$TiCl_4$−*n*-Bu_4NX (X = I, Br, and Cl) Combination-Induced Coupling of α,β-Unsaturated Ketones with Aldehydes

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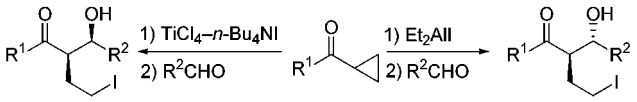
A three-component coupling reaction between vinyl ketones, aldehydes, and halides has been developed with $TiCl_4$−*n*-Bu_4NX combined reagents. Treatment of vinyl ketones with a $TiCl_4$−*n*-Bu_4NI combination followed by an addition of a variety of aldehydes provides *syn*-α-iodomethyl-β-hydroxy ketones with high stereoselectivity. Methyltriphenylphosphonium iodide as well as *n*-Bu_4NI acts efficiently as a halide source. The combination of $TiCl_4$−*n*-Bu_4NBr provides the corresponding bromo compounds in good yields. *syn*-α-Chloromethyl-β-hydroxy ketones are obtained with the $TiCl_4$−*n*-Bu_4NCl combination. A competitive experiment reveals that the order of relative reactivity of the combinations is $TiCl_4$−*n*-Bu_4NI > $TiCl_4$−*n*-Bu_4NBr > $TiCl_4$−*n*-Bu_4NCl.

Introduction

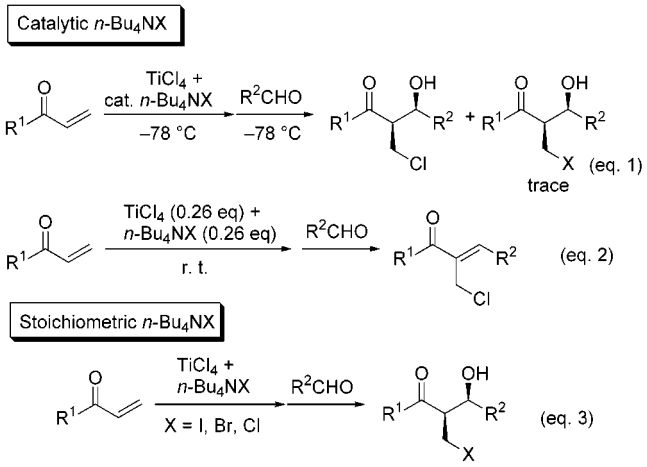
A multicomponent coupling reaction in one-pot promoted by various organometallic reagents represents a powerful means in organic synthesis.[1] It has been regarded as a highly convergent strategy to access complex molecules. Very recently, its divergent aspect has received increasing attention. A multicomponent coupling reaction serves as a key tool in constructing a library of series of compounds.[2]

We have recently reported that metal iodides induce a highly stereoselective three-component coupling reaction between cyclopropyl ketones, aldehydes, and iodide (Scheme 1).[3] Very recently, several research groups have independently reported Baylis−Hillman-type reactions using $TiCl_4$.[4,5] For example, Shi and co-workers have shown that $TiCl_4$ combined with 5 mol % of *n*-Bu_4NX (X = Br or I)[6] provided only chlorinated aldol-type adducts with no trace of the corresponding bromides or iodides (eq 1, Scheme 2). Li et al. have also reported that iodide was not incorporated in coupling products at all, when $TiCl_4$ was combined with 0.26 equiv of *n*-Bu_4NI (eq 2, Scheme 2). These reports surprised us because we had already observed incorporation of the corresponding halides in the aldol adducts by the use of a stoichiometric amount of quaternary ammonium salts (eq 3, Scheme 2).[7] To rationalize the discrepancy between the stoichiometric and catalytic reactions, we examined these reactions in detail.

Scheme 1



Scheme 2



Results and Discussion

(1) The Coupling of Vinyl Ketones with Aldehydes Promoted by the $TiCl_4$−*n*-Bu_4NI Combinations. Treatment of tetrabutylammonium iodide with

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(1) Hall, N. *Science* **1994**, *266*, 32. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.

(2) (a) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3169. (b) Tieze, L. F.; Evers, H.; Töpken, E. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 903.

