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Metal Triflate-Catalyzed Cationic Benzylation and Allylation of 1,3-Dicarbonyl Compounds

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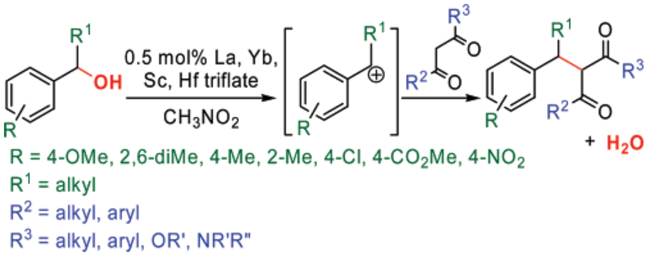

The rare earth metal and hafnium triflate-catalyzed secondary benzylation and allylation of 1,3-diketones, ketoesters, and ketoamides are described. The procedure was carried out under non-anhydrous conditions. Various 1-phenylethyl cations were generated from substituted 1-phenylethanols using 0.5 mol % of the metal triflates in CH_3NO_2. The cations reacted with 1,3-diketones and ketoesters to give benzylated products in high yields. Following the GC analysis, the reaction conditions were easily optimized by the selection of catalysts based on the Lewis acidity of the triflates and reaction temperature. A tertiary-alkylated diketone and a corresponding ketoester were also benzylated to afford products with a quaternary carbon atom in 57−84% yield. The ketoamide reactions required stronger Lewis acids than those used in the diketone and ketoester reactions. The reactions of benzylic alcohols possessing various substituents on the aromatic ring and dibenzoylmethane (**2b**) as a diketone were examined in the presence of $Hf(OTf)_4$. Electron-rich benzylic alcohols reacted with **2b** in 86−96% yield, and electron-deficient alcohol gave the desired product in 79−65% yield. Despite possessing a strong electron-withdrawing group, the reaction of 1-(4-nitrophenyl)ethanol gave the corresponding product in 61% yield. It was also possible to use allylic alcohols directly for the allylation of diketone **2b**. The catalyst can be recovered by water extraction and reused up to five times.

Introduction

A carbocation is one of the most important intermediates in carbon−carbon bond formation in organic synthesis. Various methods for the generation of carbocations have been reported, including the Brønsted or Lewis acid-catalyzed cleavage of carbon−heteroatom bonds, protonation or addition to olefins, and electrochemical oxidation.[1,2] These reactions have been used for the alkylation of aromatic compounds, olefins, allylsilanes, and enol ethers.[3] The secondary and tertiary alkylations of 1,3-dicarbonyl compounds have also been carried out via carbocations[4] prepared from alkyl halides,[5] alcohols,[6] and olefins.[7,8] From the atom-economical and synthetic points of view, alcohols are an attractive source of electrophiles as compared to alkyl halides because the only byproduct they produce is water and not HX; moreover, alcohols can be obtained more easily than the corresponding halides. However, the hydroxyl group

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(3) Review: Mayer, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.

(4) Since many secondary and tertiary alkyl halides undergo HX elimination under the basic conditions, the alkylation using enolate anion and alkyl halide is limited to primary S_N2-active electrophiles. Review: (a) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 55−58. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96−108.

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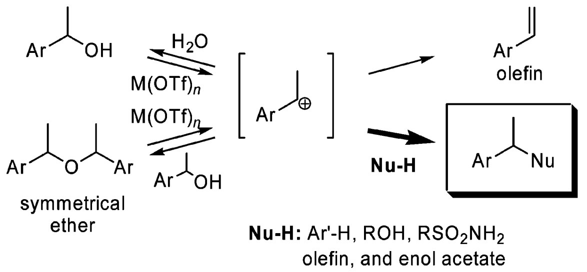
is not a good leaving group, and water is released as the reaction proceeds and rapidly deactivates the Lewis acids. Most of these methods require both anhydrous reaction conditions and more than 1 equiv of Lewis acid.[9] Therefore, few reports of the Lewis acid-catalyzed alkylation of 1,3-dicarbonyl compounds using alcohols are known.[10,11]

We have recently developed a highly efficient benzylation system using benzylic alcohol catalyzed by hafnium triflate and some rare earth metal triflates in nitromethane under non-anhydrous conditions.[12] Mechanistic investigations revealed that the benzylation system soon attained equilibrium with alcohol, symmetrical ether, and water via the benzylic cation. The cation either reacts with various nucleophiles or decomposes to an olefin depending on the reactivity of the nucleophile and the reaction temperature. Our previous research focused on the reaction with aromatic compounds, olefins, allylsilane, alcohols, amides, and enol acetates as nucleophiles (Scheme 1).

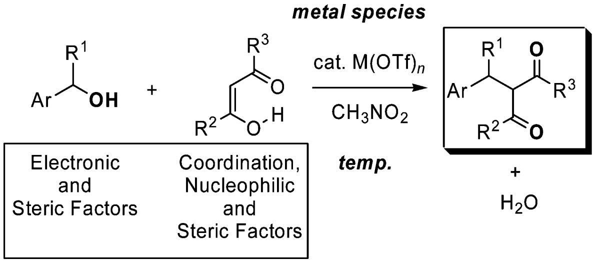
SCHEME 1. Catalytic Generation of Benzylic Cation and Benzylation of Various Nucleophiles



Silylenol ethers derived from monocarbonyl compounds have been known to react with benzylic cations to afford secondary- or tertiary-alkylated ketones.[13] Consequently, we are interested in probing the scope and limitation of the C−C bond formation of enolized compounds and cationic species. In this paper, we report the benzylation and allylation of 1,3-dicarbonyl compounds.

