JOC*Note*

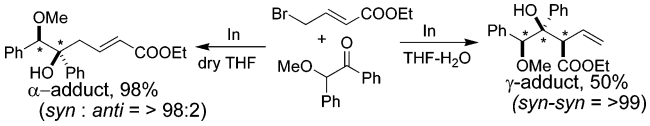
Diastereoselective Production of Homoallylic Alcohols Bearing Quaternary Centers from γ-Substituted Allylic Indiums and Ketones

Srinivasarao Arulananda Babu, Makoto Yasuda, and Akio Baba*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan

baba@chem.eng.osaka-u.ac.jp

Received August 29, 2007



Highly stereoselective In-employed addition of γ-substituted allylic halides (cyclohexenyl halides, cinnamyl halides, and ethyl 4-bromocrotonate) to ketones is established to produce homoallyl alcohols bearing quaternary centers. The reactivity patterns and relative stability of allylic indiums were studied. The addition of water characteristically affected the reactions. Cyclohexenyl indium addition was completely disturbed, but a clear reaction was observed in the cinnamyl and crotonate-indium addition. In the case of ethyl 4-bromocrotonate, an interesting conversion of a γ-adduct into an α-adduct was observed in anhydrous conditions.

The C−C bond-forming reactions between carbonyl compounds and allylic metals are one of the outstanding processes.[1,2] In this line, the diastereoselective addition of the γ-substituted allylic metals to aldehydes has been extensively studied. The addition with ketones is a promising protocol for the stereoselective construction of quaternary centers; however, there exist only a few exceptional methods in this regard.[1−3] This is perhaps because of (a) the lower reactivity of ketones than aldehydes[4] and (b) smaller difference in steric demand between two substituents on the carbonyl carbon of ketones than that of aldehydes. We have reported the highly diastereoselective additions of the γ-substituted allylic tin(II) species generated in situ with simple ketones.[3a] Recently, during the course of our investigations, the preparation of γ-substituted allylic zinc as well as its reaction with ketone appeared.[3b] Notably, in these versatile methods (e.g., tin,[3a] zinc,[3b,c] and Grignard[3d]) there is a need for the prior preparation of allylic metal reagents before their reactions with ketones.

In recent years, the In-mediated allylations[5a] of carbonyl compounds have attracted many synthetic chemists[5] because this protocol has the advantage that the direct use of In and allylic halides in the allylations of carbonyl compounds is highly possible, thereby skipping the prior preparation of allylic indiums. The utility of unsubstituted allyl halides was well-studied even in aqueous conditions,[5−7] but the employment of γ-substituted allylic halides is often limited to reactions with aldehydes.[5−7] Hence, it remains a challenging task that the direct stereoselective addition of γ-substituted allylic halides to simple ketones needs to be established.

In recent years, we have been involved on the establishment of metal-employed diastereoselective reactions of simple ketones.[3a,8a−d] Thus, herein we report an efficient stereo- and regio-controlled production of homoallyl alcohols bearing quaternary centers from the direct reaction of the γ-substituted allylic halides, ketones, and In, in which plausibly, a highly reactive RIn(I) species is generated and the addition of water crucially controls the outcome of the stereoselection.

Reactions with Cyclohexenyl Halides. Primarily, the optimization of the In-mediated direct reactions of cyclohexenyl halides and 4-chloroacetophenone (**1a**) was carried out. Smooth

(1) (a) *Comprehensive Organic Syntheses*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 2. (b) *Comprehensive Organic Syntheses*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 1. (c) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (d) Denmark S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (e) Hall, D. G. *Synlett* **2007**, 1644.

(2) (a) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 10. (b) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 11.

(3) For stereoselective additions to simple ketones, see: (a) Using tin-based reagents see: Yasuda, M.; Hirata, K.; Nishino, M.; Yamamoto, A.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13442 and see references cited therein. (b) For a zinc version (allylic zincs were prepared from Zn (5 equiv), LiCl (1.2 equiv), and allyl halides (1 equiv)) see: Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 5376. (c) In another Zn version, using a pre-prepared dry Zn, a mixture of both γ-adduct and α-adduct with a moderate to very good selectivity was observed for aldehydes and ketones, and the stereochemistry assignment of the γ-adducts was not established due to their decomposition. And only a pre-prepared Zn−Cu couple under acidic condition afforded the α-adducts, see: Rice, L. E.; Boston, M. C.; Finklea, H. O.; Suder, B. J.; Frazier, J. O.; Hudlicky, T. *J. Org. Chem.* **1984**, *49*, 1845. (d) A cinnamyl Grignard reagent with acetophenone gave a modest selectivity (ds 70:30), see ref 3a. (e) Tietze, L F.; Kinzel, T.; Schmatz, S. *J. Am. Chem. Soc.* **2006**, *128*, 11483. (f) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (g) Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 14556.