(3) Han, Z.; Uehira, S.; Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2001**, *57*, 987.

(4) For $TiCl_4$−*n*-Bu_4NX combinations, see: (a) Shi, M.; Feng, Y.-S. *J. Org. Chem.* **2001**, *66*, 406. (b) Li, G.; Gao, J.; Wei, H.-X.; Enright, M. *Org. Lett.* **2000**, *2*, 617.

(5) (a) For a $TiCl_4$-mediated reaction without activators, see: Wei, H.-X.; Kim, S. H.; Caputo, T. D.; Purkiss, D. W.; Li, G. *Tetrahedron* **2000**, *56*, 2397. (b) For a $TiCl_4$-charcogenide combination, see: Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2358. (c) For a $TiCl_4$-*n*-Bu_3P combination, see: Shi, M.; Jiang, J.-K.; Cui, S.-C.; Feng, Y.-S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390.

(6) For $TiCl_4$−*n*-Bu_4NI-mediated reactions, see: (a) Taniguchi, M.; Hino, T.; Kishi, Y. *Tetrahedron Lett.* **1986**, *27*, 4767. (b) Yachi, K.; Maeda, K.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1997**, *38*, 5161. (c) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1999**, *40*, 8121. (d) Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2000**, *65*, 5066. See also ref 3.

(7) A part of this work has been reported as a communication. Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1383. This work was first reported at the 45th Symposium on Organometallic Chemistry, Japan, 1998. Uehira, S.; Shinokubo, H.; Oshima, K. *Abstracts of the 45th Symposium on Organometallic Chemistry*, Japan, Sep 14; Kinki Chemical Society: Osaka, 1998; p 344.

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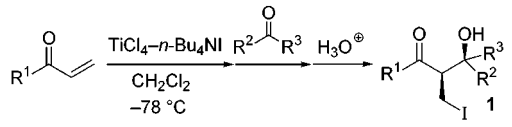
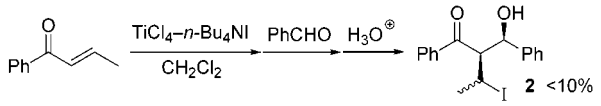
Table 1. Iodide-Induced Aldol Reaction of Vinyl Ketones[a]



R^1	R^2	R^3	product	yield (%)	selectivity (syn/anti)
Ph	Ph	H	**1a**	89	>99:1
Ph	*n*-C_4H_9	H	**1b**	73	>99:1
Ph	CH_3	H	**1c**	96	>99:1
Ph	*i*-Pr	H	**1d**	70	89:11[b]
Ph	Et_2CH	H	**1e**	79	96:4[b]
CH_3	Ph	H	**1f**	84	96:4[b]
CH_3	*n*-C_6H_{13}	H	**1g**	80	>99:1
CH_3	$-(CH_2)_5-$[c]		**1h**	70	

[a] Conditions: $TiCl_4$ (2.0 mmol), *n*-Bu_4NI (2.0 mmol), vinyl ketone (1.0 mmol), aldehyde (1.5 mmol), −78 °C. [b] Diastereomers are inseparable. [c] The reaction mixture was stirred for 4 h at −78 °C after the addition of cyclohexanone (1.5 mmol).

Scheme 3



$TiCl_4$ in dichloromethane at 0 °C provided a dark-red solution. To the resulting solution was added vinyl phenyl ketone at −78 °C. After 1 h, benzaldehyde was added, and the reaction mixture was stirred for another 2 h. Extractive workup afforded the syn aldol adduct **1a** in 89% yield. None of the anti adduct was detected in the crude reaction mixture. Results of the $TiCl_4$−*n*-Bu_4NI-induced aldol reaction with various aldehydes are summarized in Table 1. Both aromatic and aliphatic aldehydes were equally reactive and gave aldol adducts in good yields in this coupling reaction. For example, acetaldehyde afforded the syn adduct **1c** in 96% yield without contamination by the anti isomer. The use of methyl vinyl ketone in place of phenyl vinyl ketone also provided the desired aldol adducts in good yields.[8] Cyclohexanone could be converted into the corresponding aldol adduct **1h** in 70% yield.[9] Contrary to the report by Shi, no trace of chlorinated aldol adducts was observed. It is striking that the reaction with aldehydes went to completion within 2 h.[10] Unfortunately, the use of phenyl 1-propenyl ketone as an α,*β*-unsaturated ketone gave a disappointing result. The reaction was sluggish to afford the desired adduct **2** in low yield (ca. 10%) (Scheme 3).