Results and Discussion

The generation of cations may be influenced by the electronic and steric factors of benzylic alcohols, and the nucleophilic reaction may depend on the keto/enol ratio and the steric factor of the 1,3-dicarbonyl compounds. In addition, 1,3-dicarbonyl compounds act as bidentate ligands to decrease the Lewis acidity of the catalysts. Therefore, the best reaction conditions should be adjusted to the combination of benzylic alcohols and 1,3-dicarbonyl compounds (eq 1).



(1)

Fortunately, rare earth metal triflates have similar chemical properties but different Lewis acidities.[14] We have been using four metal triflates—the rare earth metals La, Yb, Sc, and Hf

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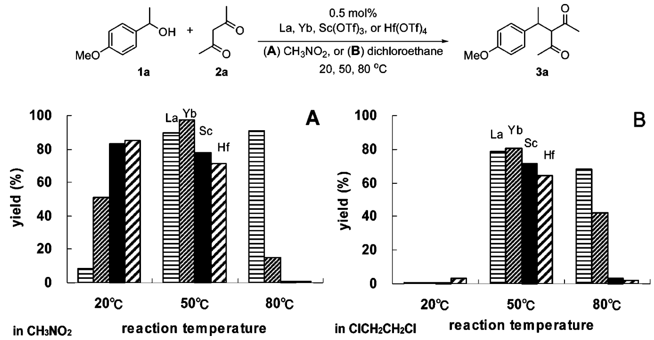


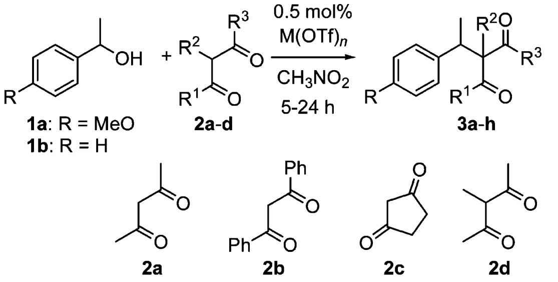
FIGURE 1. Yields of secondary-benzylated acetylacetone **3a** for La, Yb, Sc, and Hf triflate-catalyzed reactions at 20, 50, and 80 °C in nitromethane (A) and 1,2-dichloroethane (B).

triflates—whose Lewis acidities increase in the following order: $La(OTf)_3 < Yb(OTf)_3 < Sc(OTf)_3 < Hf(OTf)_4$.[15] To find the best conditions quantitatively, reactions with different catalysts and temperatures were carried out using GC analysis.

Optimization of Reaction Conditions. For optimizing the reaction conditions, the general procedure was as follows: A nitromethane solution of benzylic alcohol (1 equiv), diketone (1 equiv), and an internal standard (ca. 0.2 equiv of nitrocyclohexane or nitrohexane) was partitioned into 12 reaction vessels containing La, Yb, Sc, and Hf triflates. The mixtures were stirred at 20, 50, and 80 °C either until the complete consumption of the alcohol and symmetrical ethers[16] or up to 24 h. Then, the reaction mixtures were analyzed by GC. Figure 1 shows the yield of **3a** obtained from the reaction of 1-(4-methoxyphenyl)ethanol (**1a**) and acetylacetone (**2a**) in nitromethane (**A**) and 1,2-dichloroethane (**B**).[17]

At 20 °C, a considerable amount of **1a**, **2a**, and symmetrical ether **12**[18] remained in the $La(OTf)_3$- and $Yb(OTf)_3$-catalyzed reaction mixtures using nitromethane and 1,2-dichloroethane. In both solvents, the best results were obtained with $Yb(OTf)_3$-catalyzed reactions conducted at 50 °C (98%).[19] The decrease in the yields at 80 °C were due to the formation of olefins, 4-vinylanisole, and 1,3-bis(4-methoxyphenyl)-1-butene as byproducts. The structure and formation mechanism of the butene from 1-(4-methoxyphenyl)ethyl cations were previously reported.[20] The best reaction temperatures were higher than those for ether formation and lower than those for olefin formation. The bisbenzylation and O-benzylation[21] of **2a** were not observed in all cases. Nitromethane has compatibility over a wide range of catalysts and temperature conditions.

TABLE 1. Reaction of Various 1,3-Diketones 2a−d



entry	1	2	cat.[a]	temp (°C)	time (h)	3	yield[b] (%)
1	**1a**	**2a**	Yb	50	24	**3a**	97
2	**1a**	**2b**	Hf	20	7	**3b**	89
3	**1a**	**2c**	Yb	50	13	**3c**	75
4	**1a**	**2d**	La	50	11	**3d**	54
5	**1b**	**2a**	Sc	70	21	**3e**	83
6	**1b**	**2b**	Hf	60	5	**3f**	94
7	**1b**	**2c**	Hf	70	24	**3g**	31
8	**1b**	**2d**	La	90	13	**3h**	56

[a] La: $La(OTf)_3$, Yb: $Yb(OTf)_3$, Sc: $Sc(OTf)_3$, Hf: $Hf(OTf)_4$. [b] Isolated yield.

