

141 (MH<sup>+</sup>) [lit.<sup>4</sup> <sup>1</sup>H NMR  $\delta$  0.86 (3 H, d,  $J$  = 7 Hz), 0.88 (3 H, d,  $J$  = 7 Hz), 1.17 (3 H, s), 1.66 (3 H, bs), 1.58-2.70 (3 H, m), 4.33 (1 H, bs); <sup>13</sup>C NMR  $\delta$  (C<sub>6</sub>D<sub>6</sub>) 13.87, 17.38, 23.81, 37.44, 39.75, 89.27, 93.14, 153.69.

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**Supplementary Material Available:** <sup>1</sup>H NMR spectra of compounds (*R*)-1,  $\alpha$ -(*R*)-6,  $\alpha$ -(*S*)-6, (*S*)-8, and (*RS*)-2/2'/3 (6 pages). Ordering information is given on any current masthead page.

## Solid Superacid-Catalyzed Organic Synthesis. 4.<sup>1a</sup> Perfluorinated Resinsulfonic Acid (Nafion-H) Catalyzed Friedel-Crafts Benzoylation of Benzene and Substituted Benzenes

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Nafion-H, a perfluorinated resinsulfonic acid, catalyzes Friedel-Crafts benzoylation of benzene and substituted benzenes with benzyl alcohols under relatively mild experimental conditions. Reactions are clean, and water formed as a byproduct does not deactivate the catalyst. It was also found that this method is applicable to the intramolecular cycloalkylation and oligomerization of methoxybenzyl alcohols.

### Introduction

Friedel-Crafts alkylation reactions in solution generally give complex reaction mixtures. The formation of reactant (and product) catalyst complexes, the increased tendency of alkylated products toward further alkylation and isomerization, coupled with the long contact of the reactant with the catalyst, result in complex mixtures of products. Polyalkylation, isomerization, transalkylation, dealkylation, and polymerization all occur under the reaction conditions.

There is, therefore, of substantial interest to catalyze alkylation reactions with solid acids which decrease these side reactions.<sup>2</sup> Gas-phase alkylation performed over catalysts such as sulfonated polystyrene resins allows for short contact time and weak complexation of the reactants with the catalyst, thus resulting in much cleaner and less complex product mixtures.<sup>3</sup> These beneficial results are due to the high acidity of the resin.

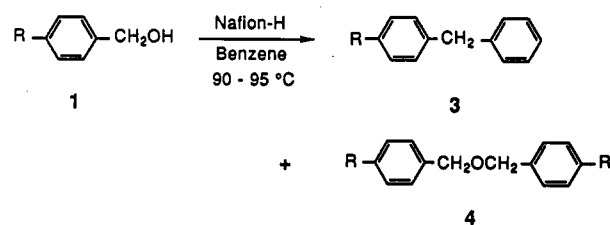
We now describe a convenient and efficient method of Nafion-H<sup>4</sup> (a solid perfluorinated resinsulfonic acid) catalyzed benzoylation of benzene and substituted benzenes with benzyl alcohols.

### Results and Discussion

The benzoylation reactions were carried out by heating a stirred mixture of the corresponding benzyl alcohols (1), aromatics (2), and the solid Nafion-H catalyst at 95-100 °C. Product diphenylmethanes (3) were simply isolated by filtering the hot reaction mixture and distilling off the solvent. The reactions are very clean; water is the only byproduct of the reaction.

The reaction is general for benzyl alcohols (see Table I) and aromatics that normally undergo Friedel-Crafts benzoylations. Benzene with benzyl alcohols (1) gave the corresponding diphenylmethanes (3) in >50% yields. As

Table I. Nafion-H-Catalyzed Benzoylation of Benzene with Substituted Benzyl Alcohols (1)<sup>a</sup>



run	R in 1	reaction time (h)	products yields (%) <sup>b</sup>	
			3	4
1	H	4	69 (54) <sup>c</sup>	22 (16) <sup>c</sup>
2	4-CH <sub>3</sub>	1	97 (81) <sup>c</sup>	3
3	4- <i>t</i> -Bu	1	90 (85) <sup>c</sup>	2
4	4-Br	12	91 (70) <sup>c</sup>	6
5	4-NO <sub>2</sub> <sup>d</sup>	24	60 (52) <sup>c</sup>	22 (19) <sup>c</sup>