Methyltriphenylphosphonium iodide instead of tetrabutylammonium iodide also acts efficiently as an iodide source. Thus, Ph_3MePI combined with $TiCl_4$ furnishes the iodo aldol adduct **1a** in 71% stereoselectively (Scheme 4). Me_4NI is not as effective as *n*-Bu_4NI because of its low solubility in CH_2Cl_2.

(2) Coupling of Vinyl Ketones with Aldehydes Promoted by the $TiCl_4$−*n*-Bu_4NX (X = Br or Cl) Combinations. The combination of $TiCl_4$−*n*-Bu_4NX (X = Br and Cl) was next investigated to clarify scope and limitation (Table 2). The use of *n*-Bu_4NBr instead of ammonium iodide yields the corresponding bromo aldol adducts **3** with high diastereoselectivity in moderate to good yields. Bromo adducts were relatively unstable, and careful workup and purification were required to prevent dehydration affording Baylis−Hilman-type products.[11] The $TiCl_4$−*n*-Bu_4NCl combined reagent also induced the similar coupling reaction. *o*-Nitrobenzaldehyde was an exceptionally good partner in the chloride-induced reaction. However, this reaction was not so efficient for the coupling with aliphatic aldehydes such as decanal. In this case, the simple chlorinated ketone, 2-chloroethyl methyl ketone, was obtained predominantly.

Scheme 4

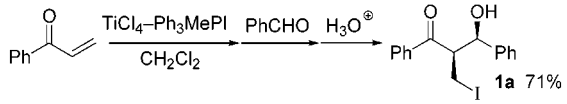
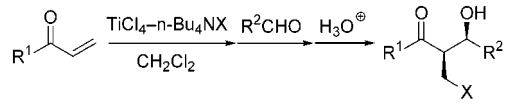


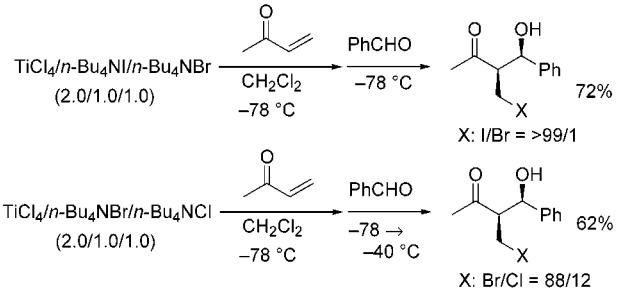
Table 2. $TiCl_4$−*n*-Bu_4NX-Induced Aldol Reaction[a]



R^1	R^2	X	product	yield (%)	selectivity (syn/anti)
Ph	*i*-Pr	Br	**3a**	60	>99:1
Ph	*n*-C_6H_{13}	Br	**3b**	66	>99:1
Ph	CH_3	Br	**3c**	68	>99:1
CH_3	Ph	Br	**3d**	90	>99:1
CH_3	Ph	Cl	**4a**	61	>99:1
CH_3	*o*-$NO_2C_6H_4$	Cl	**4b**	90	>99:1
CH_3	*n*-C_9H_{19}	Cl	**4c**	27	>99:1

[a] Conditions: $TiCl_4$ (2.0 mmol), *n*-Bu_4NX (2.0 mmol), vinyl ketone (1.0 mmol), aldehyde (1.5 mmol), −78 to −40 °C (X = Br) or −20 °C (X = Cl).