Reaction of Various 1,3-Diketones. Next, we examined the reaction of alcohols (**1a**,**b**) with various 1,3-diketones (**2a**−**d**) in nitromethane. The reaction conditions were optimized using GC analysis by the same procedure as that shown in Figure 1. The data in Table 1 were obtained from isolation reactions carried out under optimized conditions. The reactions of electron-rich benzylic alcohol **1a** and unsubstituted benzylic alcohol **1b** with acetylacetone (**2a**) and dibenzoylmethane (**2b**) gave the corresponding secondary-benzylated products **3a**, **3b**, **3e**, and **3f** in good yields (entries 1, 2, 5, and 6, respectively). The yields in entries 3 and 7 using cyclic diketone **2c** were lower than those using linear diketones **2a** and **2b**. The reason for the moderate yields of **3c** and **3g** might be the low solubility of **2c** in nitromethane. Methyl-substituted diketone **2d** also reacted to afford quaternary carbon products **3d** and **3h** in moderate yields (entries 4 and 8). The reuse of the catalyst was examined under the condition of entry 1. Ytterbium triflate was extracted directly from the reaction mixture of nitromethane solution by water. The water extract was concentrated, and the residue was dried under vacuum at 200 °C for 3 min to give a colorless crystalline $Yb(OTf)_3$ catalyst. The catalyst was used without further purification. The procedure was repeated five times, and the yields of each run were 99% (24 h), 98% (24 h), 97% (24 h), 97% (48 h), and 96% (48 h).

Reaction of Ketoesters. Next, we optimized the reactions of ketoesters **4a**−**c** using GC analyses for all the entries in Table 2. Secondary-benzylated ketoesters **5a** and **5b** were obtained in high yields by using a $Yb(OTf)_3$ catalyst (entries 1 and 2). In spite of the lower enol ratios,[22] the reactivities of ketoesters **4a** and **4b** toward **1a** were similar to that of the corresponding diketones **2a** and **2b**. The cyclic ketoester **4c** also reacted to give quaternary carbon products **5c** and **5f** in moderate yields (entries 3 and 6). The yields of **5d** and **5e** were lower than those of **5a** and **5b** (entries 4 and 5). In general, the reaction of **1b** required a stronger catalyst and higher temperature than the reaction of electron-rich **1a**. The diastereomeric ratios of the products in Table 2 were less than 1.1/1.

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[16] Mixture of DL and *meso*-bis-1-(4-methoxyphenyl)ethyl ethers. The typical structures are shown in Scheme 1.

[17] Octadecane was used as an internal standard for the reactions in 1,2-dichloroethane.

[18] See eq 2.

[19] The GC yield was calculated based on the calibration line prepared from pure **3a** and nitrocyclohexane. The isolated yield of the reaction conditions was 97%.

[20] The structure is 4-MeO-Ph-CH═CH-CH(4-MeO-Ph)-CH_3. Rao, V. J.; Prevost, N.; Ramamurthy, V.; Kojima, M.; Johnston, L. J. *Chem. Commun.* **1997**, 2209−2210.

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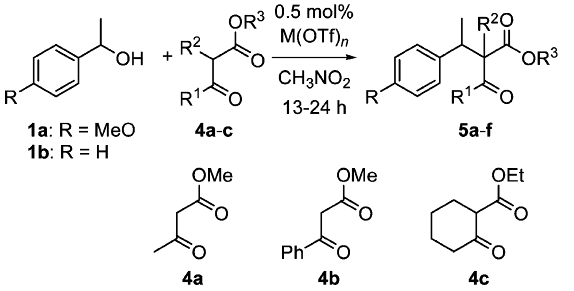
[22] Enol ratios of the 1,3-dicarbonyl compounds were measured by ^1H NMR in CD_3NO_2 at 23−25 °C. 1,3-Diketones: **2a**, 55%; **2b**, 95%; **2c**, 6%; **2d**, 34%. 1,3-Ketoesters: **4a**, 4%; **4b**, 13%; **4c**, 72%. 1,3-Ketoamides: **6a**, 11%; **6b**, 5%; **6b** (70 w/w% in H_2O), 4%. Dimethyl malonate: 0%. Detailed conditions are given in the Supporting Information.

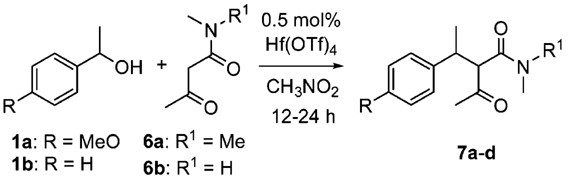
TABLE 2. Reaction of Various 1,3-Ketoesters 4a−c



entry	1	4	cat.[a]	temp (°C)	time (h)	5	yield[b] (%)
1	**1a**	**4a**	Yb	50	24	**5a**	98
2	**1a**	**4b**	Yb	60	24	**5b**	96
3	**1a**	**4c**	Hf	20	24	**5c**	84
4	**1b**	**4a**	Sc	80	12	**5d**	77
5	**1b**	**4b**	Sc	85	8	**5e**	70
6	**1b**	**4c**	Hf	60	21	**5f**	57

[a] La: La(OTf)$_3$, Yb: Yb(OTf)$_3$, Sc: Sc(OTf)$_3$, Hf: Hf(OTf)$_4$. [b] Isolated yield.

TABLE 3. Reaction of 1,3-Ketoamides 6a,b



entry	1	6	temp (°C)	time (h)	7	yield[a] (%)
1	**1a**	**6a**	60	12	**7a**	98
2	**1a**	**6b**	60	12	**7b**	80 (76)[b]
3[c]	**1b**	**6a**	100	24	**7c**	35
4[c]	**1b**	**6b**	100	24	**7d**	11 (6)[b]

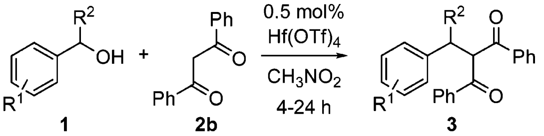
[a] Isolated yield. [b] Values in parenthesis are the yields obtained using a commercially available 70% water solution of **6b**. [c] 5 mol % of Hf(OTf)$_4$ was used.

