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A Method To Accomplish a 1,4-Addition Reaction of Bulky Nucleophiles to Enones and Subsequent Formation of Reactive Enolates

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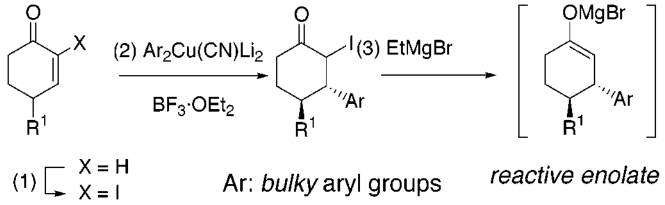
ABSTRACT



BF$_3$-promoted 1,4-addition of bulky aryl groups to α-iodo enones, prepared from the parent enones, afforded *β*-aryl-α-iodo ketones. Subsequent reaction with EtMgBr furnished the magnesium enolates, which upon reactions with ClP(O)(OEt)$_2$ and aldehydes gave enol phosphates and aldols, respectively. This method was applied successfully to a synthesis of Δ^1-*trans*-tetrahydrocannabinol.

1,4-Addition of organocopper reagents to α,*β*-unsaturated carbonyl compounds assisted by BF$_3$·OEt$_2$ is a standard method to introduce a *bulky* group at the *β*-position of the carbonyl compounds (for example, **1** + **2** → **3** in Scheme 1).[1] Unfortunately, the unreactive nature of the resulting boron enolates is described by Lipshutz,[1c] and hence it seems impossible to enjoy the benefit of the enolate chemistry. To the best of our knowledge, neither reaction at the α position nor formation of enol esters (or ethers) for further reactions has been reported.

In our investigation of the synthesis of tetrahydrocannabinol (THC), use of BF$_3$·OEt$_2$ was indeed *indispensable* for the 1,4-addition reaction of the bulky cuprate **2a** to enone **1a** (R^1 = CMe$_2$(OTES)) (Et$_2$O, −78 °C, 1.5 h), and the addition product (structure not shown) was isolated in 90% yield after aqueous workup (Scheme 1). However, the enolate generated in situ by the above BF$_3$·OEt$_2$-assisted 1,4-addition showed no reactivity, as suggested by Lipshutz,[1c] toward PhN(Tf)$_2$, Tf$_2$O, or ClP(=O)(OEt)$_2$.[2] Since a silyl enol ether could be metalated to a reactive enolate, we also attempted reaction of **1a** and **2a** with TMSCl and HMPA in THF according to Nakamura.[3] However, the reaction did not furnish the corresponding TMS ether. Addition of *n*-BuLi to the boron enolate did not increase the reactivity toward ClP(=O)(OEt)$_2$.[4] In contrast to the bulky cuprate **2a**, the phenyl cuprate **2e**, in a control experiment, underwent reaction with enone **1a** smoothly without the assistance of BF$_3$·OEt$_2$ (Et$_2$O, −78 °C, 2 h), and the resulting enolate, upon reaction with ClP(O)(OEt)$_2$ (−78 °C to rt, 1 h), afforded enol phosphate **4h** (R^1 = CMe$_2$(OTES), Ar = Ph, E = P(O)-(OEt)$_2$) in 63% yield. On the other hand, the enolate produced in situ from **1a** and **2e** in the presence of BF$_3$·OEt$_2$ did not react and therefore did not furnish the phosphate. These

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[1] (a) Tius, M. A.; Kannaangara, G. S. K. *J. Org. Chem.* **1990**, *55*, 5711−5714. (b) Rickards, R. W.; Rönneberg, H. *J. Org. Chem.* **1984**, *49*, 572−573. (c) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959−5962.