Scheme 5



(3) Competitive Reaction between $TiCl_4$−*n*-Bu_4NI, $TiCl_4$−*n*-Bu_4NBr, and $TiCl_4$−*n*-Bu_4NCl. To evaluate the nucleophilicity of the $TiCl_4$−*n*-Bu_4NX combinations, we have conducted competitive reactions as illustrated in Scheme 5. A mixed reagent containing iodide and bromide was prepared by mixing $TiCl_4$, *n*-Bu_4NI, and *n*-Bu_4NBr in a 2:1:1 ratio at 0 °C. The mixed reagent, $TiCl_4$−*n*-Bu_4NI/*n*-Bu_4NBr, furnished only the iodo aldol adduct in good yield. None of the corresponding bromo compound was observed in the crude reaction mixture. In a similar fashion, we compared the reactivity of bromide with that of chloride. The bromo aldol adduct was obtained predominantly with the mixed reagent, $TiCl_4$−*n*-Bu_4NBr/*n*-Bu_4NBCl. On the basis of this obser-

(8) The aldol adducts from phenyl vinyl ketone were more stable than the corresponding methyl ketone derivatives, which required careful workup and purification to prevent dehydration affording Baylis−Hilman-type products. Methyl ketones **1f**, **1g**, and **1h** were not suitable for the elemental analysis. The reduction products with *n*-Bu_3SnH were identical with authentic samples.

(9) Unfortunately, acetophenone and cycloheptanone did not afford the desired aldol adducts.

(10) The reaction reported by Shi et al. requires a much longer reaction period (at least 24 h).[4a]

(11) Bromo ketones **3a**, **3b**, and **3d** were not suitable for the elemental analysis. The reduction products with *n*-Bu_3SnH were identical with authentic samples.

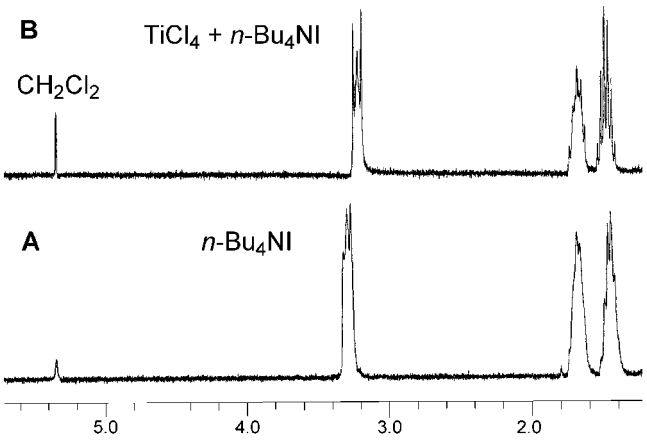


Figure 1. ^{1}H NMR spectrum of (A) n-Bu_4NI and (B) $TiCl_4$ + n-Bu_4NI in CD_2Cl_2 at room temperature.

vation, the order of the relative nucleophilic reactivity of three combinations proved to be $TiCl_4$−n-Bu_4NI > $TiCl_4$−n-Bu_4NBr > $TiCl_4$−n-Bu_4NCl. This order is in good agreement with the general trend of the reactivity of halide ions in usual nucleophilic substitution reactions.

(4) ^{1}H NMR Study on the Enolate Formation from Vinyl Ketones with the $TiCl_4$/n-Bu_4NI Combination. We have assumed the formation of a titanium enolate as an intermediate in this aldol-type coupling reaction.[6] To ascertain the existence of the enolate species, we have carried out spectroscopic study by ^{1}H NMR.

An addition of $TiCl_4$ to a solution of n-Bu_4NI in CD_2Cl_2 caused a slight upfield shift of α-methylene protons of n-Bu_4NI (Figure 1). When methyl vinyl ketone was added to the $TiCl_4$−n-Bu_4NI solution, new signals were detected around δ 4.0−4.2 and the signals of methyl vinyl ketone disappeared (Figure 2, B). Upon quenching this NMR sample with a small amount of water, a triplet (δ = 3.8), which was assigned to methylene protons of 2-iodoethyl methyl ketone, appeared with concurrent disappearance of the signals around δ 4.0−4.2. The absence of olefinic protons indicates that none of methyl vinyl ketone coordinated by titanium exists in the reaction mixture. On the basis of these facts, we have assigned the signals around δ 4.0−4.2 to a vinylic proton of titanium enolate species.[12]

