

Nickel-catalyzed indium(I)-mediated double addition of aldehydes to 1,3-dienes

Tsune-hisa Hirashita,* Shinya Kambe, Hiromitsu Tsuji and Shuki Araki

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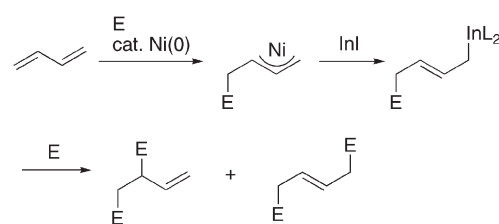
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In the presence of InI, Ni(acac)₂ and PPh₃, several 1,3-dienes were reacted with two molecules of aldehyde to give the corresponding 1,4- and 1,6-diols. The regioselectivity of the 1,4-/1,6-diol was efficiently regulated by the addition of water; the 1,6-diol was obtained selectively in dry THF, whereas the 1,4-diol was obtained predominantly in DMI containing a small amount of water.

Allylic indium compounds have widely been used for carbon–carbon bond formations in both organic and aqueous media.¹ The preparation of allylic indium compounds is based on oxidative additions toward allylic halides² or transmetalations from allylic lithium, magnesium, tin and palladium compounds.³ We have recently reported a new preparation of allylic indium reagents *via* a reductive transmetalation of π -allylnickel complexes, where allylic alcohols serve as a good allylic source.⁴ As π -allylnickel complexes are alternatively available by reactions of dienes with Ni(0) complexes,⁵ a broad range of allylindium compounds are expected to be prepared from various dienes. We describe here the double addition of aldehydes to 1,3-dienes *via* two distinct types of allylation; *i.e.*, the first addition of Ni–diene complexes to aldehyde gives π -allylnickel intermediates, which undergo a reductive transmetalation with InI generating allylindium compounds; then, the second addition of aldehyde furnishes three-component coupling products (Scheme 1). When buta-1,3-diene and benzaldehyde were treated with InI in the presence of Ni(acac)₂ (10 mol%) and PPh₃ (40 mol%) in DMI

(1,3-dimethyl-2-imidazolidinone), a mixture of 1,4-diol **2** (36%) and 1,6-diol **3** (54%) was obtained, together with a small amount of **1** (Scheme 2 and Table 1, entry 1). The use of cycloocta-1,5-diene (cod) as a ligand resulted in a decrease of the total yield (entry 2) and a large drop of the yield was observed in the case using 1,4-bis(diphenylphosphino)butane (dppb) (entry 3). The addition of InCl₃ as a Lewis acid showed no change in the yield or the distribution of the products (entry 4). However, the existence of a small amount of water predominantly gave rise to **2** in 64% yield (entries 5 and 6). The formation of **2** was not increased by the use of *t*-BuOH as a protic solvent in place of water (entry 7). By the combined use of dppb and water, homoallylic alcohol **1** was formed exclusively (entry 8). In contrast, the reaction performed in carefully dried THF produced diol **3** selectively in 87% yield (entry 9). The Ni-catalyzed reactions of dienes with aldehydes have hitherto been documented,⁵ where the initial reaction proceeds *via* a nucleophilic attack of Ni–diene complexes toward aldehydes activated by Lewis acid to produce π -allylnickel species. In all cases previously reported,⁵ the allylnickel species are used only for a single coupling with carbonyl components. In our present reaction, however, the subsequent



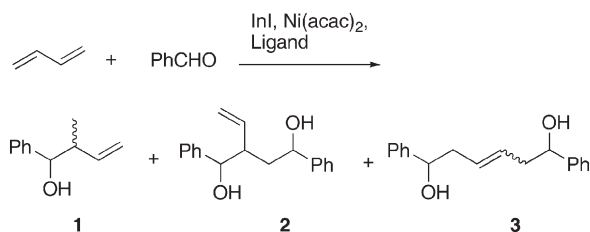
Scheme 1

Department of Materials Science and Engineering, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa, Nagoya, 466-8555, Japan. E-mail: hirashita@nitech.ac.jp; Fax: +81-52-735-5206; Tel: +81-52-735-5206