Reaction of Ketoamides. Ketoamides were more Lewis basic nucleophiles than diketones and ketoesters because of the electron donation by the amide nitrogen to the carbonyl group. Therefore, a stronger Lewis acid catalyst, Hf(OTf)$_4$, was necessary for the reaction. The reactions (Table 3) using electron-rich **1a** proceeded well and afford the corresponding products in yields ranging from excellent (entry 1) to good (entry 2) even with the use of a commercially available 70% water solution of **6b**. In our previous report,[12] we showed that the addition of water prolonged the reaction time due to the Lewis basic nature of water. However, in this case, the electron densities of the benzylic alcohols were more critical than the effect of water, and the reaction of **1b** was very slow; moreover, even after 24 h, a considerable amount of alcohol and ketoamide remained unchanged.

Although we attempted the reaction of dimethyl malonate with **1a**, only a trace amount (0.5%) of the benzylated product was obtained.[23] The enol ratio of the malonate ester was not sufficient for benzylation to occur because the ester group decreases the enol ratio of 1,3-dicarbonyl compounds.[24]

Reaction of Various Benzylic Alcohols. The reactions of various primary and secondary benzylic alcohols were investigated with dibenzoylmethane (**2b**) as a nucleophile using Hf(OTf)$_4$ in nitromethane. Each reaction temperature in Table 4 was obtained from preliminary GC analyses before the isolation of the products.

TABLE 4. Reaction of Various Benzylic Alcohols



entry	R^1	R^2	temp (°C)	3	time (h)	yield[b] (%)
1	4-MeO	Me	20	**3b**	7	89
2	2,6-di-Me	Me	60	**3i**	13	86
3	4-Me	Me	40	**3j**	12	93
4	2-Me	Me	45	**3k**	13	96
5	H	Me	60	**3f**	5	93
6	4-Cl	Me	60	**3l**	6	79
7	4-CO$_2$Me	Me	90	**3m**	19	65
8[a]	4-NO$_2$	Me	100	**3n**	24	61
9	1-ferrocenylethanol		20	**3o**	0.5	99
10	4-MeO	H	20	**3p**	7	89
11	H	H	100	**3q**	4	44

[a] 2.5 mol % of Hf(OTf)$_4$was used. [b] Isolated yield.

Sterically hindered 1-(2,6-dimethylphenyl)- and 1-(2-methylphenyl)ethanol also gave products **3i** and **3k**, respectively, in high yields (entries 2 and 4, respectively). A relatively low reaction temperature was suitable for the reaction of benzyl alcohols possessing electron-donating alkyl and alkoxy groups because olefinic byproducts were formed at higher temperatures (entries 1−4). Although the reactions of electron-deficient 4-chloro-, 4-methoxycarbonyl-, and 4-nitrophenethylalcohols required a higher temperature, the corresponding desired benzylated products were obtained in 79−61% yield (entries 6−8). On the other hand, ferrocenylethanol, which is the most electron-rich alcohol in Table 4, reacted smoothly at 20 °C to give product **3o** in 99% yield (entry 9). For the primary benzylation, the electron-donating methoxy group was necessary to increase the yield of the desired product (entry 10). In entry 11, the Hf(OTf)$_4$-catalyzed reaction at 100 °C, benzylalcohol, and dibenzyl ether[25] were completely consumed even though the yield was moderate, and a considerable amount of a viscous residue was obtained. It appears that the primary unstable carbocation reacted unselectively to afford polymeric byproducts. The role of the hyperconjugation[26] of the methyl group is more significant than that of the electronic character of the aromatic ring.

A tertiary benzylated product was difficult to obtain in this system. Although we attempted the reactions of several tertiary alcohols (e.g., 2-phenyl-2-propanol, 1-phenylcyclohexanol, and 1-methyl-1,2,3,4-tetrahydronaphthol) with dibenzoylmethane

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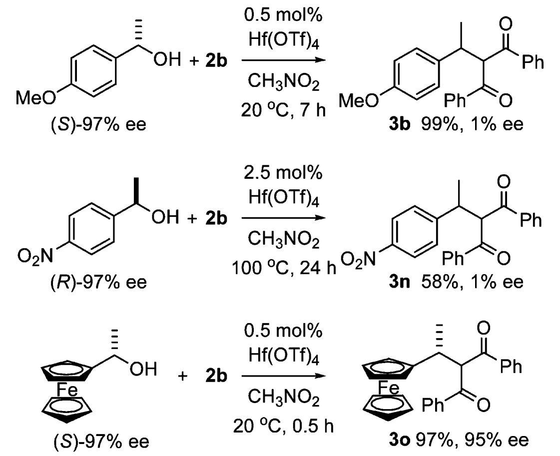
(23) The reaction of **1a** with dimethyl malonate was carried out with 0.5 mol % of Yb(OTf)$_3$ at 100 °C for 19 h to give the benzylated product in 0.5% yield.

(24) Reported enol ratio of diketone, ketoester, and diester in pure liquid form; acetylacetone (81%, rt), ethyl acetoacetate (8%, 33 °C), diethyl malonate (7.7×10^{-3}%, rt). (a) Gero, A. *J. Org. Chem.* **1954**, *19*, 1960−1970. (b) Burdett. J. L.; Rogers, M. T. *J. Am. Chem. Soc.* **1964**, *86*, 2105−2109.