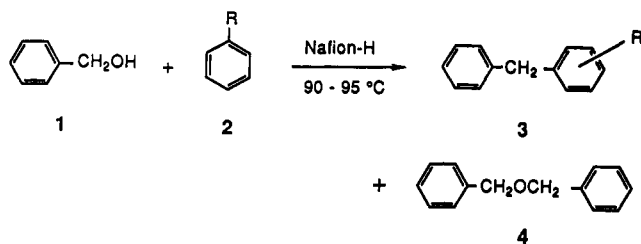
<sup>a</sup> [Benzene]/[benzyl alcohol] = 30:1; catalyst 10 wt %. <sup>b</sup> The yields were determined by GLC analyses unless otherwise indicated. <sup>c</sup> Isolated yields are shown in parentheses. <sup>d</sup> The starting compound was recovered in 15% yield.

shown in Table I, the present method provides excellent yields of diphenylmethanes (3), and no concomitant *trans-tert*-butylation and *transbromination* were observed under the reaction conditions (runs 3, 4). The amount of the catalyst used relative to the benzyl alcohol was between 5% and 10% by weight. Optimum yields were obtained with 10% of catalyst (Table I), whereas 5% gave only slightly lower yields.

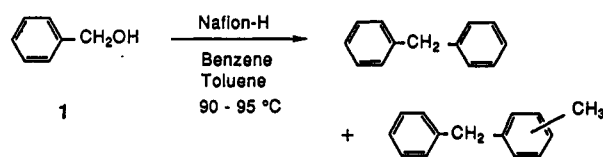
The benzoylation reaction was further studied by reacting various substituted benzenes (2) with benzyl alcohol (1) under similar conditions (Table II). The yields of 3 are comparable for toluene, ethylbenzene, *o*-xylene, *m*-xylene, *p*-xylene, and mesitylene, and somewhat lower for benzene because of formation of the dehydration products, dibenzyl ethers (4).

The isomeric composition of the diphenylmethanes (3) resulting from alkylbenzenes were determined by GLC. The results (Table III) show that the reactions give predominantly *ortho-para* substitution, in accordance with

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**Table II. Nafion-H Catalyzed Benzylolation of Benzene and Alkylbenzenes with Benzyl Alcohol<sup>a</sup>**

run	R in 2	time (h)	product yield (%) <sup>b</sup> 3	bp, °C (Torr)	4
1	H	4	68 (54) <sup>c</sup>	120-122 (9)	22
2	CH <sub>3</sub>	2	86 (70) <sup>c</sup>	114-115 (3)	5
3	C <sub>2</sub> H <sub>5</sub>	2	90 (73) <sup>c</sup>	118-119 (3)	6
4	1,2-CH <sub>3</sub>	1	88 (70) <sup>c</sup>	137-140 (5)	7
5	1,3-CH <sub>3</sub>	1	88 (71) <sup>c</sup>	124-126 (3)	4
6	1,4-CH <sub>3</sub>	1	87 (73) <sup>c</sup>	120-122 (3)	2
7	1,3,5-CH <sub>3</sub>	1	93 (79) <sup>c</sup>	142-144 (5)	3

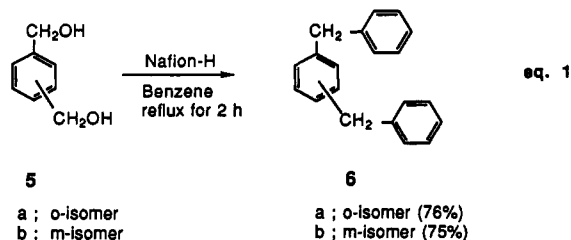
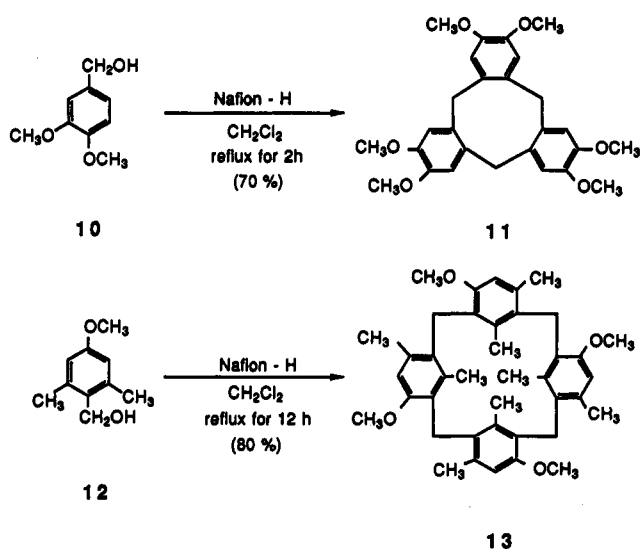
<sup>a</sup>[Alkylbenzenes]/[benzyl alcohol] = 30:1; catalyst 10 wt %.<sup>b</sup>The yields were determined by GLC analyses. <sup>c</sup>Isolated yields are shown in parentheses.**Table III. Competitive Benzylolation of Toluene and Benzene in the Presence of Various Catalysts<sup>a</sup>**

catalyst	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> X	temp (°C)	k <sub>T</sub> /k <sub>B</sub>	ortho	meta	para
Nafion-H <sup>a</sup>	OH	90	3.6	41.9	2.8	55.3
AlCl <sub>3</sub> -CH <sub>3</sub> NO <sub>2</sub>	Cl	25	3.2	43.5	4.5	52.0
AlCl <sub>3</sub> -CH <sub>3</sub> NO <sub>2</sub>	Cl	50	4.5	42.4	6.2	51.4
TiCl <sub>4</sub>	Cl	50	6.0	41.0	4.5	54.5