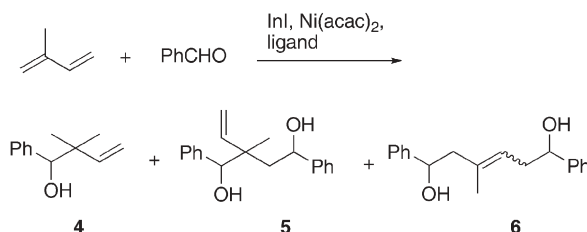
Table 1 The Ni-catalyzed InI-mediated reaction of buta-1,3-diene with benzaldehyde^a

Entry	Solvent	Ligand	Additive/mmol	Time/h	Yield (%) (diastereomeric ratio) ^b		
					1 (<i>syn</i> : <i>anti</i>)	2	3
1	DMI	PPh ₃	None	3	4 (73 : 27)	36 (19 : 81)	54 (27 : 19 : 54)
2 ^c	DMI	cod	None	24	5 (57 : 43)	31 (20 : 80)	23 (22 : 48 : 30)
3	DMI	dppb ^d	None	20	8 (73 : 27)	7 (20 : 80)	3 (23 : 42 : 35)
4	DMI	PPh ₃	InCl ₃ (0.5)	2	4 (75 : 25)	27 (12 : 88)	56 (22 : 32 : 46)
5	DMI	PPh ₃	H ₂ O (1)	3	15 (77 : 23)	64 (23 : 77)	8 (22 : 53 : 25)
6	DMI	PPh ₃	H ₂ O (3)	3	21 (75 : 25)	63 (19 : 81)	11 (20 : 49 : 31)
7	DMI- <i>t</i> -BuOH (1 : 1) ^e	PPh ₃	None	24	2 (77 : 23)	30 (23 : 77)	23 (19 : 33 : 48)
8 ^f	DMI	dppb	H ₂ O (3)	18	74 (80 : 20)	Trace	Trace
9	THF	PPh ₃	None	4	5 (79 : 21)	5 (30 : 70)	87 (7 : 16 : 77)

^a All reactions were carried out with buta-1,3-diene (0.50 mmol), benzaldehyde (0.50 mmol), InI (0.50 mmol), Ni(acac)₂ (10 mol%) and ligand (40 mol%) in solvent (1 mL) at room temperature unless otherwise mentioned. ^b The ratio was estimated by GC analysis for the acetylated products. ^c Ni(cod)₂ (20 mol%) was used. ^d 20 mol%. ^e 2.0 mL. ^f Buta-1,3-diene (0.50 mmol), benzaldehyde (0.25 mmol), Ni(acac)₂ (20 mol%) and dppb (40 mol%) were used.



Scheme 2



Scheme 4

reductive transmetalation of the π -allylnickel species by InI generates allylic indium compounds, which react further with another molecule of benzaldehyde to give **2** and **3** (Scheme 3). The selectivity **2/3** depends largely on the amount of water and this fact can be rationalized in terms of an equilibrium of two intermediates **A** and **B**. Under aqueous conditions, a contribution of linear allylindium **A** leading to **2** is predominant, whereas under anhydrous conditions secondary allylic indium **B** is considered to be much favored by intramolecular chelation; hence, **3** is obtained selectively in dry THF. When the initial reaction of the diene occurs with water in place of benzaldehyde, the resulting crotylindium reacts with benzaldehyde to give **1**, where dppb efficiently works as a bulky ligand to prevent the attack of benzaldehyde (entry 8).

Next, isoprene was subjected to the Ni-catalyzed reactions (Scheme 4 and Table 2). In DMI, a mixture of 1,4-diol **5** and 1,6-diol **6** was obtained with a similar selectivity to the case of buta-1,3-diene (entry 1). The effect of water was also evident; in the presence of water, **5** was obtained with higher selectivity than that involving buta-1,3-diene (entry 2). The formation of **6** was predominant in dry THF (entry 3). The use of dppb in place of PPh₃ resulted in a selective formation of **4** in a modest yield (entry 4).

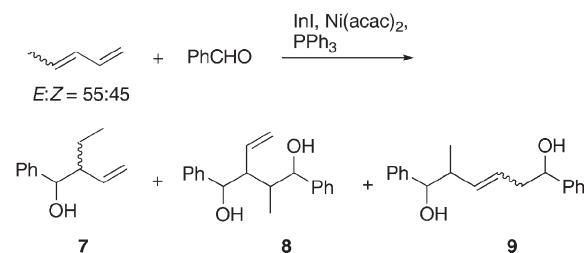
Piperylene was also proved to be useful for the present allylation as a diene unit (Scheme 5 and Table 3). To obtain the 1,4-diol selectively, the reaction was performed under aqueous conditions. However, an almost 1 : 1 mixture of 1,4-diol **8** and 1,6-diol **9** was obtained (entry 1). In contrast, the reaction in dry THF gave **9** selectively (entry 2).