(25) The structure was PhCH$_2$-O-CH$_2$Ph, which is an intermediate of the reaction. See Scheme 1.

(26) (a) *Carbocation Chemistry*; Olah, G. A., Prakash, G. K. S., Eds.; John Wiley & Sons: New Jersey, 2004, p 29. (b) Krygowski, T. M.; Stępień, B. T. *Chem. Rev.* **2005**, *105*, 3482−3512. (c) Vrček, V.; Kronja, O.; Siehl, H.-U. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1317−1321.

SCHEME 2. Reaction of Optically Active Alcohols

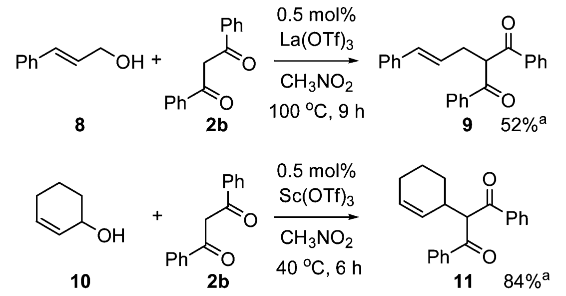


(**2b**) at 20−100 °C using La, Yb, Sc, and Hf catalysts, no desired products were obtained without the olefinic byproduct formation. In contrast, the less sterically hindered diketone, 1-phenyl-1,3-butanedione, reacted with 2-phenyl-2-propanol at 20 °C when $Hf(OTf)_4$ was used to afford a tertiary benzylated product in 9% yield.[27]

Reaction of Optically Active Alcohols. We have proposed a mechanism involving discrete cationic intermediates for the direct substitution of benzylic hydroxy groups. The cationic mechanism is certainly suitable for the reaction of phenylethyl alcohols bearing electron-donating substituents. However, a change in the reaction mechanism has been reported[28] for the reaction of 1-phenylethyl substrates from the cationic S_N1 to the concerted S_N2 as the carbocation becomes less stable. Therefore, electron-deficient 1-(4-nitrophenyl)ethanol might proceed under a concerted S_N2 mechanism. The reactions of optically active alcohols were examined for the possibility of concerted substitution with an inversion of the configuration. Optically active alcohols were prepared by the oxazaborolidine-catalyzed asymmetric borane reduction[29] of corresponding ketones. The reactions were carried out under the same reaction condition shown in Table 4, and the enantiomeric excesses of the products were examined by HPLC (Scheme 2).

In both the electron-rich and electron-deficient cases, the chemical yields of **3b** and **3n** were almost the same as those of the reactions in Table 4. No enantiomeric excess was observed for **3n**. Unfortunately, these results cannot exclude the concerted S_N2 mechanism for 1-(4-nitrophenyl)ethyl alcohol because the repeated S_N2 reaction of the hydroxy group by water before the S_N2 reaction of **2b** would give racemic **3n**. Kinetic measurements of the reaction are necessary for further investigation. The ferrocenylethyl cation is known to react with the retention of configuration.[30] In our system, the reaction of (*S*)-ferrocenyl ethanol (97% ee) and **2b** gave (−)-**3o** in 95% ee.

SCHEME 3. Reaction of Allylic Alcohols

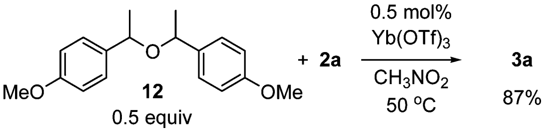


[a] Isolated yield.

Reaction of Allylic Alcohols. Next, we examined the allylation of 1,3-dicarbonyl compounds (Scheme 3). The allylations are usually carried out by using allyl ester or allyl halide derivatives with the metal enolate of 1,3-dicarbonyl compounds using palladium catalysts in an inert atmosphere.[31] In our system, allylic alcohols can be directly used as allylic cation precursors without any inert atmosphere.

Cinnamyl alcohol (**8**) and 2-cyclohexenol (**10**) were examined for this system using preliminary GC analyses. A cinnamyl product **9** was obtained in moderate yield with several unidentified products. The reactivity of **10** was similar to that of 1-phenylethanol (**1b**), and **11** was obtained in good yield. In both cases, symmetrical ethers were observed by GC−MS at a reaction temperature of 40 °C.

Use of Symmetrical Ether as Cation Precursor. Symmetrical ethers were frequently observed at the initial stage of the reactions. We tried to use one of the ethers as a source of benzylic cations. The symmetrical ether **12** was synthesized from 4-methoxyphenethylalcohol (**1a**) using a $La(OTf)_3$ catalyst in CH_3NO_2 at 20 °C as a *meso* and DL mixture (89%, 27% de).[32] Under the best benzylation condition in Figure 1A, the reaction of half-equivalent ether **12** with 1 equiv of **2a** gave **3a** in 87% yield (eq 2). The yield was lower than that in entry 1 of Table 1. Because **12** was less Lewis basic than benzylic alcohol **1a**, the best condition for **1a** was slightly stronger than that for **12**.



(2)

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[27] The reaction with 2-phenyl-2-propanol with 2 equiv of 2-methylfuran (Friedel−Crafts alkylation) using 0.5 mol % of $Yb(OTf)_3$ in nitromethane at 60 °C for 2 h gave 2-methyl-5-(1-methyl-1-phenyl)ethylfuran in 99% yield.

[28] (a) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689−4691. (b) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4691−4692. (c) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361−1372. (d) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373−1383. (e) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383−1396. (f) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1396−1401. (g) Ta-Shama, R.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 8040−8050.

