Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3225–3228
Tetrahedron Letters

Reaction of indium ate complexes with allylic compounds. Controlling S_N2/S_N2' selectivity by solvents

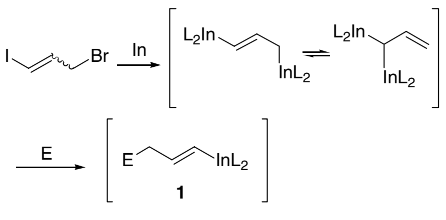
Tsunehisa Hirashita,* Yousuke Hayashi, Kazuma Mitsui and Shuki Araki

Omohi College, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466-8555, Japan

Received 6 February 2004; revised 24 February 2004; accepted 26 February 2004

Abstract—Vinyl and methylindium ate complexes (indates) were prepared and both the tendency of immigration and regioselectivity toward cinnamyl bromide were investigated. The vinyl group was more preferably transferred than the Me group, giving a regioisomeric mixture of S_N2 and S_N2' products. The ratio of S_N2/S_N2' selectivity can be controlled by solvents; in the presence of polar solvents, such as *N*-butylpyrrolidone (NBP) and THF, the S_N2' product was mainly obtained, whereas the S_N2 product was selectively prepared in solutions containing hexane. The vinylindium compound, generated by the reaction of allylic-type diindium reagents with imine, was also converted to the corresponding vinyl indate, which was allowed to react with allyl chloride to give a three-component coupling product.

Organoindium reagents have been extensively applied for carbon–carbon bond formation in the past decade.[1] Although initial studies focused on the reaction of allylindium reagents, a broad range of alkyl organoindium compounds have recently been used for carbon–carbon bond formation by the aid of transition metal catalysts.[2] In contrast, application of tetraorganoindium ate complexes (indates) in organic synthesis has been limited to the reduction of carbonyl compounds by lithium indium tetrahydride,[3] the addition to α,β-unsaturated compounds,[4] and the substitution of allylic halides by tetra(*n*-butyl)-, tetramethyl-, and allylindates.[5] In the course of our study of organoindium reagents, we found that vinylindium compounds **1** are prepared by the reaction of allylic-type diindium reagents with carbonyl compounds or imines (Scheme 1).[6] However, the vinylindium compounds **1** are inert to electrophiles such as carbonyl compounds and allylic halides due to the poor nucleophilicity of the vinylic indium bond. In order to exploit **1** for a further carbon–carbon bond formation in the consecutive coupling reaction, we examined a conversion of **1** into the corresponding indates. The nucleophilicity of vinylindium **1** is considered to be strongly enhanced by ate-complexation. As the study of vinylindium ate complexes remains unexplored, we first prepared trimethylvinylindate and examined an allylic substitution of cinnamyl bromide as a model reaction.[7] Trimethylvinylindate was prepared by the reaction of methyllithium or methylmagnesium bromide with indium(III) halides, followed by the addition of vinylmagnesium bromide (Eqs. 1 and 2).



Scheme 1. Preparation of vinylindium from allylic-type diindium.

$$3MeM^1 + InX_3 \rightarrow Me_3In + 3M^1X \quad (1)$$

$$Me_3In + CH_2{=}CHM^2 \rightarrow [Me_3(CH_2{=}CH)In]M^2 \quad (2)$$

The reaction of trimethylvinylindate with cinnamyl bromide gave a mixture of coupling products **2a**,**b** and **3a**,**b**. The results are summarized in Table 1. The coupling products were obtained totally in 33% yield (Table 1, entry 1). The vinyl group was preferably transferred to cinnamyl bromide in the ratio of 82:18. Addition of *N*-butylpyrrolidone (NBP) improved the total yield (entry 2), where the S_N2' reaction predominantly

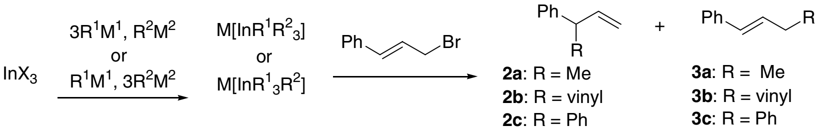
---

Keywords: Indium; Ate complex; Allylic alkylation.