(5) Mechanistic Considerations. ^{1}H NMR study has elucidated the formation of a titanium enolate as an intermediate. Consequently, we propose the following reaction mechanism involving the conjugate addition of titanium iodide species[13] toward α,β-enones for the stoichiometric reaction (Scheme 6). If one takes account of the order of relative reactivity ($TiCl_4$−n-Bu_4NI > $TiCl_4$−n-Bu_4NBr > $TiCl_4$−n-Bu_4NCl), which we have discussed above, it is paradoxical that none of iodide is incorporated in the products in the catalytic reactions. One difference between Shi's procedure and ours is the order of the addition of aldehydes and enones. We added enones to $TiCl_4$−n-Bu_4NX to prepare titanium enolates, while aldehydes were added prior to enones in Shi's procedure. Aldehydes can react with $TiCl_4$−n-Bu_4NX to

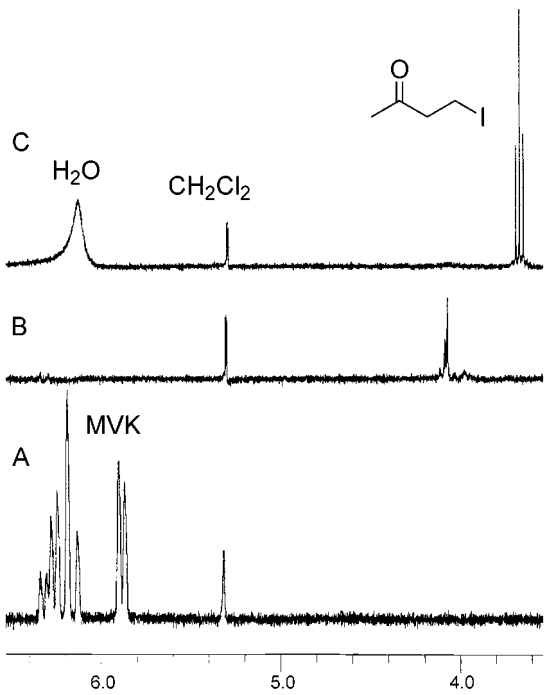
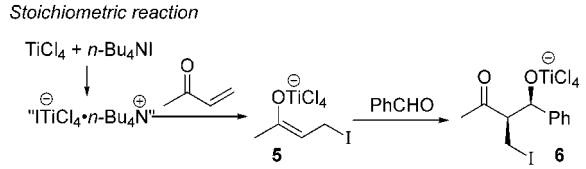
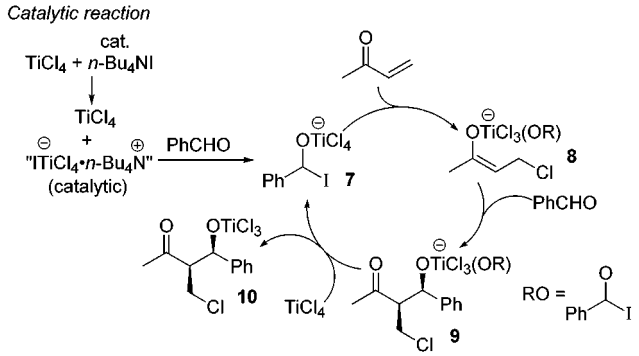


Figure 2. ^{1}H NMR spectra of (A) methyl vinyl ketone, (B) methyl vinyl ketone + $TiCl_4$−n-Bu_4NI, and (C) water + methyl vinyl ketone +$TiCl_4$−n-Bu_4NI in CD_2Cl_2 at room temperature.