[29] (a) Xu, J.; Wei, T.; Zhang, Q. *J. Org. Chem.* **2004**, *69*, 6860−6866. (b) Wright, J.; Frambes, L.; Reeves, P. *J. Organomet. Chem.* **1994**, *476*, 215−217.

[30] (a) Turbitt, T. D.; Watts, W. E. *J. Chem. Soc., Chem. Commun.* **1973**, 182−183. (b) Ratajczak, A.; Misterkiewicz, B. *J. Organomet. Chem.* **1975**, *91*, 73−79. (c) Patin, H.; Mignani, G.; Mahe, C. *J. Organomet. Chem.* **1980**, *193*, 93−103. (d) Woltersdorf, M.; Kranich, R.; Schmalz, H.-G. *Tetrahedron* **1997**, *53*, 7219−7230.

[31] (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385−393. (b) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730−4743. (c) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140−145.

[32] Other examples of cationic etherification of benzylic alcohols: (a) Kim, S.; Chung, K. N.; Yang, S. *J. Org. Chem.* **1987**, *52*, 3917−3919. (b) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1996**, *61*, 324−328. (c) Bouquillon, S.; Hénin, F.; Muzart, J. *Organometallics* **2000**, *19*, 1434−1437. (d) Kawada, A.; Yasuda, K.; Abe, H.; Harayama, T. *Chem. Pharm. Bull.* **2002**, *50*, 380−383. (e) Manabe, K.; Ilimura, S.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 11971−11978. (f) Miller, K. J.; Abu-Omar, M. M. *Eur. J. Org. Chem.* **2003**, 1294−1299. (g) Kim, S. L.; Shin, C.; Pae, A. N.; Koh, Y. H.; Chang, M. H.; Chung, B. Y. *Synthesis* **2004**, 1581−1584. (h) Firouzabadi, H.; Iranpoor, N.; Jafari, A. A. *J. Mol. Catal. A* **2005**, *227*, 97−100. (i) Shibata, T.; Fujiwara, R.; Ueno, Y. *Synlett* **2005**, 152−154. (j) Handlon, A. L.; Guo, Y. *Synlett* **2005**, 111−114.

Conclusion

We have developed a convenient secondary benzylation system for 1,3-dicarbonyl compounds. During the optimization process, the formation of symmetrical ether was observed at lower temperatures. The cation generation and nucleophilic attack of the alcohols proceeded faster than the reaction of the dicarbonyl compounds. In most cases, the reaction conditions of various combinations of benzylic alcohols and nucleophiles were easily optimized by the two-dimensional catalyst temperature screenings by GC analysis.

Diketones (**2a**,**b**,**d**), ketoesters (**4a**−**c**), and ketoamides (**6a**,**b**) exhibit similar reactivities toward the benzylic cation, but the ketoamides required a stronger Lewis acid because of their higher Lewis basicities. The benzylation of dimethyl malonate was unsuccessful under these conditions probably due to the low enol ratio. Methyl acetoacetate (**4a**) has a 4% enol ratio, and it reacted with **1a** to give **5a** in 97% yield. An enol ratio of more than 4% may be sufficient for the benzylation. The effect of the hyperconjugation of the alkyl group that stabilized the cation was more important than the electronic character of the aromatic ring, and the yields of the primary benzylation were lower than that of the secondary one. Although the generation of tertiary cations from tertiary benzylic alcohols proceeded readily at a lower temperature when weaker catalysts were used, the tertiary benzylation of **2b** did not proceed and the cation rapidly decomposed to form the corresponding olefins. Allylic alcohols (**8**, **10**) also reacted with **2b** without using any inert atmosphere; this reaction would be a convenient alternative for the Pd-catalyzed allylic substitution.

Experimental Section

Typical Procedure for Optimizing Reaction Conditions. A nitromethane solution (20 mL) of 1-(4-methoxyphenyl)ethanol (**1a**) (3.04 g, 20.0 mmol, 1 mol/L), acetylacetone (**2a**) (2.00 g, 20.0 mmol, 1 mol/L), and nitrocyclohexane (995 mg, 7.71 mmol, as an internal standard, 0.3−0.4 mol/L) was prepared. (***Warning***: Nitromethane is hazardous because of the possibility of an explosion.) The solution was mixed with catalysts in 20 mL test tubes equipped with glass stoppers. At 20 °C: 2.97 mg of La(OTf)$_3$ and 1.01 mL of the solution; 4.50 mg of Yb(OTf)$_3$ and 1.45 mL of the solution; 2.70 mg of Sc(OTf)$_3$ and 1.10 mL of the solution; 4.60 mg of Hf(OTf)$_4$ and 1.19 mL of the solution. At 50 °C: 2.31 mg of La(OTf)$_3$ and 0.79 mL of the solution; 5.20 mg of Yb(OTf)$_3$ and 1. 68 mL of the solution; 2.25 mg of Sc(OTf)$_3$ and 0.91 mL of the solution; 4.72 mg of Hf(OTf)$_4$ and 1.22 mL of the solution. At 80 °C: 3.14 mg of La(OTf)$_3$ and 1.07 mL of the solution; 4.46 mg of Yb(OTf)$_3$ and 1.44 mL of the solution; 2.70 mg of Sc(OTf)$_3$ and 1.10 mL of the solution; 3.89 mg of Hf(OTf)$_4$ and 1.00 mL of the solution. The mixtures in the test tubes were stirred at the corresponding temperatures. The reactions were followed by TLC. After the complete consumption of **1a** and the symmetrical ethers (*meso*- and DL-1-(4-methoxyphenyl)ethyl ethers), 65 μL of the reaction mixtures was taken and filtered through a short silica gel pad with 2 mL of ethyl acetate to remove insoluble materials. The filtrates were analyzed by GC and GC−MS. The programmed GC analysis temperature condition was 150 °C for 2 min, 10 °C/min, 260 °C for 17 min. The yields were determined using the calibration line prepared from nitrocyclohexane and **3a** using GC. For preparing the calibration line, three standard samples containing nitrocyclohexane (50, 50, 50 mg) and pure **3a** (50, 100, 150 mg) were analyzed by GC and [GC area (**3a**)]/[GC area (nitrocyclohexane)] was then plotted against [mol (**3a**)]/[mol (nitrocyclohexane)] to obtain the slope.[33] The yields of the reaction were as follows: 8% (La), 51% (Yb), 83% (Sc), and 85% (Hf) at 20 °C; 90% (La), 98% (Yb), 78% (Sc), and 71% (Hf) at 50 °C; 91% (La), 15% (Yb), 1% (Sc), and 0% (Hf) at 80 °C.