(4) (a) Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445. (b) Yasuda, M.; Kitahara, N.; Fujibayashi, T.; Baba, A. *Chem. Lett.* **1998**, 743. (c) Casolari, S.; D'Addario, D.; Tagliavini, E. *Org. Lett.* **1999**, *1*, 1061.

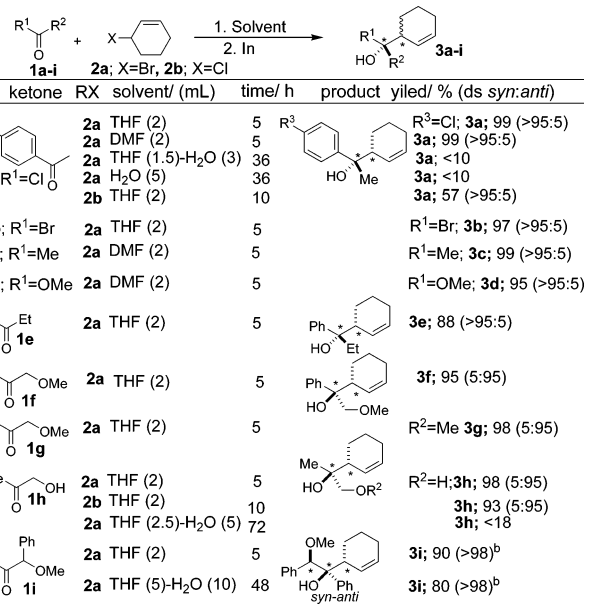
(5) (a) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831. (b) Peppe, C. *Curr. Org. Synth.* **2004**, *1*, 227. (c) Araki, S.; Hirashita, T. *Main Group Met. Org. Synth.* **2004**, *1*, 323. (d) Frost, C. G.; Hartley, J. P. *Mini-Rev. Org. Chem.* **2004**, *1*, 1. (e) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959. (f) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (g) Marshall, J. A. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 1, p 453. (h) Ranu, B C. *Eur. J. Org. Chem.* **2000**, 2347. (i) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16. (j) Cintas, P. *Synlett* **1995**, 1087. (k) Loh, T.-P. *Sci. Synth.* **2004**, *7*, 413.

(6) For some innovative reports on In-mediated diastereoselective allylations with unsubstituted allyl halides, see: (a) Lobben, P. C.; Paquette, L. A. *J. Org. Chem.* **1998**, *63*, 6990. (b) Paquette, L. A.; Bennett, G. D.; Isaac, M. B.; Chhatriwala, A. *J. Org. Chem.* **1998**, *63*, 1836. (c) Paquette, L. A.; Lobben, P. C. *J. Org. Chem.* **1998**, *63*, 5604. (d) Paquette, L. A.; Rothhaar, R. R. *J. Org. Chem.* **1999**, *64*, 217.

(7) (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (b) Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017. (c) Chan, T. H.; Li, C.-J.; Lee, M. C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181. (d) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228. (e) Miao, W.; Chung, L. W.; Wu, Y.-D.; Chan, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 13326. (f) Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958. (g) Isomers and their ratio could not be precisely determined.

