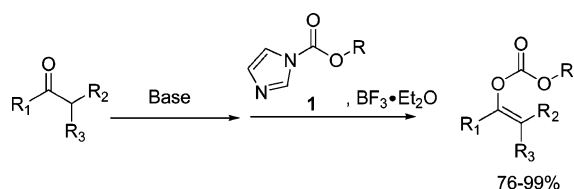## The O-Acylation of Ketone Enolates by Allyl 1*H*-Imidazole-1-carboxylate Mediated with Boron Trifluoride Etherate—A Convenient Procedure for the Synthesis of Substituted Allyl Enol Carbonates

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A convenient access to substituted allyl enol carbonates was established through the reaction of ketone enolates with the complex of allyl 1*H*-imidazole-1-carboxylates and boron trifluoride etherate.

Allyl enol carbonates and allyl β-keto esters have received more and more attention as useful precursors in the palladium-catalyzed synthesis of enantiomeric enriched α-allyl ketones, which are important building blocks in asymmetric organic synthesis.[1] The preparation of allyl enol carbonates and allyl β-keto esters can be performed by the treatment of the corresponding enolates with an acylating agent, usually allyl chloroformate.[2] However, very few substituted allyl chloroformates are commercially available, and the preparation[3] of such compounds is limited not only by their poor thermal stability and the use of excess highly toxic phosgene but also by the hydrogen chloride generated from the reaction, which may not be compatible with acid-sensitive functional groups on the molecule. Furthermore, the higher reactivity of the allyl enol carbonates and the frequently low yields in their synthesis with

more highly substituted allyl chloroformates focused our attention on developing a convenient high yielding process. In addition, although substituted allyl β-keto esters can be more readily synthesized by ester exchange reactions of simple β-keto esters with the corresponding allyl alcohol,[4] there is still an absence of a convenient procedure for the preparation of substituted allyl enol carbonates from simple ketones. Notably, the role of allyl β-keto esters and that of allyl enol carbonates are not completely exchangeable in the Pd-catalyzed decarboxylative allylic alkylation reactions.[5] Therefore, the development of a convenient approach to access substituted allyl enol carbonates will significantly broaden the scope of the asymmetric synthesis of α-allyl ketones.
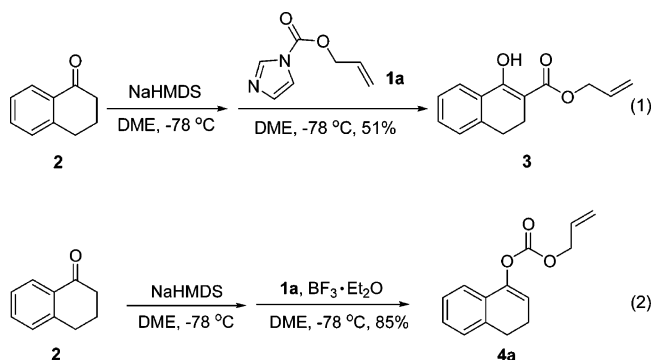
The regioselectivity in the acylation of metal enolates in general is dependent on the acylating reagent (acetic anhydride favors O-acylation better than acetyl chloride), the metal (K favors O-acylation while Mg favors C-acylation), the solvent (chelating solvent such as 1,2-dimethoxyethane favors O-acylation while nonpolar solvent such as toluene favors C-acylation), and the reaction temperature (higher temperature favors O-acylation while lower temperature favors C-acylation).[6]

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(2) (a) Olofson, R. A.; Cuomo, J.; Bauman, B. A. *J. Org. Chem.* **1978**, *43*, 2073. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793. (c) Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, *3*, 169. (d) Harwood, L. M.; Houminer, Y.; Manage, A.; Seeman, J. I. *Tetrahedron Lett.* **1994**, *35*, 8027.

(3) (a) Nystrom, R. F.; Brown, W. G. *J. Am. Chem. Soc.* **1957**, *79*, 1197. (b) Young, W. G.; Clement, R. A.; Shih, C. H. *J. Am. Chem. Soc.* **1955**, *77*, 3061. (c) Oliver, K. L.; Young, W. G. *J. Am. Chem. Soc.* **1959**, *81*, 5811.