Typical Procedure for Isolating Benzylated Product. Table 1, Entry 1. 3-[1-(4-Methoxyphenyl)ethyl]pentane-2,4-dione (3a). To a mixture of Yb(OTf)$_3$ (9.68 mg, 15.6 μmol) and **2a** (323.86 mg, 3.235 mmol) in CH_3NO_2 (3.12 mL) was added **1a** (487.53 mg, 3.203 mmol) at room temperature. The resulting mixture was stirred at 50 °C for 24 h under a rubber balloon stopper. After the reaction mixture was filtered through a short silica gel pad with ethyl acetate, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, hexane/ethyl acetate = 20/1 to 4/1) to afford **3a** (728.62 mg, 97%) as a colorless prism: mp 52−53 °C; TLC R_f = 0.40 (hexane/ethyl acetate = 3/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (2H, d, J = 8.8 Hz), 6.83 (2H, d, J = 8.8 Hz), 3.98 (1H, d, J = 11.4 Hz), 3.78 (3H, s), 3.55 (1H, dq, J = 11.4, 6.8 Hz), 2.26 (3H, s), 1.84 (3H, s), 1.19 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 202.9, 158.0, 134.7, 127.9, 113.8, 76.6, 55.0, 39.6, 29.7, 29.6, 20.9; IR (KBr) 1723 (s), 1518 (s), 1365 (s), 1294 (m), 1251 (s), 1183 (s), 1147 (m), 1036 (m), 818 (m) cm^{-1}; EI-MS (70 eV) *m*/*z* (relative intensity) 234 (M$^+$, 10), 191 (90), 173 (15), 135 (100), 43 (18); HRMS-EI (*m/z*) M$^+$ calcd for $C_{14}H_{18}O_3$, 234.1256; found, 234.1259. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.80; H, 7.87. GC analysis: 10.15 min (150 °C, 2 min, 10 °C/min, 260 °C, 17 min).

2-[1-(4-Nitrophenyl)ethyl]-1,3-diphenylpropane-1,3-dione (3n). Pale yellow prism: mp 100−103 °C; TLC R_f = 0.44 (hexane/ethyl acetate = 7/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08−8.04 (4H, m), 7.77−7.74 (2H, m), 7.63−7.26 (8H, m), 5.61 (1H, d, J = 10.2 Hz), 4.20 (1H, dq, J = 10.2, 6.9 Hz), 1.36 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 193.6, 151.5, 146.7, 136.6, 136.2, 133.7, 133.4, 128.9, 128.7, 128.6, 128.5, 128.3, 123.5, 64.5, 41.0, 20.3; IR (KBr) 1694 (s), 1599 (m), 1518 (s), 1448 (m), 1346 (s), 1270 (m), 1224 (m), 1201 (m), 978 (m), 859 (m), 712 (m), 688 (m) cm^{-1}; EI-MS (70 eV) *m*/*z* (relative intensity) 373 (M$^+$, 0.2), 269 (10), 268 (58), 252 (14), 251 (39), 105 (100), 77 (53); HRMS-EI (*m/z*) M$^+$ calcd for $C_{23}H_{19}NO_4$, 373.1314; found, 373.1312. Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 74.22; H, 5.40; N, 3.51. GC analysis: 25.86 min (150 °C, 2 min, 10 °C/min, 300 °C, 17 min).

Methyl 2-acetyl-3-(4-methoxyphenyl)butyrate (5a, diastereomixture). Colorless oil: TLC R_f = 0.43 (hexane/ethyl acetate = 7/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15−7.08 (2H, m), 7.15−7.11 (2H, m), 6.84−6.80 (2H, m), 6.84−6.80 (2H, m), 3.78 (3H, s), 3.77 (3H, s), 3.75 (3H, s), 3.45 (3H, s), 3.78−3.68 (1H, m), 3.78−3.68 (1H, m), 3.55−3.43 (1H, m), 3.55−3.43 (1H, m), 2.28 (3H, s), 1.91 (3H, s), 1.27 (3H, d, J = 6.9 Hz), 1.22 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.14, 202.06, 168.8, 168.4, 158.2, 158.1, 135.1, 134.7, 128.2, 128.1, 114.0, 113.7, 67.7, 67.1, 55.23, 55.23, 52.5, 52.2, 39.5, 39.1, 30.1, 30.0, 20.9, 20.3; IR (neat) 2950 (m), 1740 (s), 1710 (s), 1610 (m), 1510 (s), 1460 (m), 1440(m), 1360 (m), 1260 (s), 1190 (s), 1040 (m), 840 (m) cm^{-1}; EI-MS (70 eV) *m*/*z* (relative intensity) 250 (M$^+$, 12), 232 (19), 175 (17), 161 (8), 135 (100); HRMS-EI (*m/z*) M$^+$ calcd for $C_{14}H_{18}O_4$, 250.1205; found, 250.1208. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.43; H, 7.42. GC analysis: 10.62 min, 10.95 min (major) (150 °C, 2 min, 10 °C/min, 260 °C, 17 min).

