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Diastereoselective Friedel−Crafts Alkylation of Indoles with Chiral α-Phenyl Benzylic Cations. Asymmetric Synthesis of *Anti*-1,1,2-Triarylalkanes

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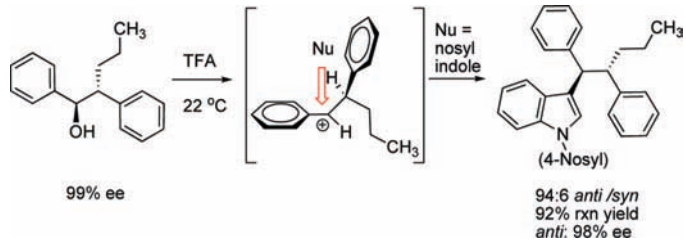
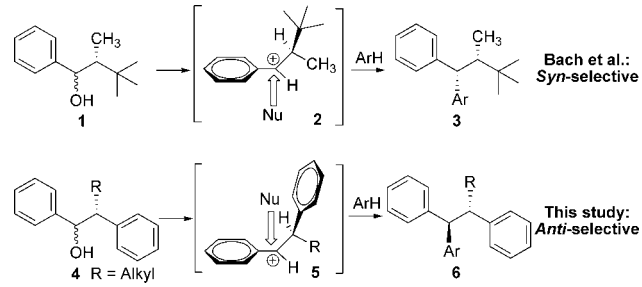
ABSTRACT



The reactions of chiral benzyl carbocations bearing α-phenyl substituents with N-sulfonylated indoles afford 1,1,2-triarylalkanes with *anti*-selectivities. This outcome is a reversal of facial diastereoselectivity relative to Bach's α-alkyl-bearing benzyl cations. The reactions are promoted by either a Brønsted acid (TFA) or Lewis acid (BF_3·OEt_2), offering differential diastereoselectivities and reactivities. The electronic properties of both reacting partners strongly influence the reaction rates and the product diastereoselectivities and appear to operate under kinetic control. This chemistry provides an efficient access to sterically congested tetrasubstituted ethanes.

Significant efforts have been dedicated to the study of strong nucleophiles adding to weakly electrophilic chiral α-branched carbonyl compounds.[1] In contrast, the addition of weak nucleophiles to chiral α-branched strong electrophiles represents a less studied combination.[2] In particular, there are only a few examples of intramolecular attack on chiral α-branched benzylic cations.[3] Bach et al. have studied the intermolecular version,[4] elegantly demonstrating that arene nucleophiles add to α-*tert*-butyl benzyl carbocations to afford 1,1-diaryl-2-*tert*-butylalkanes **3** in high *syn* diastereoselectivities (Scheme 1). In connection with a drug development

Scheme 1. Friedel−Crafts Alkylation with Chiral α-Branched Benzyl Cations



(1) (a) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145–162. (b) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151–4157. (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191–1223. (d) Takahashi, O.; Yamasaki, K.; Kohno, Y.; Ueda, K.; Suezawa, H.; Nishio, M. *Chem. Asian J.* **2006**, *1*, 852–859.

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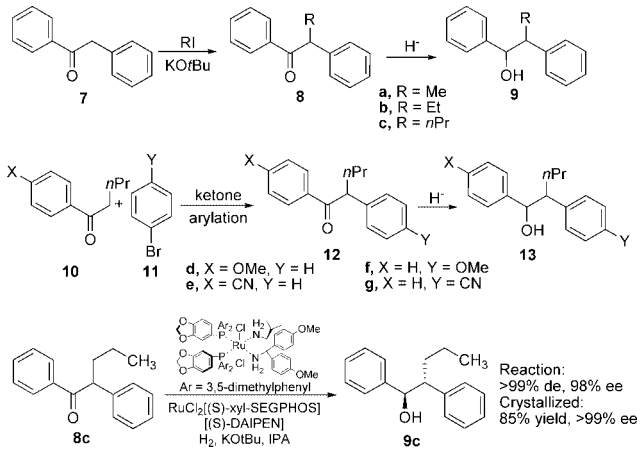
program, we were interested in applying this reactivity to α-phenyl benzylic carbocations[5] to access 1,1,2-triarylalkanes **6** (Scheme 1).[6] Herein, we report the reactions of chiral benzyl carbocations bearing α-phenyl substituents with arene nucleophiles, providing efficient access to sterically congested 1,1,2-triarylalkanes **6** in good yields and diastereoselectivities. In this chemistry, products were formed wth predominantly *anti*-selectivities, representing a *reversal* of the facial diastereoselectivity observed by Bach et al. (Scheme 1).