10.1021/jo701899j CCC: $37.00
Published on Web 11/29/2007

TABLE 1. Stereoselective Addition of 2a,b with Ketones[a]



entry	ketone	RX	solvent/ (mL)	time/ h	product	yiled/ % (ds *syn*:*anti*)
1		**2a**	THF (2)	5		R^3=Cl; **3a;** 99 (>95:5)
2		**2a**	DMF (2)	5		**3a;** 99 (>95:5)
3		**2a**	THF (1.5)-H_2O (3)	36		**3a**; <10
4	**1a**; R^1=Cl	**2a**	H_2O (5)	36		**3a;** <10
5		**2b**	THF (2)	10		**3a;** 57 (>95:5)
6	**1b**; R^1=Br	**2a**	THF (2)	5		R^1=Br; **3b;** 97 (>95:5)
7	**1c**; R^1=Me	**2a**	DMF (2)	5		R^1=Me; **3c;** 99 (>95:5)
8	**1d**; R^1=OMe	**2a**	DMF (2)	5		R^1=OMe; **3d;** 95 (>95:5)
9	**1e**	**2a**	THF (2)	5		**3e;** 88 (>95:5)
10	**1f**	**2a**	THF (2)	5		**3f;** 95 (5:95)
11	**1g**	**2a**	THF (2)	5		R^2=Me **3g;** 98 (5:95)
12	**1h**	**2a**	THF (2)	5		R^2=H;**3h;** 98 (5:95)
13		**2b**	THF (2)	10		**3h;** 93 (5:95)
14		**2a**	THF (2.5)-H_2O (5)	72		**3h;** <18
15	**1i**	**2a**	THF (2)	5		**3i;** 90 (>98)[b]
16		**2a**	THF (5)-H_2O (10)	48	*syn-anti*	**3i;** 80 (>98)[b]

[a] In (1.2 mmol), ketone **1** (1 mmol) and halide **2a** (2−2.5 mmol) or **2b** (1.7 mmol) were used. [b] Single isomer was obtained.

reactions in THF or DMF furnished the *syn* isomer **3a** with a quaternary center (yield 99% and ds >95, entries 1 and 2, Table 1). The reactions in (presence of) water strongly disturbed the formation of the product **3a** (entries 3 and 4). The reactions of analogous ketones **1b**−**e** with cyclohexenyl bromide (**2a)** were also afforded the respective *syn* isomers **3b**−**e** (entries 6−9). Employing the cyclohexenyl chloride (**2b)** also afforded the *syn* isomer **3a** in a moderate yield (entry 5).

Next, the treatment of 2-methoxyacetophenone (**1f**) with **2a** gave the *anti* isomer **3f** (95%) in THF (entry 10). Similarly, 2-methoxyacetone (**1g**) and 2-hydroxyacetone (**1h**) were afforded the *anti* isomers **3g** and **3h** bearing a quaternary center (entries 11 and 12). The reaction of **2b** with **1h** was also afforded the *anti* isomer **3h** (93%, entry 13). Benzoin methyl ether (**1i**) also smoothly afforded the single product **3i** (90%, *syn-anti* ds >98, entry 15) with three contiguous stereogenic centers. The stereochemistries of the *syn* isomers **3a**−**e** could be proposed via the chair-type TS involving a *Z*-allylic In (model A, Scheme 1). The stereochemistries of the *anti* isomers **3f**−**h** and the *syn-anti* isomer **3i**[8b,e] could be proposed via a chelation-type TS[9] (model B). The presence of water apparently suppressed the allylations (entries 3, 4, and 14). An exceptional formation of the product **3i** in a longer reaction period was plausibly due to the strong acceleration by the chelation and electron-withdrawing effect of OMe moiety (entry 16).

SCHEME 1. Plausible Transition States

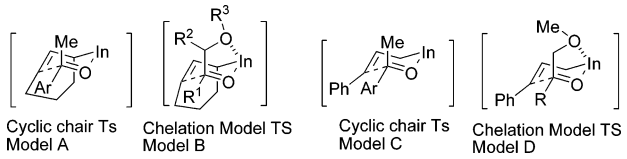
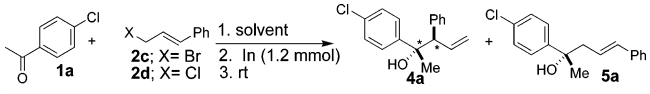


TABLE 2. Optimization of Cinnamyl Halides with 1a[a]



entry	**2c**/ mmol	time/ h	solvent (mL)	**4a**; yield/% (ds *syn*:*anti*)
1	2	5	THF (2)	37 (mixture of isomers)[b]
2	2	12	DMF (2)	68 (mixture of isomers)[b]
3	1	24	THF (5)−H_2O (10)	39 (2:98)
4	2	24	THF (10)−H_2O (5)	50 (2:98)
5	3	24	THF (5)−H_2O (10)	95 (2:98)

[a] Ketone **1a** (1 mol) was used. [b] A complex mixture was formed and the ratio could not be precisely determined including **5a**.

