Allylation Conditions



entry	catalyst	solvent	base	temp (°C)	ee (%)[b]
1	**A**	PhMe	50% aq KOH	23	15
2	**A**	PhMe	50% aq KOH	0	21
3	**B**	PhMe	$CsOH{\cdot}H_2O$	0	30
4	**B**	PhMe	$CsOH{\cdot}H_2O$	–40	44
5	**B**	PhMe	$CsOH{\cdot}H_2O$	–78	43
6	**B**	7:3 PhMe/CH_2Cl_2	$CsOH{\cdot}H_2O$	–40	49
7	**C**	PhMe	$CsOH{\cdot}H_2O$	–40	76
8	**C**	9:1 PhMe/CH_2Cl_2	$CsOH{\cdot}H_2O$	–40	78
9	**D**	9:1 PhMe/CH_2Cl_2	$CsOH{\cdot}H_2O$	–40	44
10	**E**	9:1 PhMe/CH_2Cl_2	$CsOH{\cdot}H_2O$	–40	83 (97%)[b]



[a] Determined by HPLC Chiracel OD-H. [b] % ee after recrystallization.

slightly when the reaction temperature was lowered (−40 °C, entry 4). Further cooling to −78 °C (entry 5) resulted in a longer reaction time and comparable selectivity, so we continued our optimization studies at −40 °C. While we were pleased with the slight increase in selectivity observed when employing a cosolvent (entry 6), we remained dissatisfied with the level of asymmetric induction, so we investigated other catalysts. The previously reported catalyst **C**[10] with toluene as the solvent afforded **2a** with 76% ee (entry 7), and 78% ee with 9:1 PhMe/CH_2Cl_2 as the solvent (entry 8).[11] The success of this catalyst indicates that the bulk of the substituent appended to the quinuclidine nitrogen atom is crucial for significant asymmetric induction.

The 3,5-diphenyl benzyl-ammonium catalyst **D** afforded **2a** with the same selectivity (entry 9) as observed catalyst **B** (44% ee, entry 4). After an extensive survey, the new catalyst with the specific 2,5-biaryl substitution pattern (**E**) afforded the C3-allylated isoflavanone **2a** with 83% ee (entry 10). The optical purity could be improved to 97% ee with a single recrystallization. While the lack of covalent bonding with PTC makes providing a model for stereoinduction with **E** difficult, it is clear that the placement of phenyl rings in the 2 and 5 positions on the benzyl fragment allows for the formation of the contact ion pair necessary for high levels of stereoinduction. Single crystal X-ray diffraction analysis

(6) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (b) Trost, B. M.; Xu, J. Y. *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847. (c) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924–6927.

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of salt **3**, derived from isoflavanone **2a**, allowed for the assignment of the absolute stereochemical configuration (and other products, by analogy) as the *R* enantiomer.

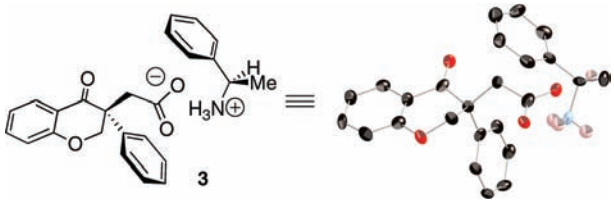


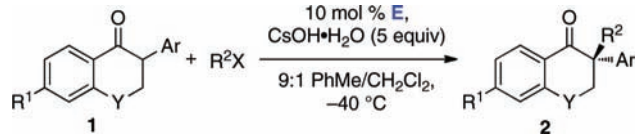
Figure 2. ORTEP of Isoflavanone **3**.

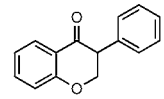
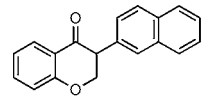
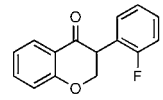
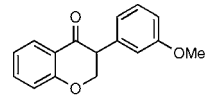
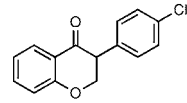
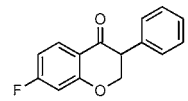
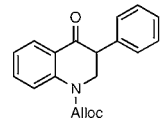
We next examined the scope of this reaction with regard to alkyl halides (Table 2). Alkylation of isoflavanone with a variety of alkyl halides gave products in good yields and with high to excellent enantioselectivities (entries 1−7). While alkylation with methallyl, and crotyl bromide gave products with 82−86% ee (entries 1−2), alkylation with cinnamyl chloride gave a selectivity of 92% ee (entry 3). Alkylations employing substituted benzyl halides typically necessitated longer reaction times, but also generally afforded products with higher selectivities (entries 5−6) as compared to the allylation processes. The reaction with TMS-propargyl bromide provided the desired product in good yield with 76% ee (entry 7).

The reaction tolerates electron-withdrawing aromatic substitution on the pendant C3 aryl ring with moderate-to-excellent levels of enantioselectivity. Alkylation of the 2-naphthyl analog of isoflavanone (entries 8−9) gave products with selectivities comparable to those of the alkylations of isoflavanone. Substrates with C3 aryl rings possessing carbon-based *ortho* substituents resulted only *O*-alkylation, but alkylation of 2′-fluoroisoflavanone (entry 10) resulted in only *C* alkylation, albeit with 80% ee. We were pleased to find that employing 4′-chloroisoflavanone afforded products with high levels of enantioselectivity (entries 12−13). However, electron-donating substituents on the C3 aryl ring (entry 11) consistently afforded products with lower selectivities. Electron-donating groups at the C7 position also afforded products with lower selectivities (<60% ee, not shown), but interestingly, C7 electron-withdrawing groups (entry 14) did not dramatically increase or decrease selectivity.