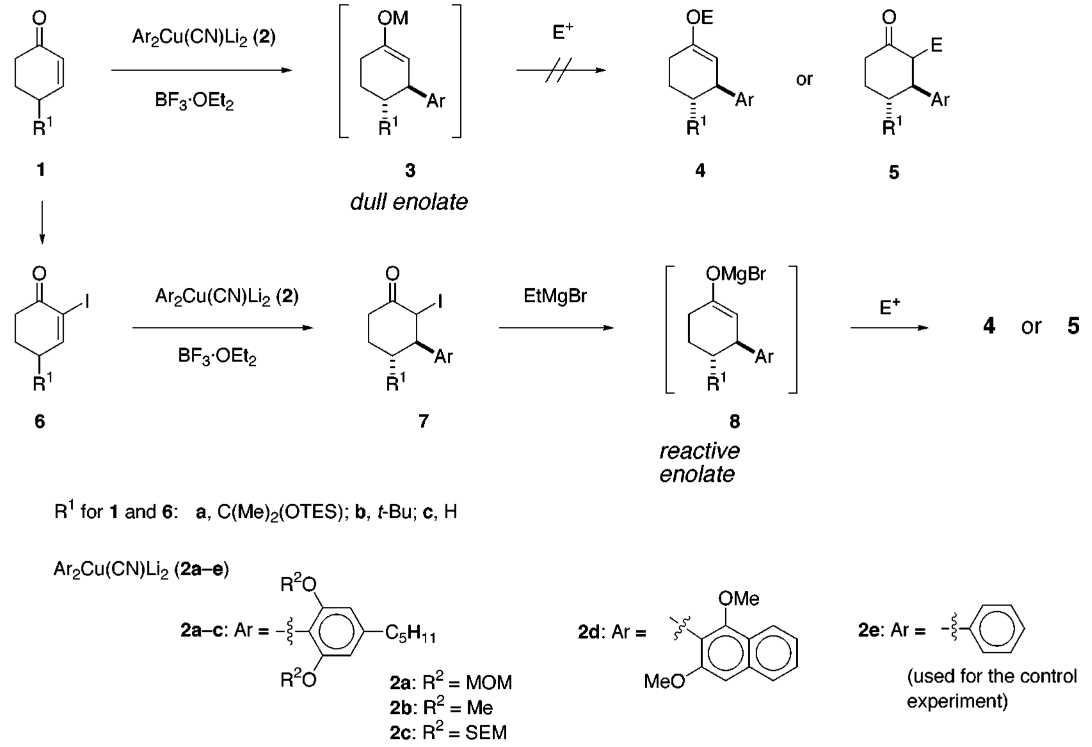
[2] McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979−982.

[3] Nakamura, E.; Matsuzawa, S.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4029−4032.

[4] Addition of *n*-BuLi to the (presumed) copper enolate is reported to increase the reactivity of the given enolate: Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353−3354.

10.1021/ol010071i CCC: $20.00

Scheme 1. A Method To Generate the Reactive Enolates



preliminary results prompted us to devise an indirect method. Shown in Scheme 1 is one such method which consists of 1,4-addition of the cuprate **2** to α-iodocycloalkenones **6** and subsequent transformation of the resulting α-iodo ketones **7** to reactive enolates **8**. In the following paragraphs, we present the fruitful results of this study.

Conversion of enones **1a** and **1b** to α-iodocyclohexenones **6a** and **6b**, respectively, with I_2 and pyridine in CCl_4 proceeded in good yield by the protocol of Johnson,[5] which was originally developed for preparation of **6c**. 1,4-Addition of bulky $Ar_2Cu(CN)Li_2$ (**2a**−**d**) to α-iodocyclohexenones **6a**−**c** promoted by BF_3·OEt_2 was carried out in good yields to furnish ketones **7a**−**g** (Figure 1) after aqueous workup and purification by chromatography.[6] The result is delineated in Table 1. No difficulty was incurred in the installation of the bulky aryl groups of **2a**−**d** (entries 1−7), and the yields of **7a**−**g** were almost the same as that obtained in a control experiment with the phenyl cuprate **2e** and enone **6a** (entry 8). A control experiment using **6a** and **2a** in the absence of BF_3·OEt_2 did not furnish the addition product **7a**; instead, **6a** was recovered. In addition, the compounds which might be produced by reaction at the α-position of **6a**−**c** with the cuprates **2a**−**d** were not detected by TLC and ^{1}H NMR spectroscopy.[7]