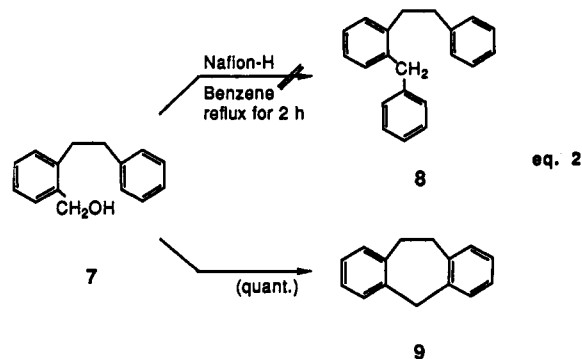
<sup>a</sup>[Toluene]:[benzene]:[benzyl alcohol] = 15:15:1; catalyst 10 wt %.

a typical electrophilic aromatic substitution pathway. The ortho:para ratio is almost the same as that obtained by the reaction with benzyl halides under the usual solution-phase Friedel-Crafts conditions using AlCl<sub>3</sub>-CH<sub>3</sub>NO<sub>2</sub> as the catalyst.<sup>5</sup> It is difficult, however, to assess properly the selectivity of the reactions and the exact nature of the reaction. The substrate and positional selectivity of the benzylolation reaction under the Nafion-H catalyst was found to be almost the same as that obtained by the reaction with benzyl halides under the AlCl<sub>3</sub>-CH<sub>3</sub>NO<sub>2</sub> catalyst<sup>6</sup> (Table III).

The Nafion-H-catalyzed benzylolation was further applied to bis(hydroxymethyl)benzenes (5). The reaction was again carried out in refluxing benzene solution and the results are shown in eq 1.

(5) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1962**, *84*, 1688.(6) Olah, G. A.; Kobayashi, S.; Tashiro, M. *J. Am. Chem. Soc.* **1972**, *94*, 7448.**Scheme I**

It was also found that when 2-(hydroxymethyl)di-phenylethane (7) was treated in refluxing benzene for 2 h in the presence of Nafion-H, the desired product (8) was not obtained. Only the intramolecular benzylolation product, 10,11-dihydro-5H-dibenzo[*a,d*]cycloheptene (9) was formed in quantitative yield. Compound 9 was also obtained when 7 was treated in refluxing dichloromethane for 2 h in the presence of Nafion-H (eq 2).



Moreover, the presently developed procedure offers advantages for the trimerization and tetramerization of methoxybenzyl alcohols (10) and (12) over the previously reported Lewis acid catalyzed methods<sup>7,8</sup> (Scheme I). These results indicate that in solution the benzylolation reaction occurs at the catalytic surface. A specific advantage of using insoluble resins as catalysts include the prevention of intermolecular reaction of reactive species or functional groups by simulating high dilution conditions.

The present method provides excellent yields, easy isolation of the products, and ready regeneration of the catalyst without loss of activity.

### Experimental Section

Benzyl alcohols used in the current study were of highest purity available commercially except 2,6-dimethyl-4-methoxybenzyl alcohol (12),<sup>9</sup> which was prepared according to the reported method. The Nafion-H catalyst was prepared from commercial (Du Pont) Nafion-K resin as previously described.<sup>4</sup> All melting points are uncorrected.

(7) Lindsey, A. S. *J. Chem. Soc.* **1965**, 1685.(8) Wu, T.; Speas, J. R. *J. Org. Chem.* **1987**, *52*, 2330.(9) James, B. G.; Pattenden, G.; Barlow, L. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1466.

**General Procedure for the Benzoylation of Substituted Benzyl Alcohols (1) with Benzene in the Presence of Nafion-H.** A mixture of substituted benzyl alcohols (1) (30 mmol) and Nafion-H (10 wt %) in benzene (0.9 mol) was refluxed with stirring until completion of the reaction as monitored by GLC analysis (OV-1, 2 m). The solid resinsulfonic acid was then filtered off, and the filtrate was analyzed by GLC. The reaction conditions and yields are summarized in Table I.