* Corresponding author. Tel./fax: +81-52-735-5206; e-mail: hirasita@nitech.ac.jp

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.02.129

Table 1. The reaction of heteroindates with cinnamyl bromide[a]



Entry	R^1M^1 (mol%)	R^2M^2 (mol%)	X	Solvent	*T* [°C]	Yield (%)[b]				Ratio	
						2a	**3a**	**2b**	**3b**	**a**:**b**	**2**:**3**
1	MeMgBr (300)	VinylMgBr (100)	Cl	THF	−78	4	2	13	14	18:82	52:48
2	MeMgBr (300)	VinylMgBr (100)	Cl	THF–NBP (3:1)	−78	16	4	53	14	23:77	79:21
3	MeMgBr (300)	VinylMgBr (100)	I	THF–NBP (3:1)	−78	8	3	60	25	11:89	71:29
4	MeLi (300)	VinylMgBr (100)	I	THF–Et_2O–hexane (1:5:5)	0	0	13	0	18	58:42	0:100
5	VinylMgBr (100)	MeLi (300)	Cl	THF–Et_2O (1:1)	0	8	5	21	35	19:81	42:58
6	VinylMgBr (100)	MeMgBr (300)	Cl	THF	0	3	2	8	19	16:84	34:66
7	VinylMgBr (100)	MeLi (300)	Cl	THF–Et_2O–hexane (1:5:5)	0	1	38	1	40	49:51	2:98
8	MeLi (300)	PhLi (100)	Cl	THF–*c*-hexane–Et_2O (4:7:3)	0	32	8	3[c]	16[d]	68:32[e]	59:41
9	PhLi (100)	MeLi (300)	Cl	THF–*c*-hexane–Et_2O (4:7:3)	0	40	10	9[c]	21[d]	62:38[b]	61:39

[a] Indate was prepared from InX_3 (1 mmol) and R^1M^1/R^2M^2 at −78 or 0 °C, and the reactions were carried out with indate (1 mmol) and cinnamyl bromide (1 mmol) at room temperature for 17 h.

[b] Determined by GC analysis.

[c] Yield of **2c**.

[d] Yield of **3c**.

[e] **a**:**c**.

proceeded giving **2b** as a main product. NBP may promote the ate-complexation and/or activate the indate. The use of InI_3 in place of $InCl_3$ gave similar results (entry 3). In a solution containing hexane the S_N2 selectivity was highly improved but with a loss of the group selectivity (**a**:**b**) (entry 4).[8]

Next, the order of addition of the organometallic reagents was inversed and the resulting ate complex was subjected to the reaction with cinnamyl bromide. An equal molar of vinylmagnesium bromide and $InCl_3$ was premixed (Eq. 3), followed by the addition of 3 equiv of another organometallic compound (Eq. 4).