Determination of the relative stereochemistry at the β and γ positions of the 1,4-addition products **7** by ^{1}H NMR spectroscopy was ambiguous due to the somewhat small coupling constants between the protons at these positions

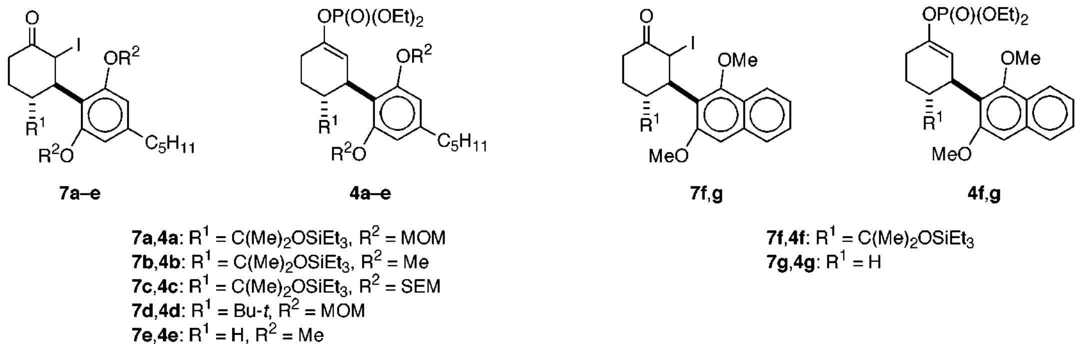


Figure 1.

Table 1. Synthesis of Iodides **7** and Enol Phosphates **4**

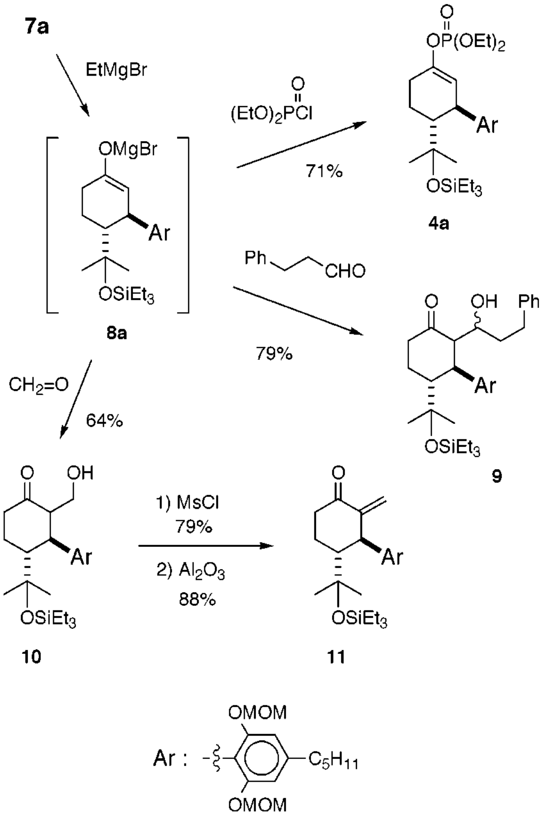
entry	substrate	copper reagent	product **7** no.	product **7** yield, %	product **4** no.	product **4** yield, %
1	**6a**	**2a**	**7a**	72	**4a**	71
2	**6a**	**2b**	**7b**	67	**4b**	70
3	**6a**	**2c**	**7c**	[a]	**4c**	53
4	**6a**	**2d**	**7f**	74	**4f**	60
5	**6b**	**2a**	**7d**	67	**4d**	63
6	**6c**	**2b**	**7e**	60	**4e**	58
7	**6c**	**2d**	**7g**	68	**4g**	62
8	**6a**	**2e**	**7h**	65	**4h**	63

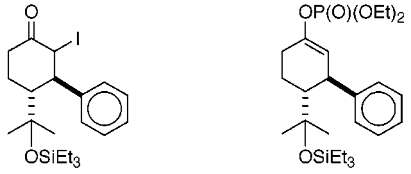
[a] Semipurified **7c** was converted into **4c**.