In our investigations of the nucleophile scope of this reaction, we tested different benzocyclic ketones, modifying the ring size and also the substitution of **Y**. Alkylation of tetralones (Y = CH_2) proved to be surprisingly difficult; the reactions rarely went to completion, even over a period of seven days, and the selectivity was surprisingly low (<50% ee). While the alkylations of 2-phenyl 1-indanone resulted in complete conversion to the desired products, selectivities comparable to those of tetralones were observed. We hypothesize that the planarity of the enolate is crucial for formation of a tight, contact ion pair with the cinchonidine-derived catalyst.[7a] This optimal planarity is achieved with

Table 2. Reaction Scope[a]



entry	ketone	R^2X	pdt	ee (%)[b]	yield (%)[c]
1		methallyl bromide	**2b**	86	70
2		crotyl bromide	**2c**	82	70
3		cinnamyl chloride	**2d**	92	62
4		benzyl bromide	**2e**	86	69
5		4-Br-$C_6H_4CH_2Br$	**2f**	87	67
6		4-F-C_6H_4Cl	**2g**	91	69
7		BrH_2C—≡—TMS	**2h**	76	85
8		methallyl bromide	**2j**	81	99
9		benzyl bromide	**2k**	87	76
10		benzyl bromide	**2l**	80	96
11		benzyl bromide	**2m**	77	66
12		methallyl bromide	**2n**	90	76
13		benzyl bromide	**2o**	90	82
14		benzyl bromide	**2p**	85	69
15		allyl bromide	**2q**	89	70
16		cinnamyl bromide	**2r**	91	84
17		4-Br-$C_6H_4CH_2Br$	**2s**	86	76

[a] General conditions: ketone **1** (1 equiv), R^2X (1.5 equiv), catalyst **E**, CsOH•H_2O, 9:1 PhMe/CH_2Cl_2 (0.1 M), −40 °C. [b] Enantiomeric excess determined by HPLC Chiralcel O−DH, AD-H, or Whelk-O1. [c] Isolated yields.

the flavanones but not with tetralones or indanones.[12] To test our hypothesis, we subjected various protected 3-phenyl-2,3-dihydroquinolin-4(1*H*)-ones (**1**, Y = NP) to the reaction conditions above. We were pleased to find that employing the *N*-Alloc quinolone gave products between 86 and 91% ee (entries 15−17). These molecules are of particular interest to us given their limited biological and synthetic studies.[13]

(9) (a) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415. (b) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598.

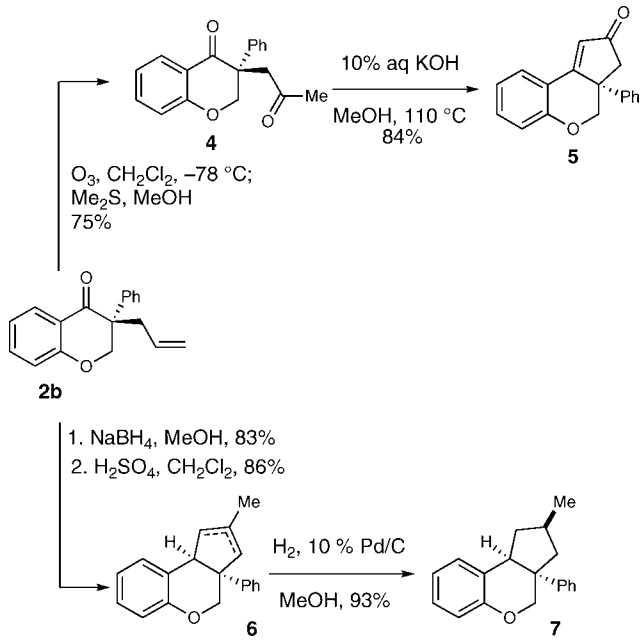
(10) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897–6899.

(11) Using polar aprotic solvents as the sole solvent for the reaction (not shown) resulted in significantly lower selectivities.

(12) The impact of these subtle structural changes is under investigation.

(13) (a) Daruwala, A. B.; Gearien, J. E.; Dunn, W. J.; Benoit, P. S.; Bauer, L. *J. Med. Chem.* **1974**, *17*, 819–824. (b) See ref 2b.

Scheme 1. Functionalization of Isoflavanone **2b**



With an efficient pathway to access alkylated isoflavanones and aza-isoflavanones, we have started to explore the synthetic utility of these compounds (Scheme 1). An ozonolysis/aldol condensation sequence from **2b** delivers enones such as **5** with high optical purity.[14] Alternatively, the exposure of ketone **2b** to reducing conditions followed by strong acid facilitates a Prins cyclization to afford a mixture of alkenes with >20:1 cis relative stereochemistry at the ring fusion. A subsequent reduction (Pd/C, hydrogen) approaches from the convex face of the tricyclic system and generates cyclopentane **7** in excellent yield.

Driven by the potential utility of optically active C3-substituted isoflavanones, we have developed the first enantioselective alkylation of these heterocycles (**1**, Y = O) and related nitrogen analogs (**1**, Y = NAlloc) employing a new cinchonidine-derived phase transfer catalyst **E**. The process accommodates a variety of isoflavanones and activated electrophiles and installs a stereogenic quaternary center in high yield and with good to excellent levels of enantioselectivity. This mild alkylation adds isoflavanones to the general compound classes for successful and useful enantioselective PTC and affords products from simple starting materials that can be easily transformed into novel heterocycles. Further reaction development with this new PTC catalyst and the application of the polycyclic products are ongoing in our laboratory.

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

OL901676F

(14) For the 2-methyltetralone analog of **5**, see: Clift, M. D.; Taylor, C. N.; Thomson, R. J. *Org. Lett.* **2007**, *9*, 4667–4669.