

Secondary Benzylolation Using Benzyl Alcohols Catalyzed by Lanthanoid, Scandium, and Hafnium Triflate

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The combination of a secondary benzyl alcohol and a metal triflate (e.g., La, Yb, Sc, and Hf triflate) in nitromethane was a highly effective secondary-benzylolation system. Secondary benzylolation of carbon (aromatic compounds, olefins, an enol acetate), nitrogen (amide derivatives), and oxygen (alcohols) nucleophiles was carried out with a secondary benzyl alcohol and 0.01–1 mol % of a metal triflate in the presence of water. Secondary benzyl alcohols and nucleophiles bearing acid-sensitive functional groups (e.g., *tert*-butyldimethylsilyloxy and acetoxy groups and methyl and benzyl esters) could be used for alkylation. Hf(OTf)₄ was the most active catalyst for this alkylation, and trifluoromethanesulfonic acid (triflic acid, TfOH) was also a good catalyst. The catalytic activity of metal triflates and TfOH increased in the order La(OTf)₃ < Yb(OTf)₃ < TfOH < Sc(OTf)₃ < Hf(OTf)₄. A mechanistic study was also performed. The reaction of 1-phenylethanol (**4a**) in the presence of Sc(OTf)₃ in nitromethane gave an equilibrium mixture of **4a** and bis(1-phenylethyl) ether (**54**). Addition of a carbon nucleophile to the equilibrium mixture gave alkylated product in high yield.

Introduction

The Friedel–Crafts reaction is a very important method for introducing alkyl substituents to an aromatic ring. However, Friedel–Crafts alkylation¹ is used less than Friedel–Crafts acylation in fine organic synthesis. In many cases, an alkyl halide or olefin is used as the electrophile source, and large amounts of an aromatic nucleophile and Lewis or Brønsted acid are necessary for alkylation. Alcohol is also used as an electrophile for Friedel–Crafts alkylation,² and 1 equiv of water is released as the reaction proceeds; thus, excess sulfuric acid, polyphosphoric acid,³ or a stoichiometric amount of Lewis acid⁴ is required. Therefore, it is difficult to fine tune Friedel–Crafts alkylation for various functionalized substrates.⁵ Recently, lanthanoid triflates have been used in various synthetic reactions⁶ and have been shown to act as catalysts even in the presence of water.⁷ Therefore, a catalytic amount of lanthanoid triflate can complete

Friedel–Crafts alkylation using alcohols. Hf(OTf)₄ and Sc(OTf)₃ are also effective catalysts⁸ in the Friedel–Crafts acylation and alkylation of benzene derivatives with acid anhydrides, allyl alcohols,⁹ and benzyl halides. Sc(OTf)₃ is also stable and acts as a Lewis acid in the presence of water, and a benzylic cation can be generated from not only benzylic halide but also benzylic alcohol¹⁰ and benzylic ether.¹¹

However, most metal triflate-catalyzed Friedel–Crafts alkylations require more than 5 mol % of the triflate

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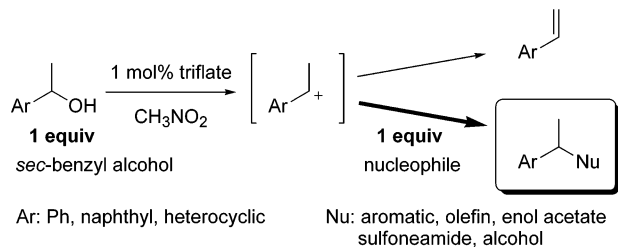
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SCHEME 1. Metal Triflate-Catalyzed *sec*-Benzylolation of Various Nucleophiles

TABLE 1. Effects of Catalyst Loading and the Addition of H₂O

| entry | Lewis acid | loading, mol % | time, h | yield, % |
|----------------|-----------------------------------|----------------|------------------|----------|
| 1 ^a | TiCl ₄ | 100 | 1 | 6 |
| 2 ^a | BF ₃ ·OEt ₂ | 100 | 1 | 96 |
| 3 ^a | BF ₃ ·OEt ₂ | 10 | 1 | 6 |
| 4 ^b | La(OTf) ₃ | 1 | 0.5 | 99 |
| 5 ^b | La(OTf) ₃ | 0.1 | 1 | 98 |
| 6 ^b | La(OTf) ₃ | 0.01 | 24 | 93 |
| 7 ^b | La(OTf) ₃ | 1 | 1.5 ^c | 98 |
| 8 ^b | Yb(OTf) ₃ | 1 | 0.33 | 96 |
| 9 ^b | Yb(OTf) ₃ | 0.1 | 0.25 | 94 |

^a Reaction conditions: in dichloromethane (250 mmol/L for **1**), 0 °C. ^b Reaction conditions: in nitromethane (250 mmol/L for **1**), 100 °C. ^c H₂O (10 equiv) was added.

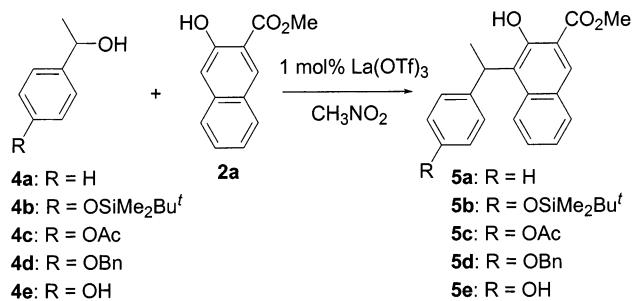
catalyst. In addition, the functional groups of the substrates (electrophile and nucleophile) are limited; the functional groups are usually simple ethers or alkyl groups. While the reaction of a secondary benzylic alcohol generally gives the corresponding carbocation more easily than that of a primary benzylic alcohol, the secondary carbocation readily decomposes into a corresponding olefin.¹² Therefore, only a few examples of secondary alkylation have been reported.¹³ We studied the effective generation of secondary carbocations by the combination of a secondary benzyl alcohol and a metal triflate in nitromethane. This reaction system is easily tunable for various substrates and is suitable for aromatic, olefin, enol acetate, sulfonamide, and alcohol nucleophiles. We report here a widely applicable secondary-alkylation system using secondary benzyl alcohols and a mechanistic investigation.