$$CH_2{=}CHMgBr + InCl_3 \rightarrow CH_2{=}CHInCl_2 + MgBrX \tag{3}$$

$$CH_2{=}CHInCl_2 + 3MeM^2 \rightarrow [Me_3(CH_2{=}CH)In]M^2 \tag{4}$$

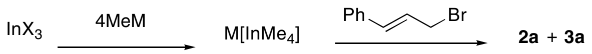
This inversed addition did not essentially affect both the group and the S_N2'/S_N2 selectivity (entries 1 vs 6 and 4 vs 7). Again, dependence of both the group and the regioselectivity on the solvent was observed; high S_N2 selectivity at the sacrifice of the group selectivity was observed in the reaction using hexane as a co-solvent (entry 7). The indate prepared by adding Grignard reagents to triorganoindium gave lower yields than that prepared by the treatment of MeLi as the complexing reagent (entries 1, 4, and 6 vs 5 and 7). To compare the effect of the inversed addition exactly, trimethylphenylindate was prepared from MeLi and PhLi (entries 8 and 9). This procedure permits access to trimethylphenylindate independent of the organometals and solvents used in the ate-complexation. The methyl group on the indium atom was transferred more preferably than the phenyl group, where S_N2'/S_N2 selectivity was different in the methyl and the phenyl group; the methyl group was transferred with the S_N2' mode, whereas the phenyl group was preferably introduced with the S_N2 mode. The tendency of immigration and the regioselectivity was almost coincident, showing both indates are identical irrespective of the order of addition.

Tetramethylindate also showed the dependence on the solvent for the regioselectivity and reactivity, as observed in the reaction of trimethylvinylindate. Tetramethylindate prepared in THF gave the S_N2' product selectively (Table 2, entries 1–4). Again, the indate prepared with MeLi as the complexing reagent gave a higher yield than that with MeMgBr (entries 1 and 2). The S_N2' selectivity was not further improved by the addition of NBP (entry 3). NBP must be added at low temperature to prevent a decrease of the yield (entries 3 and 4). Trimethylindium scarcely reacted with cinnamyl bromide under these conditions (entry 5). In the absence of indium salts MeLi and MeMgBr gave the product in 7% (**2a**:**3a** = 71:29) and 17% (**2a**:**3a** = 41:59) yields, respectively. These results clearly support that the present reaction proceeded via indium ate complexes.[†] Although the reaction of $MgBr[InMe_4]$ in ether–hexane did not reverse the S_N2'/S_N2 selectivity (entry 6),

---

[†] The presence of tetramethylindate was confirmed by ^1H NMR spectroscopy. Me_3In prepared from $InCl_3$ and MeMgBr in THF showed a singlet at δ −0.10 ppm in C_6D_6 at room temperature. By the addition of MeMgBr (100 mol%) in THF, the singlet shifted to δ −0.32 ppm, which can be assigned to $MgBr[InMe_4]$. MeMgBr resonates at δ −1.47 ppm.

Table 2. The effect of solvent on the reaction of tetramethylindate with cinnamyl bromide[a]



Entry	RM	X	Solvent	T [°C]	Yield (%)[b]		Ratio[b]
					2a	**3a**	**2a**:**3a**
1	MeMgBr	Cl	THF	−78	57	13	81:19
2	MeLi	Cl	THF–Et_2O (1:2)	−78	86	9	91:9
3	MeLi	Cl	THF–Et_2O–NBP (1:4:1)	−78	69	11	86:14
4	MeLi	Cl	THF–Et_2O–NBP (1:4:1)	0	31	4	89:11
5[c]	MeMgBr	Cl	THF–NBP (5:2)	−78	6	1	86:14
6	MeMgBr	Cl	Et_2O–hexane (1:1)[d]	−78	38	19	67:33
7	MeLi	I	Et_2O–hexane (7:5)	0	1	80	1:99

[a] Indate was prepared from InX_3 (1 mmol) and MeMgBr or MeLi (4 mmol) at −78 or 0 °C, and the reactions were carried out with cinnamyl bromide (1 mmol) at room temperature for 17 h.

[b] Determined by GC analysis.

[c] MeMgBr (3 mmol) was used to form trimethylindium.

[d] Indate was prepared in THF, then the solvent was removed under reduced pressure and Et_2O–hexane (1:1) was added.

Li[$InMe_4$] exclusively afforded the S_N2 product in ether–hexane (entry 7).

This dramatic solvent effect prompted us to investigate other reaction conditions for controlling the regioselectivity. As it has been reported that leaving groups play an important role to determine the regioselectivity in the allylic substitution reaction,[8b,9] we examined the reaction of tetramethylindate by employing various cinnamyl compounds with different leaving groups (Table 3). The coupling occurred regioselectively at the α-position of cinnamyl alcohol derivatives in Et_2O (Table 3, entries 1–5). The best results were obtained with cinnamyl bromide and iodide. In contrast, the reaction in THF–Et_2O showed diverse regioselectivity; cinnamyl chloride and acetate gave the S_N2 product and cinnamyl bromide, iodide, and phosphate gave the S_N2' product.