(4.5−7.5 Hz). However, the stereochemistry of **7b** was determined to be *trans* by synthesis of Δ^1-*trans*-THC (vide infra).[8] This assignment is consistent with the steric control approach of the cuprate **2b** to enone **1a**. We are speculating that the reaction of other enones and cuprates proceeds in the same manner to produce the *trans* stereochemistry as depicted in structure **7**.

The next step, conversion of the α-iodo ketones **7** to the corresponding enolates **8**, was explored first with **7a** as a representative case under the conditions of Borowitz ($(EtO)_3P$ in EtOH or $CHCl_3$; Ph_2POMe in $CHCl_3$),[9−11] Utimoto (EtMgBr in Et_2O; Et_3B in Et_2O or PhH),[12,13] and Joshi (Zn/TMSCl/THF).[14] Among these protocols, use of EtMgBr was successful to generate the corresponding enolate **8a** from iodide **7a**, and reaction of enolate **8a** and $(EtO)_2P(O)Cl$ afforded the enol phosphate **4a** in 71% yield (Scheme 2 and entry 1 of Table 1). This procedure was then applied to α-iodo ketones **7b**−**g** to furnish the successful results shown in Table 1.[15] The yields were almost identical as those obtained from a control experiment with **7h** (entry 8). Note that in most cases the enolate generation from **7** was accomplished in THF rather than Et_2O and was better in the TLC pattern than in Et_2O, though THF had been ineffective in the original report.[12]

Scheme 2. Generation of the Reactive Enolate **8a** and Its Reactions with Electrophiles





7h **4h**

7h,**4h**: Ar = Ph

To investigate further the reactivity of the enolates possessing bulky groups at the *β*-position, aldol reaction of

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(5) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovi′c, M. R. *Tetrahedron Lett.* **1992**, *33*, 917−918.

(6) **Representative procedure for the 1, 4-addition:** To an ice-cold solution of the bis MOM ether of olivetol (**2a**) (0.72 g, 2.69 mmol) in Et_2O (5 mL) was added *n*-BuLi (1.57 mL, 2.01 M, 3.14 mmol) in hexane over 10 min. The mixture was stirred at 0 °C for 10 min and then at ambient temperature for 2 h. In a separate flask was placed CuCN (0.12 g, 1.35 mmol) in Et_2O (5 mL), and the flask was cooled to −78 °C. The lithiated olivetol solution was transferred to the copper suspension over 10 min at −78 °C. After the addition, the reaction mixture was stirred at 0 °C for 10 min, recooled to −78 °C, and stirred for an additional 30 min. To the resulting pale yellow solution was slowly added a solution of α-iodocyclohexenone **6b** (0.25 g, 0.90 mmol) and $BF_3{\cdot}Et_2O$ (0.13 mL, 1.07 mmol) in Et_2O (5 mL) at −78 °C. After 2 h at −78 °C, the solution was poured into saturated NH_4Cl. The product was extracted and purified as usual to furnish ketone **7d** (0.33 g) in 67% yield. Iodides **7a**−**7h** were stable during purification and handling for the next reaction.

(7) Reactions at the α-position of α-halo ketones and organometallics have been reported: (a) Negishi, E.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453−4456. (b) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919−922. cf. Jabri, N.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1981**, *22*, 959−962.

(8) The characteristic signals for Δ^1-*trans*- and Δ^1-*cis*-THCs in the ^1H NMR spectra appear at 3.14 and 3.59 ppm, respectively: Taylor, E. C.; Lenard, K.; Shvo, Y. *J. Am. Chem. Soc.* **1966**, *88*, 367−369.