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(12) The reaction with a secondary benzylic alcohol, 1-phenylethanol, as an alkylating agent gave styrene as a major product, and several unidentified products were also formed. See ref 10b.

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TABLE 2. Alkylation of 2a with Acid-Sensitive Functional Group Substituted Benzylic Alcohols


| entry | R | temp, °C | time | yield, % |
|-------|--------------------------------|----------|--------|----------|
| 1 | H | 100 | 15 min | 99 |
| 2 | OSiR ₃ ^a | 100 | 2 h | 93 |
| 3 | OAc | 80 | 6 h | 95 |
| 4 | OBn | 50 | 14 h | 97 |
| 5 | OH | 50 | 2.5 h | 65 |

^a SiR₃ = *tert*-butyldimethylsilyl.

Results and Discussion

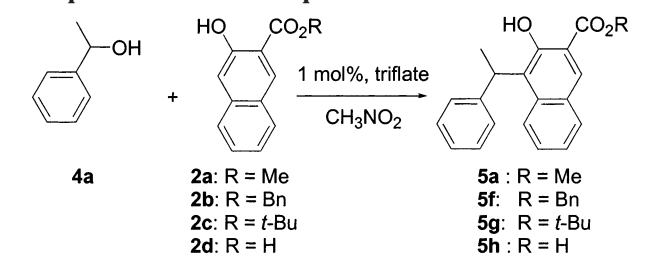
1.1. Examination of Reaction Conditions **1.1. Alkylation with Lanthanoid Triflates and Conventional Lewis Acids.** To compare the reactivity of a lanthanoid Lewis acid with that of a conventional Lewis acid, we studied the reaction of 1-(2-naphthyl)ethanol (**1**) with 1 equiv of methyl 3-hydroxy-2-naphthoate (**2a**).¹⁴

Titanium tetrachloride did not promote alkylation. Carbonyl and hydroxy groups on **2a** inhibited the reaction by chelation to titanium (Table 1, entry 1). The reaction using 1 equiv of BF₃·OEt₂ in CH₂Cl₂ gave the alkylated product **3** in 96% yield (entry 2). However, BF₃·OEt₂ did not act as a catalyst (entries 2 and 3). On the other hand, lanthanoid triflate was a very good catalyst and the product was isolated in high yield. In the La(OTf)₃-catalyzed reaction, alkylated product **3** was obtained in high yield (99%, 1 mol % La(OTf)₃ (entry 4); 93%, 0.01 mol % of La(OTf)₃ (entry 6)). Even in the presence of 10 equiv of water, the yield of **3** was 98% (entry 7). The yields of the reactions using La(OTf)₃ and Yb(OTf)₃ were almost identical.

1.2. Tolerance of Acid-Sensitive Functional Groups. Next, we examined the tolerance of acid-sensitive functional groups on benzylic alcohols (**4a–e**)¹⁵ with La(OTf)₃. The reaction of TBDMS ether **4b** proceeded smoothly to give TBDMS ether **5b** in 93% yield (Table 2, entry 2). Although acetate **4c** and benzyl ether **4d** were slightly decomposed at 100 °C, the reaction at lower temperature gave better results (entries 3 and 4). Notably, the unprotected hydroxy group of **4e** did not disturb the alkylation of **2a**. However, additional alkylation at the ortho position of the phenol group of **5e** decreased the yield of **5e** (entry 5). The protecting groups TBDMS, Ac, and Bn prevented additional alkylation of the products.

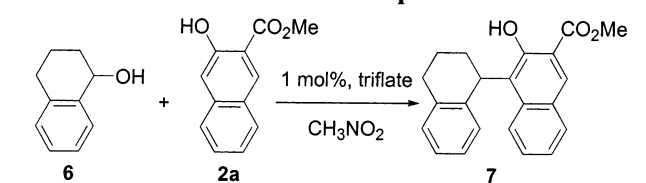
(14) **2a** is suitable as a nucleophile for investigating the reactivity of the generated cation, since **2a** is selectively alkylated at the 4 position on the naphthalene ring, and unalkylated **2a** is recovered without decomposition and is easy to detect by UV absorption. The selective alkylation is due to the electron-withdrawing ester group; therefore, **2a** is less nucleophilic than an electron-rich aromatic compound, such as anisole or furan (Chart 1).

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TABLE 3. Alkylation of Acid-Sensitive Functional Group Substituted Nucleophiles with **4a**

| entry | R | triflate | temp, °C | time | yield, % |
|-------|--------------|-----------------------------|----------|--------|-----------------|
| 1 | Me | Hf | 50 | 5 min | 89 |
| 2 | Me | H ⁺ ^a | 50 | 15 min | 87 |
| 3 | Me | Sc | 50 | 15 min | 99 |
| 4 | Me | Yb | 50 | 25 min | 99 |
| 5 | Bn | La | 100 | 2.5 h | 99 |
| 6 | <i>t</i> -Bu | La | 40 | 19 h | 59 |
| 7 | <i>t</i> -Bu | Sc | 100 | 20 min | 89 ^b |

^a TfOH, 3 mol %. ^b The product was **5h**.