**General Procedure for the Benzoylation of Benzyl Alcohol (1) with Alkylbenzenes (2) in the Presence of Nafion-H.** A mixture of benzyl alcohol (1) (30 mmol) and Nafion-H (10 wt %) in alkylbenzenes (0.9 mol) was heated at 90–95 °C with stirring until completion of the reaction as monitored by GLC analysis (OV-1, 2 m). The solid resinsulfonic acid was then filtered off, and the filtrate was analyzed by GLC. The reaction conditions and yields are summarized in Table II.

**Competitive Benzoylation of Benzene and Toluene with Benzyl Alcohols.** A mixture of benzyl alcohol (1) (30 mmol) and Nafion-H (10 wt %) in benzene (0.45 mol) and toluene (0.45 mol) was refluxed with stirring for 2 h. The solid resinsulfonic acid was then filtered off, and the filtrate was analyzed by GLC. The reaction conditions and yields are summarized in Table III.

**General Procedure for the Benzoylation of Bis(hydroxymethyl)benzenes (5) in the Presence of Nafion-H.** A mixture of bis(hydroxymethyl)benzenes (5) (1.45 mmol) and Nafion-H (300 mg) in 30 mL of benzene was refluxed with stirring for 2 h. The reaction mixture was treated as described above to give 6a and

6b in yields of 76% and 75%, respectively.

**Benzoylation of 2-(Hydroxymethyl)diphenylethane (7) with Benzene in the Presence of Nafion-H.** A mixture of 2-hydroxydiphenylethane (7) (1 mmol) and Nafion-H (300 mg) in 30 mL of benzene was refluxed with stirring for 2 h. The reaction mixture was treated as described above to give 193 mg (99.5%) of 9 as colorless prisms (hexane): mp 75–76 °C (lit.<sup>10</sup> mp 78–79 °C).

**General Procedure for the Trimerization and Tetramerization of Methoxybenzyl Alcohols (10 and 12).** A mixture of methoxybenzyl alcohols (10 mmol) and 300 mg of Nafion-H in 30 mL of CH<sub>2</sub>Cl<sub>2</sub> was refluxed with reflux for 2 h. The reaction mixture was treated as described above to give 70% of 11 and 80% of 13, respectively.

11: colorless prisms (benzene); mp 232–234 °C (lit.<sup>7</sup> mp 234 °C).

13: colorless prisms (CH<sub>2</sub>Cl<sub>2</sub>); mp >300 °C (lit.<sup>8</sup> mp 335–365 °C); mass spectrum, *m/e* 592 (M<sup>+</sup>).

**Regeneration of Nafion-H Catalyst.** The recovered catalyst was washed several times with acetone and deionized water, followed by drying at 105 °C for 10 h. The catalyst activity of regenerated catalyst was as good as that of fresh catalyst.

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## Asymmetric Synthesis of the Corynantheine Alkaloids via an Intramolecular Blaise Reaction. (–)-Corynantheidol and (–)-Dihydrocorynantheol

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An asymmetric total synthesis of the corynantheine family of alkaloids has been accomplished, leading to corynantheidol (1a) and dihydrocorynantheol (1b). Formal syntheses to corynantheidine and dihydrocorynantheine are also shown. The key to this asymmetric route is the use of (1) chiral  $\beta$ -carboline formamidines, which allow high degrees of diastereoselection at C-3 with chloroacetonitrile, and (2) a new version of the Blaise reaction using Zn–Ag couple and ultrasonic radiation. These two synthetic techniques combine to allow an efficient entry into the title compounds. The overall yield of 1a was 16.4% in seven steps from starting carboline 5.

The class of indole alkaloids related to yohimbine and known as the ring E seco equivalents are called the corynantheines.<sup>1</sup> There have been several beautiful total syntheses of these substances, although all provided racemic material.<sup>2</sup> Our program on asymmetric synthesis of various alkaloids and other medicinally important substances<sup>3–6</sup> has relied on the use of chiral formamidines.

These versatile synthons, in both chiral and achiral forms, have provided a large array of elaborated nitrogen compounds since their introduction in 1980.<sup>9</sup>

We now report a further advance in this methodology that incorporates the use of the old, seldom-employed, Blaise reaction<sup>10a</sup> and its application toward the asymmetric total synthesis of the corynantheine alkaloids corynantheidol (1a) and dihydrocorynantheol (1b). Furthermore, the route to these systems also allows entry into two related seco alkaloids, corynantheidine (2a) and dihydrocorynantheine (2b).

Pivotal intermediates to 1 and 2 have been the tetracyclic ketones 3 and 4, the latter of which have been prepared in racemic form by Szantay,<sup>11</sup> Weisbach,<sup>12</sup>

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