TABLE 3. Stereoselective Addition of 2c,d,e to Ketones[a]

entry	ketone	RX	metal	solvent/ (mL)	time/ h	yield/ % (ds *syn*:*anti*)
1		**2c**	In	THF (5)-H_2O (10)	30	R^1= H, **4b**; 99 (2:98)
2		**2c**	In	THF (5)-H_2O (10)	30	R^1= Br, **4c**; 99 (2:98)
3	**1j**; R^1=H,**1b**;R^1=Br **1d**; R^1= OMe	**2c**	In	THF (5)-H_2O (10)	30	R^1= OMe, **4d**; <10
4		**2c**	In	THF (2)-H_2O (5)	16	**4e**; 95 (>98:2)
5	**1f**	**2d**	In	THF (2)-H_2O (5)	12	**4e**; 85 (>98:2)
6		**2d**	Zn	THF (2)-H_2O (5)	12	**4e**; <10
7	**1g**	**2c**	In	THF (2)-H_2O (5)	15	**4f**; 90 (>98:2)
8	**1k**	**2c**	In	THF (2)-H_2O (5)	12	**4g**; 85 (>98:2)
9		**2c**	In	THF (2)-H_2O (5)	15	**4h**; 80 (>98:2)
10	**1h**	**2d**	In	THF (2)-H_2O (5)	12	**4h**; 70 (>95:5)
11		**2d**	Zn	THF (2)-H_2O (5)	12	**4h**; <20 (mixture)
12	**1a** + **2e**		In	THF (3.5)-H_2O (7)	19	4-Cl-C_6H_5, **4i**; 87 (85:15)

[a] All the reactions were carried out with ln (1.2 mmol), ketone (1 mmol), and **2c**/**2d**/**2e** (2−2.5 mmol) at rt. **2e** *E*/*Z* ratio 85:15.

Reactions with Cinnamyl Halides (*E*-geometry). In contrast to the cyclohexenyl halides (*Z*-geometry), the addition of water was required for the clear reaction of cinnamyl halides (**2c**,**d)** with ketones. The reactions in dry THF or DMF gave only a complicated mixture with low selectivity (entries 1 and 2, Table 2). Other solvents such as 1,4-dioxane, MeCN, toluene, DCM, MeOH, and water were ineffective (<5−10% yields). Fortunately, the combination of THF and water was found to promote the selective formation of the *anti* isomer **4a** bearing a quaternary center (39% ds >98:2, entry 3). A further optimized condition gave the desired product **4a** with high diastereoselectivity, in which an excess of allylic species **2c** was required (95% yield and ds 98:2, entry 5).

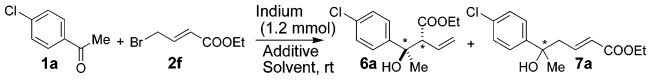
Next, the scope of these aquatic reactions was tested with various simple ketones and hydroxy/alkoxy ketones, using **2c**,**d** (Table 3). Aryl alkyl ketones such as **1b**,**j** afforded the *anti* stereoisomers **4b**,**c** in very good yields (entries 1 and 2). However, the aromatic ketone **1d** having an electron-donating group (OMe) failed to furnish the product perhaps due to a low electrophilicity (entry 3).

2-Methoxy and 2-hydroxy ketones (**1f**−**h**,**k**) were reacted with cinnamyl bromide (**2c**) and chloride (**2d)** to furnish the