TABLE 4. Effect of Reaction Temperature^a

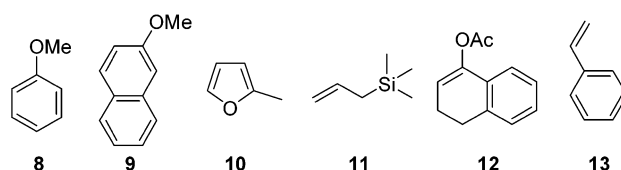
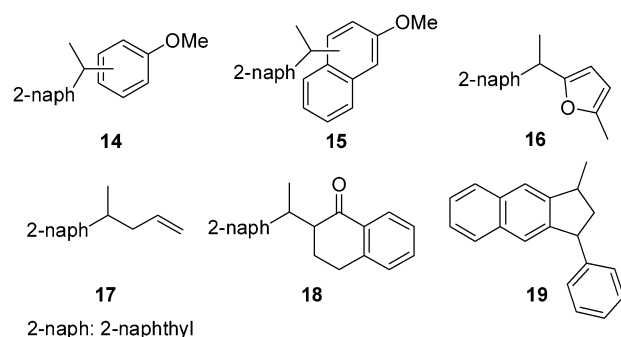
| entry | triflate | temp, °C | time | yield, % |
|-------|----------|----------|--------|----------|
| 1 | La | 100 | 30 min | 68 |
| 2 | Yb | 100 | 10 min | 59 |
| 3 | Sc | 100 | 10 min | 57 |
| 4 | La | 50 | 30 h | 88 |
| 5 | Yb | 50 | 6 h | 87 |
| 6 | Sc | 50 | 2 h | 90 |
| 7 | Sc | 20 | 24 h | 95 |

^a The reaction was carried out with 1 equiv each of **6** and **2a**.

To examine the stability of the ester group in **2**, we also investigated Sc(OTf)₃, Hf(OTf)₄, and TfOH-catalyzed reactions. Scandium and hafnium triflates have been reported to be stronger Lewis acids than lanthanoid triflate in the nitration of benzene derivatives.¹⁶ The TfOH-catalyzed alkylation of benzene derivatives has also been reported.¹⁷ Test reactions were carried out using the same amounts of **2a** and **4a** at 50 °C. The results are shown in Table 3. Hf(OTf)₄ was the most catalytically active, and the reaction was complete within 5 min, but the yield was not very high (89%). Triflic acid was also effective for this alkylation, but the yield of **5a** was only 87% (entry 2). In the reaction using Sc and Yb triflates, **5a** was obtained quantitatively (entries 3 and 4). The benzyl ester **5f** was obtained quantitatively by the La(OTf)₃-catalyzed reaction at 100 °C (entry 5). The *tert*-butyl ester of **2c** was very sensitive under the alkylation conditions, even in the La(OTf)₃-catalyzed reaction at 40 °C, and **5g** was obtained in 59% yield. Although the *tert*-butyl group underwent rapid decomposition, the carboxylic acid **5h** was obtained in 89% yield

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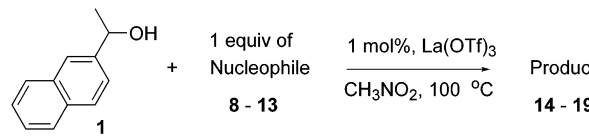
(17) Kotsuki, H.; Ohishi, T.; Ionue, M.; Kojima, T. *Synthesis* **1999**, 603–606.

CHART 1. Nucleophiles for the Reaction with **1****CHART 2.** Corresponding Products for the Reaction with **1**

(entry 7). The alkylation of carboxylic acid **2d** was very slow because of low solubility. Formation of ether **5d** (see Table 9) and the decomposition of **4a** were also observed.

1.3. Effect of the Reaction Temperature. The main decomposition pathway of secondary benzylic alcohols is via the generation of olefins. Cyclic benzylic alcohol **6** is more easily decomposed to 1,2-dihydronaphthalene than an acyclic alcohol (e.g., **1** and **4a**) in the presence of the triflates. We investigated the effect of the reaction temperature on alkylation with **6** to give **7** (Table 4). When the reaction was carried out at 100 °C, the yield of **7** was ca. 60% (entries 1–3), while at 50 °C, the yield was ca. 90% (entries 4–6). More 1,2-dihydronaphthalene was obtained in the reaction at 100 °C (~30%) than in the reactions at 50 °C (~10%) and 20 °C (~5%). We also tried the reaction of 1,2-dihydronaphthalene with **2a**. However, the alkylated product was not obtained. The greatest differences among the respective catalysts were mainly in the reaction time. When the reaction temperature was decreased to 20 °C, the yield of **7** increased to 95%. The generated cation would react with a nucleophile regardless of the kind of catalyst. Decomposition to olefin should be minimized by the proper choice of catalyst and reaction temperature.

2. Reaction of Various Benzylic Alcohols and Nucleophiles. 2.1. Reaction of Aromatic and Olefin Nucleophiles. After performing an initial survey of catalytic activity and optimal conditions, we selected the standard reaction (1 mol % of La(OTf)₃ in nitromethane at 100 °C) according to the reaction of **1** and **2a** (Table 1 entry 4). With these reaction conditions, we examined the alkylation of other aromatic nucleophiles, allylsilane, enol acetate, and olefin **8–13** (Chart 1) with **1**. The corresponding products **14–19** and yields are shown in Chart 2 and Table 5, respectively. The reactions with electron-rich aromatic compounds gave the products in high yield but, unfortunately, no selectivity. For the reaction of anisole (**8**), mono- and bis-substituted isomers were isolated separately and the total yield was 96% (Table 5, entry 1). The reaction of 2-methoxynaphthalene (**9**) gave two monosubstituted isomers and a mixture of

TABLE 5. Reaction of Various Carbon Nucleophiles with **1**


| entry | nucleophile | temp, °C | time | product | yield, % |
|----------------|------------------------|----------|--------|------------------------|----------|
| 1 ^b | 8 | 100 | 1 h | 14 ^c | 96 |
| 2 | 9 | 100 | 1 h | 15 ^d | 80 |
| 3 | 10 ^e | 60 | 1 h | 16 | 74 |
| 4 | 11 | 100 | 1 h | 17 | 54 |
| 5 | 12 | 100 | 20 min | 18 ^f | 95 |
| 6 | 13 | 100 | 40 min | 19 ^g | 88 |