(4) Gilbert, J. C.; Kelly, T. A. *J. Org. Chem.* **1988**, *53*, 449.

(5) In the reaction of Pd-catalyzed decarboxylative allylic alkylation of ketones to generate tertiary centers, the reaction mechanisms of allyl enol carbonates and that of allyl β-keto esters may be different: Intermediate **I** from enol carbonates can only undergo decarboxylation to afford Pd enolate **II** which recombines to the product. Intermediate **III** from β-keto esters, however, may undergo a facile H-shift to generate **IV** depending on the acidity of the α-proton. **IV** recombines to a β-keto acid **V**, which decarboxylates to the product. Therefore, allyl β-keto esters cannot completely replace enol allyl carbonates in this reaction. See: (a) Tsuji, J.; Minami, I. *Acc. Chem. Res.* **1987**, *20*, 140. (b) Tsuji, J.; Yamada, Y.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988.
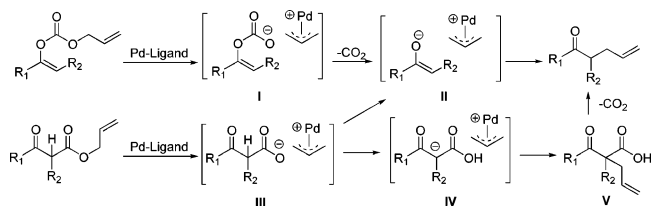
(6) (a) House, H. O.; Auerbach, R. A.; Gall, M.; Peet, N. P. *J. Org. Chem.* **1973**, *38*, 514. (b) Olofson, R. A.; Cuomo, J.; Bauman, B. A. *J. Org. Chem.* **1978**, *43*, 2073. (c) Taylor, R. J. K. *Synthesis* **1985**, *4*, 364. (d) Bairgrie, L. M.; Leung-Toung, R.; Tidwell, T. T. *Tetrahedron Lett.* **1988**, *29*, 1673. (e) Zhong, M.; Brauman, J. I. *J. Am. Chem. Soc.* **1996**, *118*, 636.

Imidazolides have been widely used in the acylation[7a] of alcohols,[7b] amines,[7c] acids,[7d] and carbanions.[7e] The reaction of ketone enolates with imidazolides favors C-acylation, and it is a better alternative to the Claisen condensation to synthesize β-keto esters and 1,3-diketones.[8] As we expected, treatment of the sodium enolate of 1-tetralone in DME at −78 °C with allyl 1*H*-imidazole-1-carboxylate **1a** gave only C-acylation product **3** (eq 1). It is a general notion that reaction of ketone enolates with "hard" electrophiles favor O-acylation while "soft" electrophiles favor C-acylation.[6] We postulated that the complex of the imidazolide with an azaphilic Lewis acid, such as boron trifluoride, is a "harder" electrophile than the imidazolide itself and it should favor O-acylation.[9] To our delight, the experimental result supported our proposal, and in contrast to eq 1, the reaction mediated with BF₃·Et₂O cleanly generated only allyl enol carbonate **4a** in 85% yield (eq 2).

To investigate the generality of the reaction, we prepared several substituted allyl 1*H*-imidazole-1-carboxylates **1** by simply mixing 1,1′-carbonyldiimidazole with the corresponding allylic alcohols in a cosolvent of THF and CH₂Cl₂ at 0 °C for several hours and then isolated the product by silica gel column chromatography. The yields are normally very good (Table 1). As a demonstration, the sodium enolate of 1-tetralone or 2-methyl-1-tetralone was treated with a variety of the BF₃ complexes of differently substituted allyl derivatives **1**, respectively, and consistently, good yields were obtained in every case. It is remarkable that, through this procedure, enol carbonates containing amino groups could be produced in the same manner (Table 1, entry 10).