Benzyl alcohols **9** and **13** were prepared by one of two methods to serve as precursors to the desired benzyl cations (Scheme 2). Alkylation of desoxybenzoin (**7**) provided

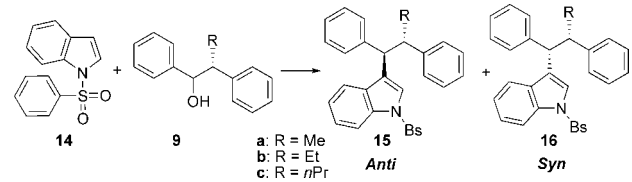
Scheme 2. Preparation of α-Phenyl Benzyl Alcohols



ketones **8**, and subsequent ketone reduction ($NaBH_4$ or DIBALH) furnished 1,2-diphenylethanol derivatives **9**. Alternatively, ketone **10** was subjected to Pd-catalyzed α-arylation[7] with *para*-substituted bromobenzene derivative **11**. Subsequent reduction afforded electronically differentiated 1,2-diarylethanols **13**. Alcohols **9** and **13** were mainly of the *anti* configuration (dr = 73/27 to 98/2). Optically active *anti*-benzyl alcohols were prepared by asymmetric hydrogenation reaction via dynamic kinetic resolution (DKR)[8] in excellent enantio- and diastereoselectivities (e.g., **8c** to **9c**).[9,10]

A screen of Brønsted/Lewis acids provided viable reaction conditions for the intermolecular Friedel−Crafts reactions: (1) 3 equiv of $BF_3{\cdot}OEt_2/CH_2Cl_2$ (method A); (2) TFA as solvent (method B). In a first set of experiments, we studied the reaction of *N*-benzensulfonyl-indole (**14**) with benzyl alcohol **9** as a function of an alkyl R group (Table 1). As

Table 1. Reaction of *N*-Besyl Indole and α-Phenyl Benzyl Alcohol **9a**−**c**[a]



entry	benzyl alcohol	R	method	**15**:**16** *anti*:*syn*[b]	conversion[c]	yield[d]
1	**9a**	Me	A	1.7:1	93%	82%
2	**9a**	Me	B	2.8:1	90%	80%
3	**9b**	Et	A	4:1	90%	85%
4	**9b**	Et	B	5.3:1	95%	80%
5	**9c**	*n*Pr	A	5.6:1	94%	80%
6	**9c**	*n*Pr	B	10:1	95%	84%

[a] Reaction conditions. Method A: 3 equiv of $BF_3{\cdot}OEt_2$, CH_2Cl_2 (0.2 M), 22 °C, 20 h. Method B: TFA (0.2 M), 22 °C, 20 h. [b] The dr of the product was determined by ^1H NMR spectroscopy and HPLC. [c] HPLC ratios of (**15** + **16**)/(**14** + **15** + **16**). [d] Yields were determined by HPLC methods based on isolated products.

the chain length of the R group was increased from methyl to ethyl and propyl (substrates **9a**−**c**), the *anti*-selectivity also increased. Under both sets of conditions, the reactions proceeded to ≥90% conversion to afford products **15**/**16** in 80−85% yields. The TFA conditions afforded better selectivities than the $BF_3{\cdot}OEt_2$ conditions for all three substrates. The best diastereoselectivity was achieved with *n*-propyl substrate **9c**, providing a 10:1 ratio of **15c**/**16c**. Identical product diastereomeric ratios were obtained independent of the starting material dr's, implicating a secondary benzylic cation as a common intermediate in these reactions. The absolute stereochemical integrity of the α-carbon center was also maintained during the reaction. We subjected 99% ee benzyl alcohol **9c** to the indole addition reaction and obtained product **15c** in 98% ee.