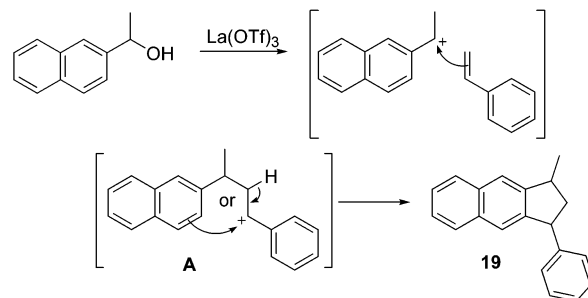
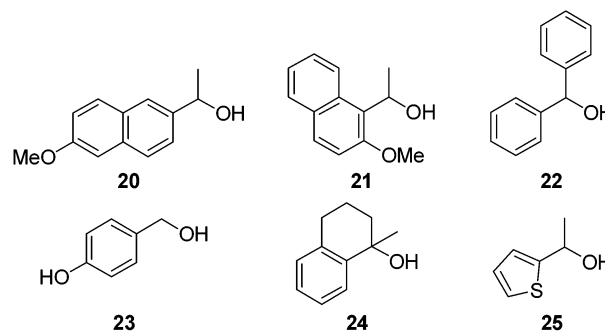
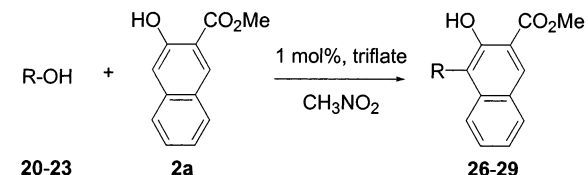
^a The yields were calculated based on **1**. ^b Yb(OTf)₃ was used. ^c The ratio of ortho-substituted isomer **14a**, para-substituted isomer **14b**, and disubstituted isomer **14c** was 7:57:32. ^d The ratio of monosubstituted isomers **15a** and **15b** and disubstituted isomer **15c** was 22:16:42. ^e 2-Methylfuran (**10**) (2 equiv) was used. ^f The ratio of the diastereomers was 1.1:1. ^g The ratio of the diastereomers was 1.8:1.

bis-substituted isomers separately (entry 2). The reaction with benzene (10 equiv) under reflux conditions gave ether **53** (see Table 9). Alkylated product of benzene was not obtained. 2-Methylfuran (**10**) was alkylated only at the 5 position and gave **16**, but the yield was only moderate (entry 3).

The allylated product **17** was obtained by the reaction of allyltrimethylsilane (**11**) (entry 4). The moderate yields of **16** and **17** are probably due to the lower boiling point of 2-methylfuran (**10**) (63 °C) and allyltrimethylsilane (**11**) (84–88 °C). When the reaction of allyltrimethylsilane (**11**) was carried out from room temperature to 80 °C, ether **53** (see Table 9) was mainly obtained. Secondary alkylated ketone **18** was obtained as a diastereomixture (1.1:1) by the reaction of 1-tetralone enol acetate (**12**). It is very difficult to obtain a secondary-alkylated product (e.g., **18**) by the alkylation of carbonyl compounds with secondary alkyl halide under basic conditions, since the elimination reaction of alkyl halide mainly occurs.¹⁸ In our reaction system, α -*sec*-alkylation of the carbonyl compound was carried out directly using alcohols.

As for the reaction of styrene (**13**), we anticipated the formation of a linear-type olefinic product¹⁹ according to the literature,²⁰ but the cyclopentane derivative **19** was formed as a diastereomixture (1.8:1). The proposed mechanism is shown in Scheme 2. The reaction with **1** and La(OTf)₃ would afford the naphthylethyl-cation, which would react with styrene (**13**) to generate a new cationic species **A**. The elimination of a proton from cation **A** give the linear-type olefinic product. In this case, cyclization would occur predominantly to give **19**.

2.2. Reaction with Various Benzylic Alcohols. The reactivity of various benzylic alcohols (Chart 3) with **2a** was investigated. The reaction was performed with 1 equiv each of benzylic alcohol and nucleophile in the presence of 1 mol % of triflate. The alcohols were classified as follows: electron-rich secondary alcohols **20**

SCHEME 2. Proposed Mechanism for the Formation of Cyclopentane Derivative **19****CHART 3.** Primary, *sec*-, and *tert*-Benzylic Alcohols for the Reaction with **2a** and **10****TABLE 6.** Reaction of **2a** with Various Benzylic Alcohols


| entry | R-OH | triflate | temp, °C | time, h | product | yield, % |
|-------|-----------|-----------------|----------|---------|-----------|----------|
| 1 | 20 | La | 80 | 0.33 | 26 | 70 |
| 2 | 21 | Yb ^a | 20 | 63 | 27 | 91 |
| 3 | 22 | Yb | 100 | 0.5 | 28 | 96 |
| 4 | 23 | Hf ^b | 100 | 24 | 29 | 50 |

^a *n*-Propylamine (1.5 mol %) was added. ^b Hf(OTf)₄ (10 mol %) was used.

and **21**, bisaromatic-substituted secondary alcohol **22**, electron-rich primary alcohols **23**, tertiary alcohol **24**, and secondary heterocyclic alcohol **25**. The reaction of an electron-deficient secondary alcohol, 1-(2-pyridyl)ethanol, with **2a** did not give the alkylated product.²¹

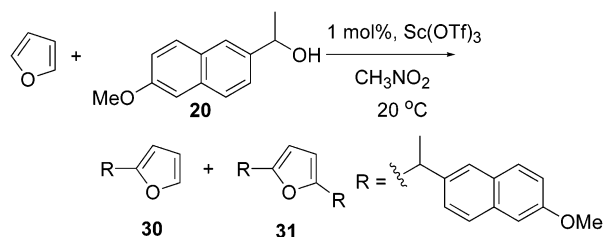
Electron-rich benzylic alcohols rapidly disappeared under La(OTf)₃-catalyzed reaction conditions (**20**, 100 °C, <10 min; **21**, 100 °C, <2 min), but the yields of the products were low (**26**, 65%; **27**, 22%). The reaction at lower temperature gave better results (Table 6, entry 1). As for the Yb(OTf)₃-catalyzed reaction of alcohol **21**, the yield of **27** was better than that of the La(OTf)₃-catalyzed reaction and the addition of 1.5 mol % of *n*-propylamine in the Yb system afforded **27** in 91% yield. Bisaryl-substituted alcohol **22** reacted cleanly to give **28** in 96% yield.