It seems difficult to employ two different aldehydes for the present sequential reactions, because the allylindium reagents generated from the π -allylnickel intermediates by *umpolung* immediately react with the remaining initial aldehyde. To aim the coupling of a 1,3-diene moiety with two distinct electrophiles, dienyl aldehyde **10** was prepared and subjected to the reaction with

Table 2 The Ni-catalyzed InI-mediated reaction of isoprene with benzaldehyde^a

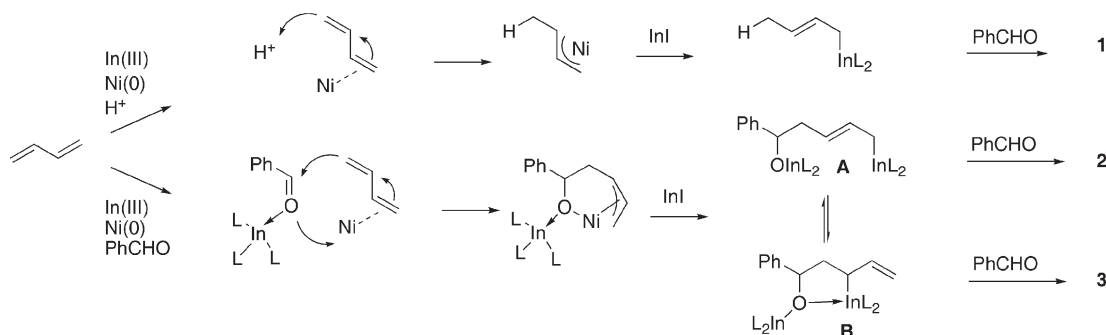
Entry	Solvent	Ligand	Additive/ mmol	Yield (%) (diastereomeric ratio) ^b		
				4	5	6
1	DMI	PPh ₃	None	3	42 (47 : 39 : 8 : 6)	52 (12 : 88)
2	DMI	PPh ₃	H ₂ O (1)	5	82 (45 : 38 : 9 : 8)	Trace
3	THF	PPh ₃	None	5	17 (38 : 45 : 9 : 8)	72 (14 : 86)
4 ^c	DMI	dppb ^d	H ₂ O (3)	20	0	0

^a All reactions were carried out with isoprene (0.50 mmol), benzaldehyde (0.50 mmol), InI (0.50 mmol), Ni(acac)₂ (10 mol%) and ligand (40 mol%) in solvent (1 mL) at room temperature for 24 h unless otherwise mentioned. ^b Isolated yield. The diastereomeric ratio was estimated by ¹H NMR analysis. ^c Isoprene (1.0 mmol) and benzaldehyde (0.50 mmol) were used. ^d 20 mol%.



Scheme 5

benzaldehyde. An intramolecular cyclization of **10** is expected to be feasible prior to an intermolecular reaction with benzaldehyde. The resulting allylnickel compound is considered to undergo a reductive transmetalation with InI to generate an allylindium reagent, which leads to an adduct with benzaldehyde. In fact, the reaction of **10** with benzaldehyde in DMI gave the expected product **11** exclusively in 55% yield (Scheme 6, Table 4, entry 1).⁶ The regioisomeric branched product was not formed. In dry THF

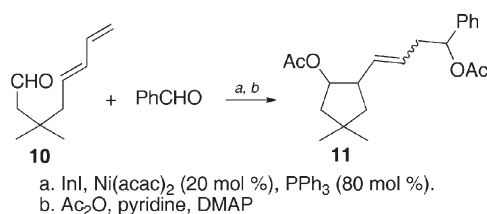


Scheme 3

Table 3 The Ni-catalyzed InI-mediated reaction of piperylene with benzaldehyde^a

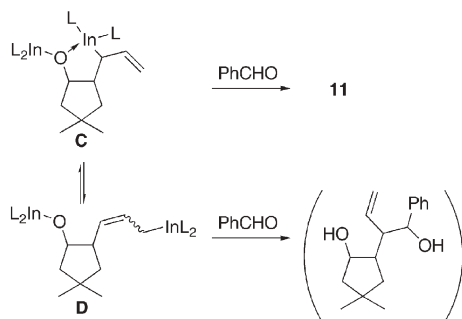
Entry	Conditions	Yield (%)
1	DMI, H ₂ O (200 mol%), 4 h	7: 5 (71 : 29), 8: 44 (77 : 11 : 6 : 6) ^d , 9: 47 ^e
2	THF, 18 h	7: trace, 8: trace, 9: 79 (28 : 2 : 26 : 12 : 28 : 4) ^d