The reaction of various sodium enolates with the BF₃ complex of **1** exclusively gave enol carbonates in high yields (Table 2, entries 7, 9, and 11), while the ones without BF₃ gave exclusively β-keto esters in Table 2, entries 1 and 6, or a mixture of both in entry 8, possibly because the steric effect of the methyl group disfavored the C-acylation. There are also some cases in which the nature of the enolate is such that the regioselectivity toward the O-acylation is not perfect even with the BF₃-activated electrophile. For instance, the reaction of the sodium enolate of 1-indanone with the **1d**−BF₃ complex in DME at −78 °C yielded a mixture of enol carbonate **8** and β-keto ester **7** in a 3:1 ratio (Table 2, entry 2). By switching to the less coordinated potassium enolate, generated by use of potassium *tert*-butoxide as base, the ratio improved to 17:1 (Table 2, entry 3). In the presence of 18-C-6, the enolate has even weaker coordination with the potassium countercation, and in this case, no **7** was observed (Table 2, entry 4). Since the reactions between enolates and **1**−BF₃ complex are fast even at −78 °C, either the thermodynamic (such as **13** in entry 9) or the kinetic product (such as **15** in entry 10) can be obtained with excellent selectivity

(7) (a) For review concerning the application of imidazolides as acylating agents, see: Staab, H. A. *Angew. Chem., Int. Ed. Engl.* **1962**, *7*, 350. (b) Bertolini, G.; Pavich, G.; Vergani, B. *J. Org. Chem.* **1998**, *63*, 6031. (c) Vatele, J.-M. *Tetrahedron* **2004**, *60*, 4251. (d) Kitagawa, T.; Kuroda, H.; Sasaki, H. *Chem. Pharm. Bull.* **1987**, *35*, 1262. (e) Werner, T.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 4302.

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(9) For reference concerning the much better reactivity of acylimidazolium salts than the corresponding imidazolides, see: (a) Anders, E.; Will, W. *Tetrahedron Lett.* **1978**, *41*, 3911. (b) Oakenfull, D. G.; Salvesen, K.; Jencks, W. P. *J. Am. Chem. Soc.* **1971**, *93*, 188. (c) Grzyb, J. A.; Shen, M.; Yoshina-Ishii, C.; Chi, W.; Brown, R. S.; Batey, R. A. *Tetrahedron* **2005**, *61*, 7153.

TABLE 1. Formation of Allyl Enol Carbonates from Various Substituted Allyl 1*H*-Imidazole-1-carboxylates

Entry	OR	Yield of **1**[a]	Ketone	Product	Yield
1		**1b** 80%	2	**4b**	88%
2			5	**6b**	99%
3		**1c** 91%	2	**4c**	76%
4			5	**6c**	76%
5		**1d** 97%	2	**4d**	80%
6			5	**6d**	94%
7		**1e** 85%	5	**6e**	89%
8		**1f** 95%	5	**6f**	96%
9		**1g** 97%	5	**6g**	92%
10		**1h** 100%	5	**6h**	76%

[a] Isolated yields of **1** from the reaction of 1,1′-carbonyldiimidazole and the corresponding allyl alcohol.

by quenching the corresponding enolates generated using different conditions. Substrates **16** and **17** have been used in the formal synthesis of (*S*)-oxybutynin, and they can be alternatively prepared by this method (Table 2, entry 11).[1d]

In summary, allyl 1*H*-imidazole-1-carboxylates are readily accessible from 1,1′-carbonyldiimidazole and allylic alcohols. They are normally stable and easy to handle. By tuning their reactivity with BF₃ in the reaction with ketone enolates, we have developed a convenient procedure for the synthesis of a broad scope of allyl enol carbonates in high yields and regioselectivity. The study of Pd-catalyzed asymmetric decarboxylative allylic alkylation reactions of substituted allyl enol carbonates and their application in organic synthesis is ongoing.