(21) While 1-(2-pyridyl)ethanol and **2a** were recovered quantitatively from the La(OTf)₃-catalyzed reaction, 1-(2-pyridyl)ethyl 3-hydroxy-2-naphthoate was obtained from the Hf(OTf)₄-catalyzed reaction.

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(19) 3-(2-Naphthyl)-1-phenyl-1-butene.

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SCHEME 3. Reaction of a Furan with **20**

furan / **20** = 1 / 1: **30**: 9% **31**: 86%
 furan / **20** = 10 / 1: **30**: 43% **31**: 49%

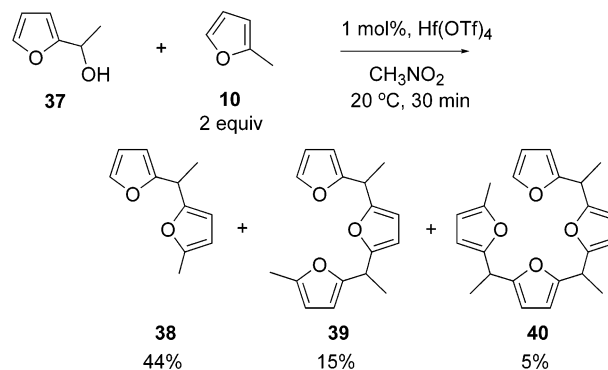
As for the reaction of primary benzylic alcohols, the Sc(OTf)₃-catalyzed alkylation of benzene derivatives has been reported previously.^{10a,b} This reaction needed 10 mol % of the catalyst and an excess amount of nucleophile. In our reaction system, the use of Hf(OTf)₄ gave better results for primary benzylation but polyalkylation was observed in many cases. Thus, the yields were moderate for the electron-rich benzylic alcohol **23** (entry 4). The yields were also moderate to low for other benzyl alcohols (3-methylbenzyl alcohol (~50%), benzyl alcohol (~35%), and 3-bromobenzyl alcohol (~16%). The reaction of **2a** with tertiary alcohol **24** (La(OTf)₃, 20 or 60 °C) failed and gave a mixture of *endo*- and *exo*-olefins.²² The reaction of **2a** with **25** gave a complex mixture.

Next, we examined the reaction of furan derivatives. Furan derivatives are useful C1–C4 synthons.²³ The oxidation of furan rings gives carboxylic acid²⁴ and γ -oxo- α,β -unsaturated carboxylic acids.²⁵ Furthermore, the ring-opening reactions under acidic conditions give diketone²⁶ and bisacetal.²⁷ The reaction of a furan as a nucleophile with benzylic alcohol **20** is shown in Scheme 3. While the reaction of a furan with **20** gave both 2-alkylated furan **30** and 2,5-bisalkylated furan **31**, the combined yield was high.²⁸ With an increase in the ratio of furan/**20** from 1/1 to 10/1, the yields of **30** and **31** varied from 9 and 86% to 43 and 49%; monoalkylated product **30** was not synthesized selectively. In contrast to these results, monoalkylated products were obtained in high yield in the reaction of 2-methylfuran (**10**) with various benzylic alcohols (Table 7). 2-Methylfuran (**10**) is volatile (boiling point, 63 °C), and the use of 2 equiv of **10** gave better results for all entries. Whereas the alcohol **6** readily decomposed (Table 4) at 60 °C, **32** was obtained in high yield (Table 7, entry 1). Electron-rich alcohols **20** and **21** also reacted cleanly to afford **33** and **34**, respectively; the relatively longer reaction time for **21** might be due to destabilization of the corresponding carbocation

TABLE 7. Reaction of 2-Methylfuran (**10**) with *sec*- and *tert*-Benzylic Alcohols

| entry | R-OH | triflate | temp, °C | time, min | product | yield, % |
|-------|-----------|----------|----------|-----------|-----------|-----------------|
| 1 | 6 | La | 60 | 20 | 32 | 99 ^a |
| 2 | 20 | Sc | 20 | 10 | 33 | 98 |
| 3 | 21 | Sc | 20 | 180 | 34 | 96 |
| 4 | 24 | La | 60 | 20 | 35 | 97 |
| 5 | 25 | Hf | 20 | 30 | 36 | 85 |

^a The yield using one equiv of **10** was 95%.

SCHEME 4. Reaction of 2-Methylfuran (**10**) with 1-(2-Furyl)ethanol (**37**)

by a peri interaction between the carbinol methyl and H-8 (entries 2 and 3). Construction of a quaternary carbon also succeeded. The reaction of alcohol **24**, which decomposes into olefin more readily than **6**, gave **35** in 97% yield (entry 4). A heteroaromatic version of a benzylic alcohol, thienylethanol **25**, reacted similarly to give thienylethylfuran **36** (entry 5), but 1-(2-pyridyl)ethanol did not react under the same reaction conditions. While the reaction of electron-rich furylethanol **37** occurred rapidly, the yield of the expected product **38** was low, and additional furyl ethylation gave **39** and **40**²⁹ (Scheme 4).