(8) For our aimed studies on the stereoselective metal-employed additions to ketones, see: (a) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *J. Org. Chem.* **2005**, *70*, 10408. (b) Babu, S. A.; Yasuda, M.; Okabe, Y.; Shibata, I.; Baba, A. *Org. Lett.* **2006**, *8*, 3029 and references cited therein. (c) Yasuda, M.; Okamoto, K.; Sako, T.; Baba, A. *Chem. Commun.* **2001**, 157. (d) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4475. (e) The stereochemistry of the product **3i** was unambiguously established from X-ray analysis. (f) During our comprehensive investigations on the In-based stereoselective additions of the substituted allylic halides to simple ketones and alkoxy/hydroxy ketones, recently, a partial report with few examples limited to benzoin and cinnamyl bromide appeared; Kumar, S.; Kaur, P.; Mittal, A.; Singh, P. *Tetrahedron* **2006**, *62*, 4018. (g) The stereochemistries of **6e** (*syn* isomer) and **6g** (*syn-syn* isomer, from benzoinmethyl ether **1i**) were unambiguously determined from the X-ray structure analyses. For an analogue compound obtained from the reaction of benzoin and cinnamyl bromide (*E*-geometry), a *syn-anti* stereochemistry was proposed, see ref 8f.

(9) (a) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (b) Sato, K.; Kira, M.; Sakurai, H. *J. Am. Chem. Soc.* **1989**, *111*, 6429.

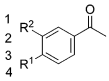
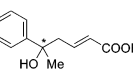
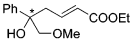
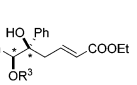
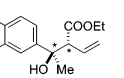
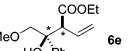
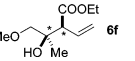
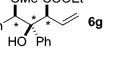
TABLE 4. Optimization of the Reaction of 1a with 2f[a]



entry	solvent (mL)	additive (mmol)	time/ h	**6a**; yield/ % (ds)	**7a**; yield/%
1	THF (5)−H_2O (10)		45	<5	0
2	THF (2)	H_2O (1.2)	17	<10	0
3	THF (2)	^{t}BuOH (1.2)	48	<5	30
4	THF (2)		0.5	50 (90:10)	0
5	THF (2)		4	40 (90:10)	<5
6	THF (2)		8	<5 (−)	64
7	THF (2)		17	0	>95
8	THF (2)	-	2	<5	50[b]

[a] **1a** (1 mmol) and **2f** (1.7 mmol) were used. [b] Reflux temperature.

TABLE 5. Stereoselective Syntheses of α/γ-Adducts from 2f[a,c]

entry	ketone	solvnet/ (mL)	time/ h	product	yield/ % (ds)
1	 **1j**;R^1= H;R^2=H	THF (2)	58		**7b**;R^1 = H; R^2 = H; 79
2	**1b**;R^1=Br;R^2=H		40		**7c**;R^1 = Br; R^2 = H; 98
3	**1c**;R^1=Me;R^2=H		48		**7d**;R^1 =Me; R^2 = H; 85
4	**1l**;R^1=H;R^2=Br		58		**7e**;R^1 =H; R^2 = Br; 75
5	 **1f**	THF (2)	20		**7f**; 99 (95)[b]
6			5		**7f**; 67
7	 **1i**;R^3= Me	THF (2)	5		**7g**; R^3=Me;98 (98:2)
8	**1m**;R^3=Et		5		**7h**; R^3=Et;98 (98:2)
9	**1n**;R^3=^{i}Pr		5		**7i**; R^3=^{i}Pr;70 (85:15)
10	**1o**;R^3=^{t}Bu		5		**7j**; R^3=^{t}Bu;70 (85:15)
11	 **1j**;R^1= H;R^2=H	THF (2)	0.5		**6b**;R^1=H,R^2=H;50 (90:10)
12	**1b**;R^1= Br;R^2=H		0.5		**6c**;R^1=Br,R^2=H;50 (90:10)
13	**1p**;R^1=F;R^2=Br		0.5		**6d**;R^1=F,R^2=Br;50 (90:10)
14	 **1f**	THF (2)	0.5	 **6e**	85 (67:33)[d]
15		THF (2):H_2O (5)	50		75 (>99:1)[e]
16		MeOH	6.5		62 (99:1)
17		THF (2):H_2O (5)	50		0[f]
18	 **1g**	THF (4):H_2O (10)	48	 **6f**	80 (>99:1)[g]
19	 **1i**	THF (2):H_2O (5)	65	 **6g**	50 (>99)[e]
20		THF (2):H_2O (5)	65		0[f]

[a] Ketone (1 mmol), halide **2f** (1.7 mmol), and In (1.2 mmol) were used at rt. [b] Refluxed for 2 h. [c] Runs 1−13 were carried out in THF. [d] See ref 7g. [e] **2f** (2 mmol) and In (1.5 mmol) were used. [f] Zn (1.5 mmol) was used instead of In. [g] **1g** (2 mmol), **2f** (4 mmol), and In (3 mmol) were used.