2-[1-(4-Methoxyphenyl)ethyl]-*N*,*N*-dimethyl-3-oxobutyramide (7a, diastereomixture). Colorless oil: TLC R_f = 0.48 (hexane/ethyl acetate = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17−7.12 (2H, m), 7.17−7.12 (2H, m), 6.84−6.79 (2H, m), 6.84−6.79 (2H, m), 3.93 (1H, d, J = 10.8 Hz), 3.79 (1H, d, J = 10.5 Hz), 3.78 (3H, s), 3.77 (3H, s), 3.74−3.60 (1H, m), 3.74−3.60 (1H, m), 3.13 (3H, s), 3.02 (3H, s), 2.78 (3H, s), 2.72 (3H, s), 2.28 (3H, s), 1.97 (3H, s), 1.23 (3H, d, J = 6.9 Hz), 1.20 (3H, d, J = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 204.4, 167.4, 167.4,

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[33] In several cases, the slopes were deduced from the isolated yields.

158.1, 158.0, 135.5, 135.1, 128.3, 128.1, 114.0, 113.6, 66.4, 65.6, 55.6, 55.2, 40.0, 39.4, 37.8, 37.5, 36.3, 35.9, 27.2, 27.0, 22.1, 19.7; IR (neat) 2950 (m), 1715 (m), 1650 (s), 1520 (m), 1475 (m), 1410 (m), 1370 (m), 1260 (s), 1195 (m), 1155 (m), 1130 (m), 1050 (m), 845 (m) cm^{-1}; EI-MS (70 eV) *m*/*z* (relative intensity) 263 (M$^+$, 11), 220 (100), 175 (22), 135 (32), 72 (17); HRMS-EI (*m/z*) M$^+$ calcd for $C_{15}H_{21}NO_3$, 263.1521; found, 263.1525. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.39; H, 8.21; N, 5.04. GC analysis: 12.72 min, 13.29 min (major) (150 °C, 2 min, 10 °C/min, 300 °C, 13 min).

Reuse of the Catalyst. In a 20 mL test tube, **1a** (488.15 mg, 3.208 mmol) was added to a mixture of $Yb(OTf)_3$ (9.77 mg, 15.75 μmol) and **2a** (316.85 mg, 3.165 mmol) in CH_3NO_2 (3.150 mL) at room temperature. The resulting mixture was stirred at 50 °C for 24 h under a rubber balloon stopper. After cooled to room temperature, the $Yb(OTf)_3$ catalyst was extracted with six 3 mL portions of water (upper phase) from the reaction mixture of CH_3NO_2 solution (lower phase). The trace amount of contaminated CH_3NO_2 in the water phase was extracted with ethyl acetate and combined with the CH_3NO_2 layer. The organic layer was concentrated under reduced pressure, and the resulting oil was purified by bulb to bulb distillation (185 °C/0.26 Torr) to afford **3a** (730.8 mg, 99%) as a colorless oil. The oil crystallized on standing at room temperature. The water extract was concentrated under reduced pressure and dried under vacuum (1 Torr) at room temperature for 10 min and then at 200 °C for 3 min with a heating gun to give a white crystalline $Yb(OTf)_3$ catalyst. The catalyst was used for the next run. For the second run, **2a** (329.5 mg, 3.291 mmol), CH_3NO_2 (3.150 mL), and **1a** (487.7 mg, 3.205 mmol) were stirred at 50 °C for 24 h. After bulb to bulb distillation, 736.8 mg of **3a** (99%) was obtained. For the third run, **2a** (328.5 mg, 3.281 mmol), CH_3NO_2 (3.150 mL), and **1a** (481.2 mg, 3.162 mmol) were stirred at 50 °C for 24 h. After bulb to bulb distillation, 716.5 mg of **3a** (97%) was obtained. For the fourth run, **2a** (329.4 mg, 3.290 mmol), CH_3NO_2 (3.150 mL), and **1a** (492.1 mg, 3.233 mmol) were stirred at 50 °C for 48 h. After bulb to bulb distillation, 733.0 mg of **3a** (97%) was obtained. For the fifth run, **2a** (327.8 mg, 3.274 mmol), CH_3NO_2 (3.150 mL), and **1a** (479.7 mg, 3.152 mmol) were stirred at 50 °C for 48 h. After bulb to bulb distillation, 708.5 mg of **3a** (96%) was obtained.

Measurement of Enol Ratio in CD_3NO_2 by NMR. The NMR spectra of dicarbonyl compounds were measured in CD_3NO_2 at 23−25 °C (0.11−0.18 mol/L, except **2b** and **2c** because of their low solubilities).

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Supporting Information Available: Tables and graphs of the GC analysis for optimizing the reaction conditions (**3a**−**n**, **3p**−**q**, **5a**−**f**, **7a**−**d**, **9**, and **11**), procedure of the isolation reaction (**3a**−**q**, **5a**−**f**, **7a**−**d**, **9**, **11**, and **12**), reuse of the catalyst, characterization of all new compounds, ^{1}H and ^{13}C spectra of the products, and the table of enol ratios for dicarbonyl compounds (**2a**−**d**, **4a**−**c**, and **6a**,**b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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