Scheme 6



Scheme 7



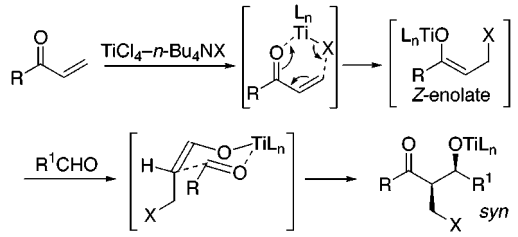
yield α-haloalkoxytitanium species **7**,[14] and it is likely that this reaction scavenges the more reactive (and catalytic) halide preferentially. Therefore, we speculate the reaction mechanism for the catalytic reaction as depicted in Scheme 7. α-Haloalkoxytitanium species **7** bearing nucleophilic chlorides on titanium acts as a chlorinating reagent of enones to provide the chloro titanium enolate **8**. The titanium enolate **8** then reacts with an aldehyde giving the aldol adduct **9**, which

(12) Judging from the complexity of the signals around δ 4.0−4.2, the titanium enolate would consist of several species in which halogen ligands coordinate to titanium in different modes.

(13) We speculate formation of an iodotitanate complex from $TiCl_4$ and n-Bu_4NI. However, we have no evidence at present.

(14) For the reaction of titanium ate complexes with aldehydes to provide titanium alkoxides, see: (a) Reetz, M. T.; Peter, R. *J. Chem. Soc., Chem. Commun.* **1983**, 406. (b) Reetz, M. T.; Wenderoth, B. *Tetrahedron Lett.* **1982**, *23*, 5259. (c) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber.* **1985**, *118*, 1421.

Scheme 8



regenerates α-haloalkoxytitanium species **7** upon the reaction with $TiCl_4$.

The selective generation of syn isomers can be explained as follows (Scheme 8): The conjugate addition of Ti−X species toward vinyl ketones of s-cis conformation provides *Z*-enolates stereoselectively. The subsequent aldol reaction of (*Z*)-titanium enolate with aldehydes proceeds through a rigid six-membered transition state to afford syn adducts.

Conclusion

A coupling reaction between vinyl ketones and aldehydes has been achieved with $TiCl_4$−*n*-Bu_4NX combined reagents. Treatment of vinyl ketones with $TiCl_4$−*n*-Bu_4-NX combinations followed by an addition of a variety of aldehydes provides *syn*-α-halomethyl-*β*-hydroxy ketones with high stereoselectivity. Our procedure requires the use of a stoichiometric amount of quaternary ammonium halide salts. However, it is beneficial that the reaction with this procedure proceeds significantly faster and provides the aldol adducts in better yields compared to the reaction with a catalytic amount *n*-Bu_4NX. The order of the relative nucleophilicity of the combined reagents is found to be $TiCl_4$−*n*-Bu_4NI > $TiCl_4$−*n*-Bu_4-NBr > $TiCl_4$−*n*-Bu_4NCl on the basis of competitive experiments.

Experimental Section

Instrumentation and Materials. ^1H NMR (300 MHz) and ^{13}C NMR (75.3 MHz) spectra were taken on a Varian GEMINI 300 spectrometer in $CDCl_3$ as solvent, and chemical shifts were given in δ with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. TLC analyses were performed on commercial glass plates bearing 0.25 mm layer of Merk silica gel $60F_{254}$. Column chromatography was done with silica gel (Wakogel 200 mesh). The analyses were carried out at the Elemental Analysis Center of Kyoto University. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification; however, aldehydes and methyl vinyl ketone were distilled and stocked under argon. Dichloromethane was dried with molecular sieves 4A.

General Procedure for the Coupling between Vinyl Ketones and Aldehydes with $TiCl_4$−*n*-Bu_4NI. To a solution of $TiCl_4$ (2.0 mL, 1.0 M solution in CH_2Cl_2, 2.0 mmol) in CH_2Cl_2 (5 mL) was added a solution of *n*-Bu_4NI (739 mg, 2.0 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After being stirred for 10 min at 0 °C, a resulting dark red solution was cooled to −78 °C, and a solution of phenyl vinyl ketone (132 mg, 1.0 mmol) in CH_2Cl_2 (2.0 mL) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C, and benzaldehyde (0.15 mL, 1.5 mmol) was introduced via a syringe. After being stirred for 2 h at −78 °C, the whole mixture was poured into saturated aqueous ammonium chloride. The mixture was extracted with hexane, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Concentration under reduced pressure and purification afforded 3-hydroxy-2-iodomethyl-1,3-diphenylpropan-1-one (**1a**, 326 mg) in 89% yield.

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Supporting Information Available: General procedures and spectral data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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