2.3. Reaction of Nitrogen and Oxygen Nucleophiles. To explore the generality, the reaction with representative nitrogen nucleophiles was examined. The reactions of Lewis base nucleophiles (benzylamine, imidazole) with **1** failed, and **1** was recovered quantitatively. On the other hand, the alkylation of amide derivatives (**41**–**44**) proceeded, but amide derivatives were less reactive than carbon nucleophiles such as **2a** and the nucleophiles in Chart 1. Therefore, a significant amount of byproducts derived from the olefin³⁰ were formed. The results are shown in Table 8. The results of the Yb(OTf)₃-catalyzed reaction were better than those obtained with La(OTf)₃ in the reaction with sulfonamides **41** (entries 1 and 2). To decrease the olefinic byproduct, we carried out the reaction at lower temperature (70 °C) and the yields improved (entries 2, 3, and 6). These reaction conditions

(22) *endo*-Olefin: 1-methyl-3,4-dihydronaphthalene. *exo*-Olefin: 1-methylene-1,2,3,4-tetrahydro-naphthalene.

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(28) The yields of **30** and **31** were calculated based on **20**.

(29) The yields were calculated based on **37**.

(30) For the reaction with **1**, 2-vinylnaphthalene was formed, and for the reaction with **4a**, styrene was formed. The structures of the byproducts derived from these olefins are shown in Figure 4.

TABLE 8. Reaction of Nitrogen Nucleophiles with **1** or **4a**

1 : Ar = 2-naphthyl
4a: Ar = phenyl

41: *p*-CH₃C₆H₄SO₂NH₂
42: *p*-CH₃C₆H₄SO₂NHPrⁿ
43: CH₃SO₂NH₂
44: PhCONH₂

| entry | Ar | Nu | triflate | temp, °C | time, h | product | yield, % |
|-------|-----------|-----------|----------|----------|---------|-----------|----------|
| 1 | 1 | 41 | La | 100 | 1.5 | 45 | 67 |
| 2 | 1 | 41 | Yb | 100 | 0.3 | 45 | 70 |
| 3 | 1 | 41 | Yb | 70 | 24 | 45 | 89 |
| 4 | 4a | 41 | Yb | 70 | 24 | 46 | 88 |
| 5 | 4a | 42 | Yb | 70 | 48 | 47 | 64 |
| 6 | 1 | 43 | Yb | 70 | 24 | 48 | 88 |
| 7 | 4a | 43 | Yb | 70 | 24 | 49 | 74 |
| 8 | 1 | 44 | Hf | 50 | 72 | 50 | 69 |
| 9 | 4a | 44 | Hf | 50 | 72 | 51 | 46 |

TABLE 9. Formation of Ethers

52: EtOH

1 : Ar = 2-naphthyl
4a: Ar = phenyl

6 :

53: Ar = 2-naphthyl
54: Ar = phenyl

55:

| entry | Ar | Nu | triflate | temp, °C | time, h | products | yield, % |
|-------|-----------|-----------------------|----------|----------|---------|------------------------|----------|
| 1 | 1 | | La | 100 | 1 | 53^{ab} | 81 |
| 2 | 4a | | La | 100 | 2 | 54^{ac} | 80 |
| 3 | 6 | | Sc | 25 | 19 | 55^d | 78 |
| 4 | 1 | 52^e | La | 100 | 1.5 | 56 | 99 |

^a The ratio of *dl*/*meso* was determined by comparison of the ¹H NMR and GC findings with those for the corresponding *meso* products (**53** and **54**), which were synthesized by the Mitsunobu reaction from the corresponding alcohols (*R*)-**1**, and (*R*)-**4a**, respectively. ^b The ratio of *dl*-**53**/*meso*-**53** was 1.9:1. ^c The ratio of *dl*-**54**/*meso*-**54** was 2.0:1. ^d The ratio of diastereomers was 1.8:1. ^e Ethanol (10 equiv).

TABLE 10. Effects of Protonic Acid

1: Ar = 2-naphthyl

59: R = Bz
60: R = Ac

| entry | C–Nu | acid | triflate | yield of 3 , % | yield of ester, % | yield of ether, % |
|----------------|-----------|-----------|----------|-----------------------|-------------------|-------------------|
| 1 | | 57 | La | | 10 | 57 |
| 2 | | 58 | La | | 15 | 78 |
| 3 | | 58 | | | 0 ^a | 0 |
| 4 | | | La | | | 11 |
| 5 ^b | 2a | 58 | La | 81 | 9 | 0 |
| 6 ^b | 2a | | La | 15 | | 24 |

^a Alcohol **1** was recovered quantitatively. ^b The reaction time was 24 h.

were also suitable for the reaction with **4a** (entries 4 and 7). In the reaction with benzamide (**44**), which was less nucleophilic than sulfonamides, the use of a stronger Lewis acid, Hf(OTf)₄, gave a better result (entry 8).

Next, the reactions of oxygen nucleophiles were examined (Table 9). The hydroxy group of the starting benzyl

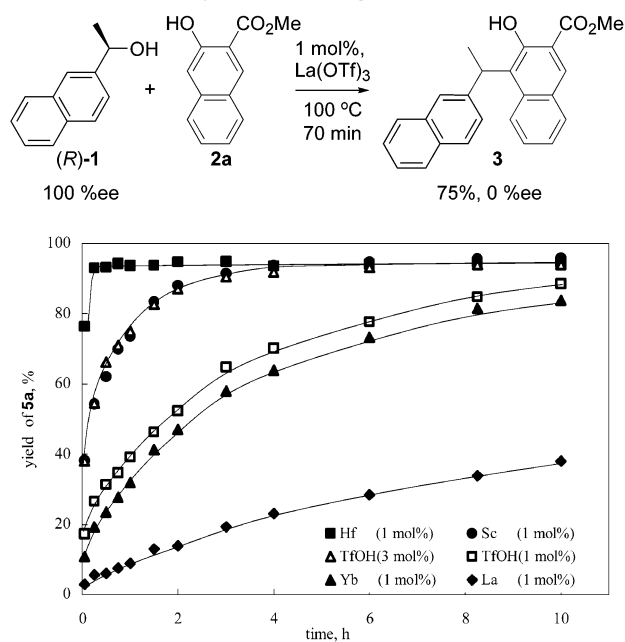
SCHEME 5. Alkylation Using (*R*)-**1**

FIGURE 1. Time evolution of the yield of alkylated product **5a**. The reactions were carried out with 1 equiv of **2a** and 1 equiv of **4a** in the presence of 1 mol % of triflate or 1 or 3 mol % of triflic acid in nitromethane at 50 °C. The analytical sample was taken from the reaction mixture and filtered through a short silica gel pad with ethyl acetate. The yields were determined by GC using nitrocyclohexane as an internal standard.