The relative stereochemistries of compounds **15** and **16** were assigned *anti* and *syn*, respectively, based on ^1H NMR coupling constants and NOE studies (Figure 1).[11] In these two series of compounds, the observed coupling constants between the two adjacent methine protons were $^3J_{Ha,b}$ =

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(7) Pd-catalyzed α-arylation of ketones: (a) Palucki, M.; Buchwald, S. L *J. Am. Chem. Soc.* **1997**, *119*, 11108–11109. (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478. (c) Fox, J. M.; Huang, X.; Chieffi, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370.

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(9) The absolute stereochemistry of the alcohol was established using Harada's MaNP ester method.[10] The relative stereochemistry was determined via NMR coupling constants and NOE studies. See Supporting Information.

(10) (a) Nishimura, T.; Taji, H.; Harada, N. *Chirality* **2004**, *16*, 13–21. (b) Kasai, Y.; Sugio, A.; Sekiguchi, S.; Kuwahara, S.; Matsumoto, T.; Watanabe, M.; Ichikawa, A.; Harada, N. *Eur. J. Org. Chem.* **2007**, *181*, 1–1826.

(11) See Supporting Information for additional NOE studies.

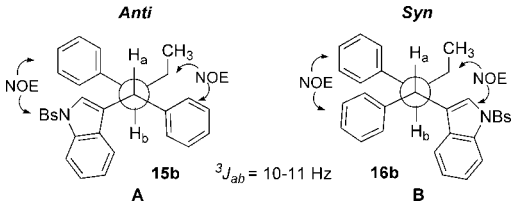


Figure 1. Determination of relative stereochemistries of **15b** and **16b** via NMR NOE studies.

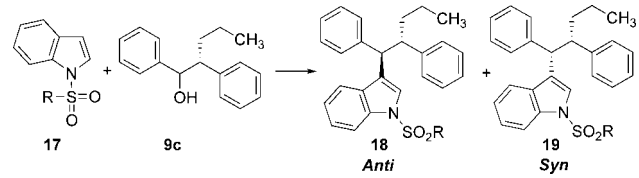
10−11 Hz, indicative of a dihedral angle of ∼180° as the preferred orientation, as illustrated in the gauche conformers **A** and **B**. On the basis of these conformations, the expected NOE correlations were observed between the correct substituents for both the *anti* and *syn* diastereomers. In addition, X-ray analysis of product **24e** was performed, corroborating the NMR stereochemistry assignments (see Supporting Information).

The *anti*-selectivity observed for the nucleophilic addition to substrates **9a**−**c** is in direct contrast to Bach's results with the α-*tert*-butyl-α-methyl benzyl cation **2**[4] (Scheme 1). On the basis of *A*-value consideration, the phenyl group (A = 2.7) is larger than the alkyl groups (Me, A = 1.7; Et, A = 1.8; *n*Pr, A = 2.1); however, it behaves as the smaller group in these substrates. A possible explanation is suggested in the energy-minimized conformer **5**,[12] in which the phenyl group may have a smaller sweep volume than the alkyl group due to rotational barriers, leading to nucleophilic addition from that face.[13] The behavior of a phenyl group as smaller than the alkyl group is consistent with the work of Eliel on 1-methyl-1-phenylcyclohexane.[14] The data in Table 1 support this hypothesis, where increasing the length of the alkyl group increases selectivity.

Arene−arene interactions are speculated to be important in this mechanistic analysis as well.[15] Specifically, the incoming indole nucleophile could $\pi-\pi$ stack with the phenyl ring of the benzyl cation, as well as support a CH−π interaction between an indole CH bond (on the five-membered ring) and the aryl ring oriented ∼90° to the benzyl cation. Further experiments are required to fully decode the underlying features of the transition states for these reactions. Phenonium ion participation is inconsistent with the observed results because it would lead to *syn*-products.