Experimental Section

General Procedures. Procedure A: A clean oven-dried 50 mL flask was charged 460 mg of sodium bis(trimethylsilyl)amide (2.4 mmol) under nitrogen. The flask was cooled to −78 °C in a dry ice/acetone bath, and 5 mL of 1,2-dimethoxyethane (DME) was added through a syringe. The flask was taken out from the bath to allow it to warm up until the solid completely dissolved. Then it was cooled to −78 °C. To the solution was added 317 mg of 1-indanone (2.4 mmol) in 2 mL of DME. The solution was stirred for 30 min before it was transferred into the solution of 384.4 mg of **1d** (2 mmol). After 10 min, the cooling bath was removed and the reaction was allowed to warm to room temperature and stirred at room temperature for 1 h. One portion of 10 mL of saturated aqueous ammonium chloride was poured into the reaction mixture

TABLE 2. The Reaction of Various Ketone Enolates with 1 or Its BF₃ Complex

Entry	Ketone	Procedure[a]	Product	Yield[b]
1	(1-indanone)	A	**7**	63%
2		B	**8** + **7** (**8:7** = 3:1)	95%
3		C	**8** + **7** (17:1)	92%
4		D	**8** only	92%
5	(2-methyl-1-indanone)	C	**9**	88%
6	(propiophenone)	A	**10**	61%
7		B	**11**	99%
8	(2-methyl-1-tetralone)	A	**12** + **4d** (**12:4d** = 1.3:1)	51%
9	(2-methylcyclohexanone)	B[c]	**13** **14** (**13:14** = 14:1)	99%
10	(2-methyl-3-pentanone)	C	**15**	93%
11	(PhC(O)CH₂OTBS)	B	**16** **17** (**16:17** = 2.5:1)	78%

[a] **A**: 1.0 equiv of NaHMDS, DME, −78 °C, then 0.8 equiv of **1**; **B**: 1.0 equiv of NaHMDS, DME, −78 °C, then a mixture of 0.8 equiv of **1** and BF₃·Et₂O or, if the product cannot be separated from the starting ketone by silica gel chromatography, 1.2 equiv of NaHMDS, DME, −78 °C, then a mixture of 1.2 equiv of **1** and BF₃·Et₂O; **C**: 1.2 equiv of KO′Bu, THF, −78 °C, then a mixture of 1.2 equiv of **1** and BF₃·Et₂O; **D**: 1.2 equiv of KO′Bu, 1.2 equiv of 18-crown-6, THF, −78 °C, then a mixture of 1.2 equiv of **1** and BF₃·Et₂O. [b] Combined isolated yield for the reactions with more than one product. [c] The enolate was formed by the addition of a solution of 1 equiv of NaHMDS into a solution of the substrate at 0 °C then cooled to −78 °C.

followed by 10 mL of diethyl ether. The aqueous layer was extracted with 10 mL of diethyl ether. The combined organic solution was washed with 10 mL of saturated brine and dried over MgSO₄. After concentration, the crude product was isolated with silica gel column chromatography eluted with 15% diethyl ether in petroleum ether to afford 323 mg of a white solid as a 5:1 mixture of **7** and its enol tautomer (63%): mp = 77−79 °C; R_f = 0.24 (diethyl ether/petroleum ether 1:9); ¹H NMR (400 MHz, CDCl₃) δ = 10.45 (br s, 1H, enol), 7.77 (m, 1H, ketone), 7.62 (m, 1H, enol),

7.62 (m, 1H, ketone), 7.50 (m, 1H, ketone), 7.45 (m, 1H, enol), 7.39 (m, 2H, enol), 7.39 (m, 1H, ketone), 5.98 (m, 1H, enol), 5.98 (m, 1H, ketone), 5.81 (m, 1H, enol), 5.74 (m, 1H, ketone), 5.47 (m, 1H, enol), 5.35 (m, 1H, ketone), 3.71 (m, 1H, ketone), 3.55 (m, 1H, ketone), 3.55 (m, 2H, enol), 3.38 (m, 1H, ketone), 3.38 (m, 1H, enol), 2.20−1.60 (m, 6H, ketone), 2.20−1.60 (m, 6H, enol).

Procedure B: To the solution of 460 mg of NaHMDS in 5 mL of DME at −78 °C was added 292 mg of 1-tetralone (2 mmol) in 2 mL of DME. The solution was stirred at −78 °C for 30 min.