corresponding *syn* isomers in high yields and selectivities. Crotyl bromide (**2e** *E*/*Z* ratio 85:15) also afforded the *syn* isomer **4i**[3a] (87%, entry 12). In contrast, using Zn under similar conditions failed to afford **4e** (entry 6), perhaps because of the instability of the generated allyl zinc species in aqueous conditions. The stereochemistries obtained here strongly indicated that the involvement of a cyclic chair TS (model C) and chelation TS (model D, derived from *E*-geometry of cinnamyl indium) is highly possible even in aqueous conditions similar to the nonaqueous Sn or Zn systems.[3a,b]

Reactions with Ethyl 4-Bromocrotonate (functionalized). Next, a functionalized allylic halide ethyl 4-bromocrotonate (**2f**) having *E*-geometry was employed. At first the optimization of the reaction conditions was performed. Surprisingly, unlike the cinnamyl halides, even a small amount of water or alcohol strongly depressed the reaction (entries 1−3, Table 4). The reaction in anhydrous THF at rt for 30 min furnished the γ-adduct **6a** (*anti* isomer) bearing a quaternary carbon (50%, ds 90:10, entry 4). In 4 h, a small amount of the α-adduct **7a** (5%) was accompanied by **6a** (40%, entry 5). Further prolongation of the reaction time for 17 h afforded the α-adduct **7a**, regioselectively, in excellent yield (95%, entry 7). An attempt to accelerate the reaction by refluxing for 2 h resulted in 50% yield of **7a**. Notably, to the best of our knowledge except for some rare reports with aldehydes,[7f] there exists no report for the direct In-mediated production of α-adducts from simple ketones.[5−7]

Now, we were focused on producing various α-adducts. Unactivated simple ketones **1b**,**c**,**j**,***l*** furnished the respective α-adducts **7b**−**e** in a longer reaction period at rt (Table 5). In contrast, the ketones **1f**,**i** and **1m**−**o** which are activated by the α-alkoxy moieties required a shorter reaction period to produce the corresponding α-adducts (entries 5−10). The reactions of benzoin alkyl ethers **1i**,**m**−**o** with **2f** successfully gave the stereoselective α-adducts **7g**−**j** (*syn*, entries 7−10). The stereochemistry of the products **7g**−**j** was assigned from the X-ray structure analysis of **7g**.

Subsequently, we also investigated the formation of various γ-adducts. In the case of the reactions involving simple ketones **1b**,**j**,**p**, quenching treatment with water in 30 min was the best condition to give 50% yields of the *anti* isomers (entries 11−13). However, 2-methoxy acetophenone (**1f**) gave a complicated mixture including a small amount of α-adduct and *syn*/*anti* isomers of the γ-adduct (85%, *syn*/*anti* = 60/40, α/γ = 1:2)[7g] even when quenching the reaction in 30 min (entry 14). This result indicated a fast transformation from an γ- into an α-adduct and the presence of an equilibrium reaction route.

Fortunately, the reactions of 2-methoxy ketones (**1f**,**g**) with **2f** in MeOH or THF−H_2O solvent exclusively afforded the γ-adducts **6e** and **6f** bearing a quaternary carbon with high *syn* stereoselectivity (ds >99:1, entries 15, 16, and 18).[8g] Next, the reaction of benzoinmethyl ether **1i** and **2f** in THF−H_2O went smoothly to afford the stereoselective γ-adduct **6g**[8g] with three stereocenters (*syn*-*syn* ds >99, entry 19). Employing Zn instead of In did not promote the addition in any way in aqueous conditions (entries 17 and 20), perhaps because the allyl In species tolerated the aqueous condition very well though the reactivity was considerably decreased.