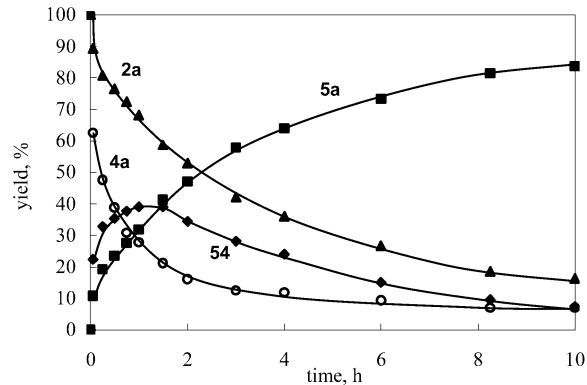


FIGURE 2. Yb(OTf)₃-catalyzed reaction of the alcohol **4a** (1 equiv) and the nucleophile **2a** (1 equiv). The reaction was carried out in the presence of 1 mol % of Yb(OTf)₃ in nitromethane at 50 °C.

alcohol also acted as a nucleophile. The reactions of **1a**, **4a**, and **6** in the absence of other nucleophiles gave symmetrical ethers **53**, **54**, and **55** as *dl* and *meso* mixtures, respectively. An excess amount of ethanol reacted cleanly with **1** to give ether **56** quantitatively (entry 4). Next, we tried to form esters (Table 10). The benzoate **59** and acetate **60** were obtained in poor yield, and the ether **53** was the main product (entries 1 and 2). The formation of ether **53** did not occur with acetic acid and without La(OTf)₃ (entry 3). On the other hand, the reaction without acetic acid with La(OTf)₃ at the same temperature was very slow (entry 4). The protonic acid should support the lanthanoid triflate-catalyzed reaction.

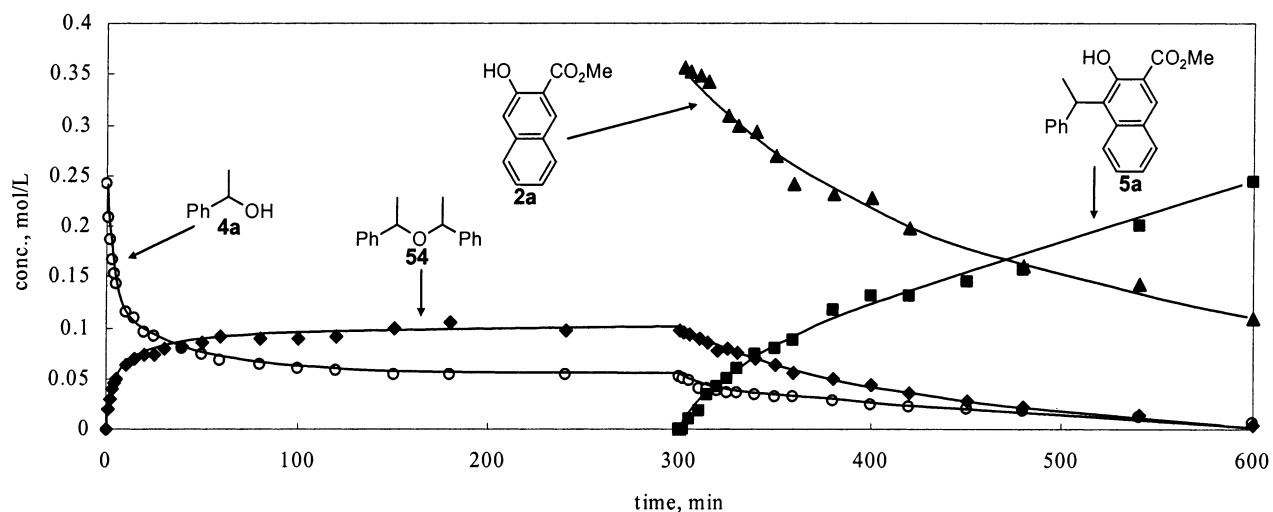


FIGURE 3. Time evolution of the reaction of **4a** and **54**. The reaction was carried out in the presence of 1 mol % of $\text{Sc}(\text{OTf})_3$ at 50°C .

We also investigated the effect of the acid on the alkylation of **2a**. $\text{La}(\text{OTf})_3$ -catalyzed alkylation was also promoted by acetic acid (**58**) (entry 5). The alkylated product **3** was obtained in 81% yield even at room temperature. The yield of the reaction without acetic acid (**58**) at room temperature was 15%, which is less than the yield of ether **53** (24%) (entry 6).

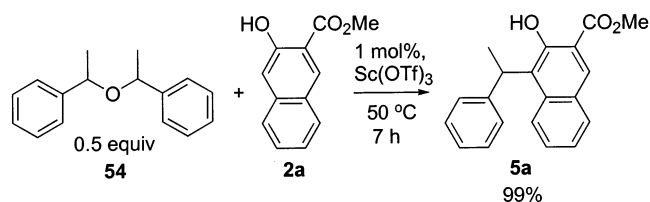
3. Mechanistic Investigations. 3.1. Generation of Carbocation. The enantioselectivity of the reaction was examined with (*R*)-**1** (Scheme 5). The reaction of (*R*)-**1** proceeded slowly, compared to the reaction of *dl*-**1** (Table 1, entry 4), and gave **3** in 75% yield in 0% ee. The reaction should proceed via a carbocation intermediate.