Table 3. The reaction of tetramethylindate with cinnamyl alcohol derivatives[a]

Entry	X	Solvent	Yield (%)[b]	**2a**:**3a**[b]
1	Cl	Et_2O	53	<1:>99
2[c]	Br	Et_2O	78	0:100
3	I	Et_2O	80	<1:>99
4	OC(O)OEt	Et_2O	26	0:100
5	$OP(O)(OEt)_2$	Et_2O	73	4:96
6	OAc	Et_2O	22	<1:>99
7	Cl	THF–Et_2O (1:1)	72	37:63
8	Br	THF–Et_2O (1:1)	95	91:9
9	I	THF–Et_2O (1:1)	47	74:26
10	$OP(O)(OEt)_2$	THF–Et_2O (1:1)	59	61:39
11	OAc	THF–Et_2O (1:1)	22	<1:>99

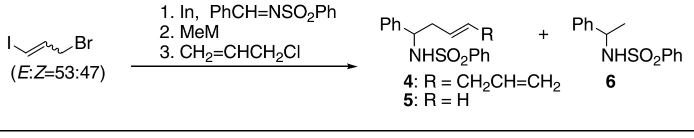
[a] All reactions were carried out with indate (0.5 mmol) and allylic compound (0.5 mmol) in solvent (2 mL) at room temperature for 17 h.

[b] The yield and ratio were determined by GC.

[c] Ref. 4.

Finally, we applied the above results to the allylation of vinylindium **1**. Vinylindium **1** was treated with MeLi and the resulting vinylindate was allowed to react with allyl chloride, bromide, and iodide. Among them, allyl chloride gave the best results; the desired homoallylic amide **4** was obtained in moderate yield together with **5** and **6** (Table 4, entry 1). An excess addition of MeLi improved the yield of **4** (entry 4). MeMgBr was capable

Table 4. The cascade reaction of diindium reagent with sulfonimine and allyl chloride[a]



Entry	MeM (mmol)	Solvent	Additive (mL)	Yield (%)		
				4	**5**	**6**
1	MeLi (1.5)	THF	—	47	18	6
2	MeLi (3.0)	THF	—	58	21	7
3	MeMgBr (2.0)	THF	NBP (0.4)	40	30	23
4	MeMgBr (2.0)	THF	NBP (2)	60	10	10
5	MeMgBr (2.0)	THF	NBP (4)	58	13	10
6	MeMgBr (2.0)	NBP	—	66	14	0

[a] All reactions were carried out in 3-bromo-1-iodopropene (0.5 mmol), imine (0.5 mmol), and indium (1.0 mmol) in solvent (2 mL) at room temperature for 4 h and then RM was added at −78 °C, followed by the addition of equimolar allyl chloride corresponding to RM.

of activating **1** and the usefulness of NBP was again observed (entries 3–6). The yield of **4** was improved by increasing the amount of NBP and the reaction performed in NBP gave the highest yield.[‡] Compound **5**, which came from protonation of **1**, was found in all cases, showing that a methyl group may be transferred from the indate to allyl chloride, giving 1-butene, to some extent, as shown in Table 1, and the resulting vinylindium was protonated to give **5**.

In summary, we have examined the reaction behavior of mixed indates in the reaction with allylic compounds and demonstrated that the group- and regioselectivity can be efficiently controlled by the solvent. The reaction of vinylic indate with allylic halide was applicable to the cascade coupling of allylic-type diindium compounds giving the linear homoallylic amines.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research (no 14340195) from the Ministry of Education, Science, Sport and Culture, Japan.