^a All reactions were carried out with piperylene (0.50 mmol), benzaldehyde (0.50 mmol), InI (0.50 mmol), Ni(acac)₂ (10 mol%) and PPh₃ (40 mol%) in solvent (1 mL) at room temperature. ^b Determined by ¹H NMR. ^c A small amount (1%) of 1-phenylhex-3-en-1-ol was also obtained. ^d Determined by GC analysis of the corresponding diacetates. ^e Diastereomeric ratio was not determined.

**Scheme 6****Table 4** The intramolecular cyclization of diene 10

Entry (mmol)	10 : PhCHO	Conditions	Yield of 11 (%) (diastereomeric ratio) ^a
1	0.25/0.50	DMI, 4 h	55 (7 : 42 : 6 : 21 : 24)
2	0.25/0.50	THF, 24 h	55 (7 : 7 : 22 : 28 : 36)
3	0.50/0.50	DMI, H ₂ O (1 mmol), 24 h	56 (6 : 57 : 3 : 10 : 24)

^a Determined by GC analysis.

**Scheme 7**

(entry 2) and even in moist DMI (entry 3), **11** was solely obtained. These facts indicate that the intramolecular chelation depicted as **C** in Scheme 7 is much tighter than that in the cases of the 1,3-dienes in Table 1, Table 2 and Table 3 and/or the bulkiness arising from the cyclopentyl substituent of **D** is crucial for preventing the reaction at the γ-position.

In conclusion, the double addition of aldehydes toward 1,3-dienes has been achieved by the Ni-catalyzed InI-mediated reaction. The regioselectivity has successfully been controlled by water in the solvent. The reaction has been applied to the coupling

of the ω-formyl diene and benzaldehyde through intramolecular cyclization. Further applications of this procedure are currently under study.

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- 2-(4-Acetyloxy-4-phenylbut-1-enyl)-4,4-dimethylcyclopentyl acetate (**11**): Anhydrous Ni(acac)₂ was prepared from Ni(acac)₂·2H₂O (15 mg, 0.050 mmol, 20 mol%) by heating with a heat gun before use. To a mixture of the Ni(acac)₂, InI (121 mg, 0.50 mmol) and PPh₃ (52 mg, 0.20 mmol, 80 mol%) in DMI (1.0 mL), 3,3-dimethylocta-5,7-dienal (38 mg, 0.25 mmol) and benzaldehyde (52 μL, 0.50 mmol) were added and the reaction mixture was stirred at room temperature for 4 h. After the reaction mixture was treated with DMAP (10 mg), pyridine (1 mL) and acetic anhydride (1 mL) at room temperature for 1 h, the reaction was quenched with H₂O (3 mL) and the products were extracted with diethyl ether. The combined ether layer was successively washed with 1 M HCl, saturated aq. NaHCO₃ and brine. The ether solution was dried over Na₂SO₄ and the solvent was removed under reduced pressure to give the crude product (158 mg). Chromatographic separation on silica gel, using hexane–EtOAc (15 : 1 to 4 : 1) as eluent, gave **11** (47 mg, 55%, dr = 7 : 42 : 6 : 21 : 24) (Found: C, 72.92; H, 8.51. Calc. for C₂₁H₂₈O₄: C, 73.23; H, 8.19%). The diastereomeric ratio was determined by GC; δ_H (200 MHz; CDCl₃; Me₄Si): (major) 2.06, 2.07 (s, total 6 H, Ac × 2), 0.99–1.02, 1.06–1.19 (m, total 6 H, Me₂), 1.25–1.84 (m, 4 H, CH₂CCH₂), 2.50–2.75 (m, 2 H, =CHCH₂), 2.62–2.80, 2.82–2.99 (m, total 1 H, CH), 5.04–5.17 (m, 1 H, CHCHOAc), 5.23–5.50 (m, 2 H, CH=CH), 5.66–5.76 (m, 1 H, CHPh), 7.23–7.34 (m, 5 H, Ph).