In a second study, we examined the impact of the electronic properties of the *N*-phenylsulfonyl protecting group on the product diastereoselectivity (Table 2). By changing the R-group from electron-donating (Table 2, entry 2) to electron-withdrawing (Table 2, entry 8), the product diastereoselectivity improved slightly from 86:14 to 94:6. This improvement in diastereoselectivity coincided with a decrease in the reaction rates. In general, the TFA conditions afforded products in higher diastereoselectivities, and the BF_3·OEt_2 conditions usually proceeded in somewhat faster rates and better reaction yields.

Table 2. Electronic Effect of Indole Protecting Groups[a]



entry	indole	R	method	**18**:**19** *anti*:*syn*[b]	yield[c]
1	**17a**	Tol	A	76:24	74%
2	**17a**	Tol	B	86:14	73%
3	**14**	Ph	A	85:15	80%
4	**14**	Ph	B	91:9	84%
5	**17b**	4-Cl-Ph	A	83:17	93%
6	**17b**	4-Cl-Ph	B	89:11	60%
7	**17c**	4-NO_2-Ph	A	85:15	94%
8	**17c**	4-NO_2-Ph	B	94:6	92%

[a] Reaction conditions. Method A: 3 equiv of BF_3·OEt_2, CH_2Cl_2 (0.2 M), 22 °C, 20 h. Method B: TFA (0.2 M), 22 °C, 20 h. [b] The dr of the product was determined by ^{1}H NMR spectroscopy and HPLC. [c] Yields were determined by HPLC methods based on isolated products.

Next, we studied the electronic effects of a *para* substituent in each of the two phenyls in the benzyl alcohol (Table 3). The electron-donating −OMe substituent in the proximal X-position dramatically accelerated the reaction rate (Table 3, entry 1). The electron-withdrawing −CN group at this position completely shut down the Friedel−Crafts reaction, trifluoroacetylation of the alcohol (**22**)[16] representing the only product formed (Table 3, entry 3). These trends are consistent with rate-limiting ionization of the benzyl alcohol. The presence of an −OMe group in the remote Y-position led to a slightly slower reaction (entry 4) relative to unsubstituted substrate **9c**. The −CN group at this position gave an expected significantly slower reaction rate (Table 3, entry 5). Here, the rate vs diastereoselectivity relationship is opposite of that observed for the study in Table 2, where the slower-reacting nucleophiles afforded better diastereoselectivities.

To probe the scope and limitation of this chemistry, we briefly examined other arene nucleophiles: pyrrole, furan, benzofuran, thiophene, benzothiophene, and 1,3-dimethoxybenzene (Table 4). These electron-rich arenes performed better under BF_3·OEt_2 conditions to afford moderate yields of the corresponding products. Benzothiophene and *N*-nosyl

(12) Molecular modelings were carried out using the Conformer Search module of CERIUS2. The DREIDING forcefield was used to describe the energetics. Partial atomic charges were assigned using the charge equilibration method. See Supporting Information.

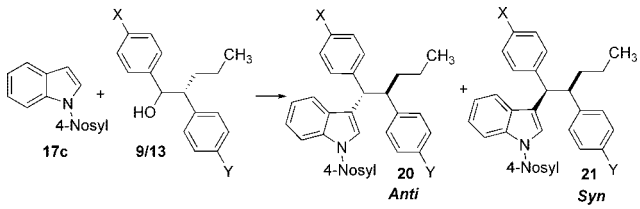
(13) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353–3361.

(14) Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959.

(15) (a) Claessens, C. G.; Stoddart, J. F. *J. Phys. Org. Chem.* **1997**, *10*, 254–272. (b) Janiak, C. *J. Chem. Soc., Dalton Trans.* **2000**, 3885–3896. (c) Takahashi, O.; Kohno, Y.; Iwasaki, S.; Saito, K.; Iwaoka, M.; Tomoda, S.; Umezawa, Y.; Tsuboyama, S.; Nishio, M. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2421–2430.