Meanwhile, another clean oven-dried 50 mL flask was charged with 365 mg of **1a** (2.0 mmol) and 5 mL of DME. The solution was cooled to −78 °C, and 0.30 mL of boron trifluoride etherate (2.4 mmol) was added dropwise and stirred for 15 min. The above solution was transferred into the solution of enolate through a cannula under nitrogen and stirred for 30 min. One portion of 10 mL of saturated aqueous ammonium chloride was poured into the reaction mixture followed by 10 mL of diethyl ether. The mixture was taken out from the bath and allowed to warm to ambient temperature. The organic layer was separated, and the aqueous layer was extracted once with 10 mL of diethyl ether. The organic layer was combined and dried over magnesium sulfate. After filtration and concentration in vacuo, the crude material was purified by silica gel column chromatography eluted with 10% diethyl ether in petroleum ether to give 392 mg of **4a** as a colorless liquid (85%): $R_f = 0.39$ (diethyl ether/petroleum ether 1:9); IR (film) 3068, 3024, 2941, 2890, 2836, 1760, 1659, 1489, 1452, 1428, 1360, 1293, 1244, 1225, 1186, 1013, 993, 944, 772, 744 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 7.2$ (m, 4H), 5.99 (m, 1H), 5.81 (t, $J = 4.6$ Hz, 1H), 5.42 (dq, $J = 17.2, 1.3$ Hz, 1H), 5.32 (dq, $J = 10.2, 1.3$ Hz, 1H), 4.71 (dt, $J = 5.6, 1.3$ Hz, 2H), 2.86 (t, $J = 8.2$ Hz, 2H), 2.45 (m, 2H).

Procedure C: Follow the details in procedure B, but potassium *tert*-butoxide was used as base and THF as solvent.

Cyclohex-2-en-1-yl 2-methyl-1*H*-inden-3-yl carbonate (9). Starting from 350 mg of 2-methyl-1-indanone (2.4 mmol) and 384.4 mg of **1d** (2 mmol) by procedure C, 474 mg of white solid was obtained after purification by silica gel chromatography (88%): mp = 66−67 °C; $R_f = 0.30$ (diethyl ether/petroleum ether 1:9); IR (film) 3034, 2944, 1756, 1656, 1397, 1336, 1242, 1165, 1140, 1033, 911, 732 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 7.34$ (m, 1H), 7.25 (m, 1H), 7.15 (m, 2H), 6.05 (m, 1H), 5.87 (m, 1H), 5.23 (m, 1H), 3.32 (s, 2H), 2.03 (s, 3H), 2.20−1.60 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) $\delta = 152.4, 144.6, 140.1, 139.6, 134.0, 128.3, 126.3, 124.6, 123.8, 117.3, 112.6, 73.1, 39.1, 28.2, 24.9, 18.6, 12.2$.

Procedure D: Follow procedure C, but 18-C-6 was added to the enolate solution.

Cyclohex-2-en-1-yl 1*H*-inden-3-yl carbonate (8). Starting from 317 mg of 1-indanone (2.4 mmol) and 384.4 mg of **1d** (2 mmol) by procedure D, 470 mg of a colorless oil was obtained after purification by silica gel chromatography (92%): $R_f = 0.47$ (diethyl ether/petroleum ether 1:9); IR (film) 3034, 2943, 2835, 1756, 1618, 1603, 1578, 1456, 1398, 1336, 1292, 1227, 1172, 1127, 1050, 1012, 918,782, 760, 717 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta = 7.41$ (m, 2H), 7.30 (m, 1H), 7.24 (m, 1H), 6.34 (t, $J = 2.4$ Hz, 1H), 6.04 (m, 1H), 5.86 (m, 1H), 5.25 (m, 1H), 3.40 (d, $J = 2.4$ Hz, 2H), 2.20−1.60 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) $\delta = 152.3, 149.4, 141.8, 138.7, 134.0, 126.3, 125.7, 124.5, 124.1, 118.2, 114.3, 72.9, 34.9, 28.2, 24.9, 18.6$. Anal. Calcd for C$_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 75.12; H, 6.11.

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

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