References and notes

1. (a) Cintas, P. *Synlett* **1995**, 1087–1096; (b) Marshall, J. A. *Chemtracts—Org. Chem.* **1997**, *10*, 481–496; (c) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149–11176; (d) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633–655; (e) Araki, S.; Hirashita, T. In *Main Group Metals in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2004.
2. (a) Pérez, I.; Sestelo, J. P.; Maestro, M. A.; Mouriño, A.; Sarandeses, L. A. *J. Org. Chem.* **1998**, *63*, 10074–10076; (b) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267–1269; (c) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095–4101; (d) Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* **2000**, *41*, 7555–7558; (e) Blum, J.; Katza, J. A.; Jabera, N.; Michman, M.; Schumann, H.; Schutte, S.; Kaufmann, J.; Wassermann, B. C. *J. Mol. Catal. A: Chem.* **2001**, *165*, 97–102; (f) Hirashita, T.; Yamamura, H.; Kawai, M.; Araki, S. *Chem. Commun.* **2001**, 387–388; (g) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997–1999; (h) Legros, J.-Y.; Primault, G.; Fiaud, J.-C. *Tetrahedron* **2001**, *57*, 2507–2514; (i) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155–4160; (j) Jaber, N.; Gelman, D.; Schumann, H.; Dechert, S.; Blum, J. *Eur. J. Org. Chem.* **2002**, 1628–1632; (k) Pena, M. A.; Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246–2247; (l) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2003**, 780–784; (m) Wallner, O. A.; Szabó, K. *J. Org. Lett.* **2003**, *5*, 2405–2408; (n) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2003**, *68*, 6627–6631.
3. (a) Yamada, M.; Tanaka, K.; Araki, S.; Butsugan, Y. *Tetrahedron Lett.* **1995**, *36*, 3169–3172; (b) Yamada, M.; Horie, T.; Kawai, M.; Yamamura, H.; Araki, S. *Tetrahedron* **1997**, *53*, 15685–15690; (c) Yamada, M.; Tanaka, K.; Butsugan, Y.; Kawai, M.; Yamamura, H.; Araki, S. *Main Group Met. Chem.* **1997**, *20*, 241–246.
4. Araki, S.; Shimizu, T.; Jin, S.-J.; Butsugan, Y. *Chem. Commun.* **1991**, 824–825.
5. Araki, S.; Jin, S.-J.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, *7*, 549–552.
6. Hitashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *J. Org. Chem.* **2003**, *64*, 172–177.
7. Recently, allylic substitution using organoindium compounds was reported Rodríguez, D.; Sestelo, J. P.; Sarandeses, L. A. *J. Org. Chem.* **2003**, *68*, 2518–2520.
8. The solvent effects on the group- or regioselectivity were reported in the reaction of zincates and cuprates (a) Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581–1593; (b) Bäckvall, J.-E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615–6621.
9. (a) Arai, M.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 5489–5491; (b) Dieter, R. K.; Velu, S. E.; Nice, L. E. *Synlett* **1997**, 1114–1116.

[‡] Cascade reaction of 3-bromo-1-iodoprop-1-ene with sulfonimine and allyl chloride: To a mixture of sulfonimine (123 mg, 0.50 mmol), indium (114 mg, 1.0 mmol) in NBP (2 mL), 3-bromo-1-iodoprop-1-ene (123 mg, 0.50 mmol) was added at room temperature and stirred for 1 h. The resulted mixture was cooled with a dry ice–acetone bath and MeMgBr (0.93 M in THF, 2.15 mL, 2.0 mmol) was added. After the reaction mixture was stirred at this temperature for 10 min, allyl chloride (164 μL, 2.0 mmol) was added and stirred at room temperature for 17 h. The reaction was quenched with hydrochloric acid (1 M, 2 mL) and the product was extracted with ether and washed with water and brine. The ether layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The product was purified by chromatography on silica gel (EtOAc–hexane = 1:15 then EtOAc) to give a mixture of **4** and **5**. The yields (**4**; 66%, **5**; 14%) were determined by ^1H NMR analysis.