Mechanism of the Conversion of γ-Adduct into α-Adduct.[10a] To a solution of ethyl 4-bromocrotonate (**2f**) in THF-d_8 was added In with vigorous stirring for 3.5 h at rt. The ^{1}H NMR spectrum revealed the formation of two new In species: species [a] (doublets at δ 1.98 (J = 9.6 Hz) and 5.46 (J = 15.6 Hz)) and species [b] (doublets at δ 2.18 (J = 9.6 Hz) and 5.59 (J = 15.6 Hz)) with other minor peaks (Figure 1, A). Addition of ketone **1a** to this solution revealed the disappearance of species [a] in 2 min (Figure 1, B). Species [b] remained even after 30 min (Figure 1, C) and then slowly disappeared. At this stage it is notable that the initial formation of the transient In intermediate of the γ-adduct took place (**11**, Scheme 2). After 20 h, the transient In intermediate of the α-adduct appeared ((**12**, Figure 1, D), spectrum E corresponds to the α-adduct **7a** after workup).

(10) (a) See SI, for full ^{1}H NMR spectral region. (b) In the case of cinnamyl bromide with In also a facile formation of two species in THF-d_8−D_2O was observed, which indicated that the γ-substituted allyl In species are also stable in aqueous condition. They would be RIn(I) and RIn(III)-type species as already discussed in refs 7d and 8a−c. Based on the observed astonishing diastereoselectivities and strong chelation as the key point; plausibly, a low-valent RIn(I)-type transient species could be projected as very reactive intermediate, see SI. (c) As noted in ref 3c about the instability of products in column purification, in our case, the homoallyl alcohols **7g**−**j**/**6a**−**g** were stable even after several months. But the products **7a**−**f** were slowly decomposed after several months. We unambiguously assigned the stereochemistry of the γ-adducts **6a**−**g**/**7g**−**j**, see SI.

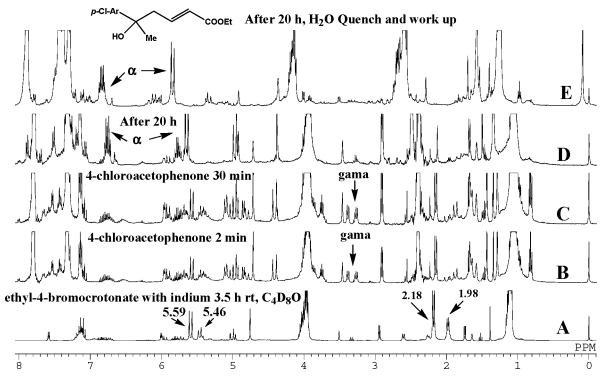
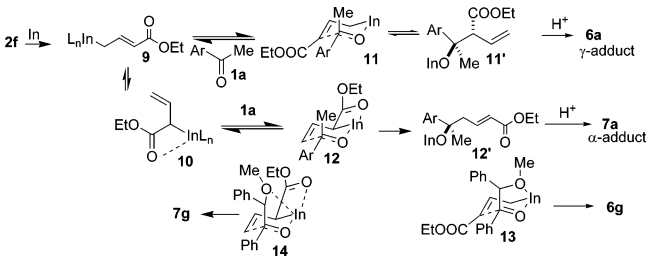


FIGURE 1. ^{1}H NMR study; conversion of γ- into α-adduct.[10a]

SCHEME 2. Mechanism: Conversion of γ- into α-Adduct



This process clearly indicated that an initially formed kinetically favored γ-adduct intermediate is converting into the thermodynamically favored α-adduct in a nonprotogenic solvent.

On the basis of these results, a plausible reaction path is shown in Scheme 2. At first, an allyl In species **9** is generated that reacts with a ketone via TS **11** to give transient γ-adduct **11′**, which gave **6a** when the reaction was quenched spontaneously or performed in water. In the absence of water and longer reaction time, the reaction leads to a thermodynamically favored transient α-adduct **12′**, thus giving **7a**.

The transformation of a γ-adduct into an α-adduct was observed only in the case of ethyl 4-bromocrotonate. This is perhaps because of the intramolecular coordination from the ester moiety to In center, which would well accelerate the formation of an allylic In-type **10** by a retro-reaction under thermodynamic equilibrium. As a result, various α-adducts could be very effectively produced in the case of ethyl 4-bromocrotonate rather than cinnamyl-type halides which are not having such functional moieties. Notably, the ^{1}H NMR spectra A and D also revealed an initial formation and the involvement of two *E*-types of transient In species **9** (J = 15.6 Hz corresponds to the olefin proton of **9** and **7a**). They would be RIn(I)- and RIn(III)-type species as already discussed in the case of In enolates and the former might be a very reactive species.[8a−c,10b] However, an isomeric allylic intermediate **10** could not be detected.