(9) Borowitz, I. J.; Anschel, M.; Firstenberg, S. *J. Org. Chem.* **1967**, *32*, 1723−1729.

(10) Borowitz, I. J.; Casper, E. W. R.; Crouch, R. K.; Yee, K. C. *J. Org. Chem.* **1972**, *37*, 3873−3878.

(11) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745−4746.

(12) Aoki, Y..; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 463−464.

(13) Nozaki, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 403−409.

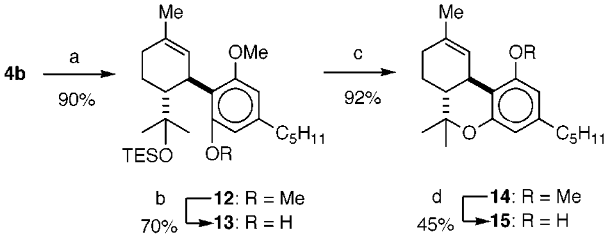
(14) (a) Joshi, G. C.; Pande, L. M. *Synthesis* **1975**, 450−453. (b) Hashimoto, S.; Itoh, A.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 4192−4194.

(15) **Representative procedure for generation of enol phosphates:** To an ice-cold solution of the iodo ketone **7d** (0.21 g, 0.38 mmol) in THF (5 mL) was added EtMgBr (0.57 mL, 1 M in THF, 0.57 mmol). After 10 min of stirring, $ClP(O)(OEt)_2$ (0.14 mL, 0.96 mmol) was added to the resulting pale yellow solution. The reaction was continued at 0 °C for 2 h and quenched with saturated $NaHCO_3$. The product was extracted with EtOAc and purified by chromatography on silica gel (pretreated with Et_3N) to afford the enol phosphate **4d** (0.14 g) in 63% yield.

8a with $Ph(CH)_2CHO$ and CH_2O was examined. The reactions proceeded as efficiently as those in the simple cases reported by Utimoto[12] to afford **9** and **10**, respectively (Scheme 2). Aldol **10** was then converted to exo enone **11** in good yield by a conventional method.[16] These experiments show that the steric hindrance derived from the bulky aryl group at the *β*-position did not diminish the reactivities of the enolates at the α-position or on the oxygen atom. Consequently, a variety of manipulations of enone **11** are possible for synthetic purposes.

Of the phosphates we examined, the synthesis of Δ[1]-*trans*-THC (**15**)[17] was best accomplished with enol phosphate **4b** (Scheme 3). Methylation[18] of **4b** with MeMgBr in the presence of $Ni(acac)_2$ afforded **12**, and subsequent exposure to EtSNa in DMF[19] resulted in deprotection of the TES group and one of the MeO groups to furnish **13**. Attempted one-step deprotection of the two MeO groups under more vigorous conditions was unsuccessful. Cyclization of **13** was carried out according to the procedure of Evans[20] in the presence of $MgSO_4$ to afford **14**[21] in 92% yield without migration of the double bond. Finally, deprotection of **14** with EtSNa afforded **15**, and its ^1H NMR spectrum was identical to the data reported.[8,20,22]

Scheme 3. Synthesis of *trans*-Δ[1]-THC[a]



[a] Reagents and conditions: (a) $Ni(acac)_2$, MeMgCl, THF, 90%; (b) EtSNa, DMF, 120 °C, 70%; (c) $ZnBr_2$, $MgSO_4$, CH_2Cl_2, 92%; (d) EtSNa, DMF, 120 °C, 45%.

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[18] (a) Hayashi, T.; Fujiwa, T.; Okamoto, Y.; Katsuro, Y.; Kumada, M. *Synthesis* **1981**, 1001−1003. (b) Sahlberg, C.; Quader, A.; Claesson, A. *Tetrahedron Lett.* **1983**, *24*, 5137−5138.

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[22] New compounds were characterized by ^1H NMR (300 MHz) and ^{13}C (75 MHz) spectroscopy.