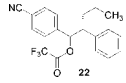
(16) Trifluoroacetylation to form **22** retained the stereochemical configuration of the alcohol, implying it formed via esterification and not ionization suppressed by the dipole−dipole repulsion from the cyano group.

Table 3. Electronic Effect of *para* Substituents on Phenyl Rings[a]



entry	benzyl alcohol	X	Y	$t_{1/2}$	t_{95}[b]	**20:21** *anti*:*syn*	yield[c]
1	**13d**	MeO	H	<5 min	5 min	29:1	95%[d]
2	**9c**	H	H	<5 min	1 h	15:1	92%
3	**13e**	CN	H	--	--	--	0%[f]
4	**13f**	H	MeO	5 min	3 h	20:1	78%
5	**13g**	H	CN	2 h	>20 h[e]	7:1	54%

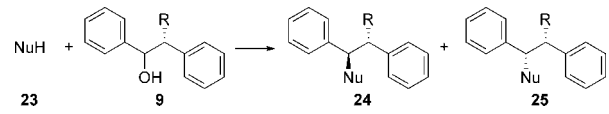
[a] Reaction conditions: Method B. [b] Time required to reach 90−95% conversion. [c] HPLC yield after 20 h. [d] Reaction quenched after 1 h. [e] 76% conversion after 20 h at rt. [f] Trifluoroacetylation of the alcohol as the only product formed (**22**).



pyrrole gave ~90:10 diastereoselectivity, whereas methylthiophene gave a slightly lower 75:25 dr. No selectivity was observed in the reaction with 1,3-dimethoxybenzene. Reactions involving benzofuran and furan suffered significant decomposition.

In summary, the reactions of chiral benzyl carbocations bearing α-phenyl substituents with *N*-sulfonylated indoles afforded 1,1,2-triarylalkanes with *anti*-selectivities. This outcome is a *reversal* of facial diastereoselectivity relative to Bach's α-alkyl-bearing benzyl cations. The reactions are promoted by either Brønsted acid (TFA) or Lewis acid (BF_3•OEt_2), offering differential diastereoselectivities and reactivities. The reaction rates and product diastereoselectivities are significantly influenced by the electronic properties of both reacting partners and appear to operate under kinetic control. Continued efforts will be dedicated to expanding the scope of weakly nucleophilic partners in this chemistry.

Table 4. Friedel−Crafts Alkylation of Arenes with Chiral Benzyl Alcohol **9c**



entry	compd	NuH	R	method[a]	**24:25** *anti*:*syn*[b]	convn	yield[c]
1	**a**		*n*Pr	A B	--	--	trace
2	**b**		*n*Pr	A B	89:11 92:8	91% 86%	36% 56%
3	**c**		Me	A B	54:46 --	95% --	81% trace
4	**d**		*n*Pr	A B	75:25 --	95% --	73%[d] trace
5	**e**		*n*Pr	A B	86:14 90:10	93% 91%	71% 66%
6	**f**		*n*Pr	A B	--	--	trace
7	**g**		*n*Pr	A B	46:54 47:53	86% 63%	51% 15%

[a] Reaction conditions. Method A: 3 equiv of BF_3•OEt_2, CH_2Cl_2 (0.2 M), 22 °C, 20 h. Method B: TFA (0.2 M), 22 °C, 20 h. [b] The dr of the product was determined by ^{1}H NMR spectroscopy and HPLC. [c] HPLC yield. [d] Isolated yield.

Acknowledgment. We thank R. Reamer and L. DiMichele, D. Steinhuebel, J. Rosen, C. Bazaral, S. Krska, and R. Ruck, all of Process Research, Merck Research Laboratories, for their help and insight.

Supporting Information Available: Representative experimental procedures, NMR data for all new compounds, selective HPLC, elemental and mass spec data, modeling programs and energy-minimized benzylic cation conformations, and crystallographic information files (CIF) for **24e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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