3.2. Relative Catalytic Activities of La, Yb, Sc, and Hf Triflates and Triflic Acid. The relative catalytic activities of La, Yb, Sc, and Hf triflates and triflic acid (1 and 3 mol %) were examined by GC analysis. The time evolution of the yield of the alkylated product **5a** is shown in Figure 1. All of the triflates and triflic acid effectively catalyzed this alkylation. The catalytic activity of $\text{Sc}(\text{OTf})_3$ (1 mol %) was almost the same as that of TfOH (3 mol %). $\text{La}(\text{OTf})_3$ (1 mol %) and $\text{Yb}(\text{OTf})_3$ (1 mol %) were less reactive than 1 mol % of TfOH . The catalytic activity of the catalysts increased in the order $\text{La}(\text{OTf})_3 < \text{Yb}(\text{OTf})_3 < \text{TfOH}$ (1 mol %) $< \text{TfOH}$ (3 mol %) $\approx \text{Sc}(\text{OTf})_3 \ll \text{Hf}(\text{OTf})_4$.

The water may hydrolyze the metal triflates to generate triflic acid, which might participate as a catalyst. On the other hand, rare-earth metal triflates are stable in water,³¹ and $\text{La}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$ showed weaker catalytic activities than triflic acid. Therefore, the amount of hydration and the generation of triflic acid would be very limited.

The full details of the yields are shown in Figure 2 for a $\text{Yb}(\text{OTf})_3$ -catalyzed reaction. Ether **54** was formed more rapidly than alkylated product **5a**, and **54** and **5a** were formed without any induction time. The yield of ether **54** was maximal at 1 h after the beginning of the reaction. These observations are consistent with a dead-end equilibrium state for **54**.

SCHEME 6. Alkylation of **2a** Using Ether **54**



3.3. Equilibrium between Benzylic Alcohols and Ethers and the Reaction with Ethers. We investigated the time evolution of ether formation and alkylation by GC analysis. The results are shown in Figure 3. First, the reaction was started only with 1-phenylethanol (**4a**) and $\text{Sc}(\text{OTf})_3$ in nitromethane. The reaction system rapidly reached an equilibrium state with **4a** and **54**. The concentrations of the ether **54** and **4a** decreased after the addition of **2a** (1.4 equiv). These results suggest the presence of an equilibrium between **4a** and **54** via a benzylic cation. This equilibrium is more rapid than the alkylation of **2a**.

The removal of water from the reaction system is important for obtaining ether products because the reaction with an oxygen nucleophile is the equilibrium reaction. Nitromethane and water form an azeotropic mixture (boiling point, 84°C). With regard to ether **54**, the reaction at 100°C with $\text{La}(\text{OTf})_3$, a weaker Lewis acid, gave better results (see Table 9).

Ether **54** also served as a source of electrophile; the reaction of 0.5 equiv of ether **54** with **2a** gave **5a** in 99% yield (Scheme 6). The formation of 1-phenylethanol (**4a**) was also observed during the reaction by GC analysis.

A proposed mechanism is shown in Figure 4. The yields of the alkylated product and the olefin were strongly affected by the reaction temperature but not by the respective catalyst (Table 4). The reaction of the cation with a nucleophile should occur independent of the catalyst. The observed differences in catalytic activity can be explained by the rate of cation generation, and the ratio of alkylated product to olefinic byproduct can be explained by the reactivity of a nucleophile toward the cation.

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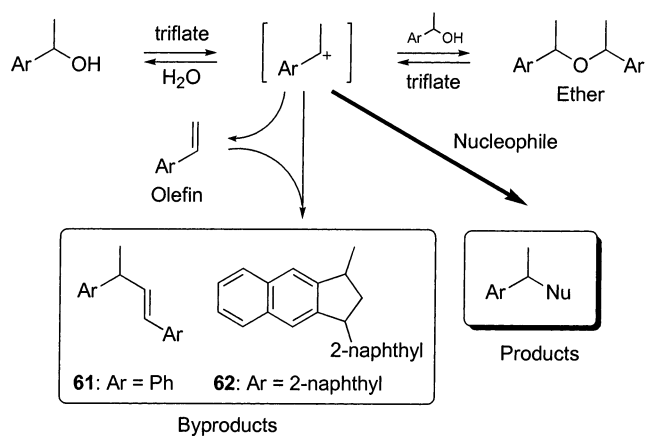


FIGURE 4. Proposed mechanism.

Diphenylbutene **61** and the cyclopentane derivative **62** were obtained as byproducts. Diphenylbutene **61** should be formed by the reaction of styrene and phenylethyl cation, and the elimination of a proton should give **61**. The cyclopentane derivative was obtained when **1** was used and should be formed by the reaction of 2-vinylnaphthalene and naphthylethyl cation, as shown in Scheme 2. In all cases, a lower reaction temperature decreased the formation of the olefinic byproducts. If the ether is the main product, the reactivity of the nucleophile should be low. The use of a less-active catalyst at a higher temperature should give better results.

Conclusion

Metal triflate-catalyzed alkylation with secondary and tertiary benzylic alcohols was investigated. Hafnium and rare-earth metal triflates and triflic acid were effective for this alkylation, and the catalytic activity increased in the order $\text{La}(\text{OTf})_3 < \text{Yb}(\text{OTf})_3 < \text{TfOH} < \text{Sc}(\text{OTf})_3 \ll \text{Hf}(\text{OTf})_4$. The reaction mechanism includes equilibrium among benzylic alcohol, ether, and water via the corresponding benzylic cation. This alkylation may proceed from the equilibrium mixture, and anhydrous conditions are not necessary. It is important to check for disappearance of the ether and the formation of olefins to optimize carbon and nitrogen alkylation. This secondary-alkylation system is suitable for a wide range of carbon, nitrogen, and oxygen nucleophiles and for some acid-sensitive functional groups.

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Supporting Information Available: Experimental procedures (**Warning:** nitromethane is hazardous because of the possibility of explosion), spectral data for all new compounds, and GC analysis data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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