The stereochemistry of isomers **6a**−**d** (*anti*) could be proposed through the chair-type TS **11**. The formation of *syn* α-adducts **7g**−**j** could be explained via the bicyclic chelation TS **14** having an In-centered three-oxygen coordination.[8b,9] Similarly, the bicyclic chelation TS **13** could be proposed for the γ-adducts **6e**,**f** (*syn*) and **6g** (*syn-syn*).[10c]

Plausibly, allylic In species that are employed here are tolerant to water, because even in a longer reaction period the allylation of ketones took place in aqueous conditions. Apparently, the reactions in (the presence of) water suppressed (decelerate) the reactivity of allylic indiums toward ketones. Characteristically, un-activated and activated ketones behaved in slightly contrasting manners. But, it is apparent that once allylic In species slowly reacted with ketones, the resulting transient In alkoxides were immediately hydrolyzed (trapped) to furnish γ-adducts successively.

In summary, we have established an expedient and direct method of In-employed regio- and diastereoselective addition of γ-substituted allylic halides to ketones for the production of homoallylic alcohols bearing quaternary centers.

Experimental Section

Representative Procedure: Preparation of 6a/7a. To a flame-dried flask were sequentially added **1a** (1 mmol), **2f** (1.65 mmol), and dry THF (2 mL). Then, to this solution In powder (1.2 mmol) was added. The reaction mixture was rapidly stirred at rt for 30 min, quenched with water (5 mL), and subjected to ultrasonication for 1 min. Extraction with diethyl ether and evaporation afforded a crude mixture. Purification through silica gel column (EtOAc/hexanes 1:10) and Kugel-rohr distillation afforded the γ-adduct **6a** (ds 90:10) as a colorless thick oil. Under similar experimental condition the above reaction in 17 h afforded the α-adduct **7a** (purified in a silica gel column EtOAc/hexanes 1:3). **6a**: IR ($CDCl_3$) ν max 3490, 1708 1184 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.08 (ddd, J_1 = 17.2 Hz, J_2 = 10.0 Hz, J_3 = 10.0 Hz, 1H), 5.36 (d, J = 10.0 Hz, 1H), 5.33 (d, J = 17.2 Hz, 1H), 4.39 (s, 1H, D_2O-exchangeable), 3.98−3.85 (m, 2H), 3.50 (d, J = 9.2 Hz, 1H), 1.39 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 145.5, 132.7, 131.6, 128.2, 126.2, 121.0, 74.8, 61.0, 59.3, 27.8, 13.7. MS (CI) *m*/*z* 269 (M^+ + 1, 0.1), 253 (32), 251 (100), 207 (1.3), 179 (2.7), 157 (14.8), 155 (45.2), 115 (31.3%). HRMS (CI) calcd for $C_{14}H_{18}ClO_3$ 269.0944, found *m*/*z* 269.0950 (M^+ + 1). **7a**: IR ($CDCl_3$) ν_{max} 3482, 1735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.82 (dt, J_1 = 15.6 Hz, J_2 = 7.2, Hz, 1H), 5.79 (d, J = 15.6 Hz, 1H), 4.10 (q, J = 7.6 Hz, 2H), 3.16 (s, 1H, D_2O-exchangeable), 2.69−2.57 (m, 2H), 1.52 (s, 3H), 1.22 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 146.0, 144.7, 132.4, 128.1, 126.1, 124.4, 73.4, 60.2, 46.5, 29.4, 13.9. MS (CI) *m*/*z* 269 (M^+ + 1, 2.9), 253 (33.5), 251 (100), 217 (1.1), 179 (3.2), 155 (15.8), 114 (4.7%). HRMS (CI) calcd for $C_{14}H_{18}ClO_3$ 269.0944, found *m*/*z* 269.0942 (M^+ + 1).

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We thank Mr. H. Moriguchi, Faculty of Engineering, for MS spectra.

Supporting Information Available: Experimental details, X-ray analyses, spectral data of products, and ^{1}H and ^{13}C NMR charts. This material is available free of charge via the Internet at http://pubs.acs.org.

JO701899J