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Direct use of 1,3-dienes for the allylation of ketones *via* catalytic hydroindation†

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In this study, *in situ* catalytically generated allylic indium from 1,3 dienes and InCl_2H was developed for use in the allylation of ketones. This protocol resulted in the unprecedented establishment of a successive combining of quaternary C–C bonds, which could then be applied to many types of ketones. Other branched 1,3 dienes and vinyl cyclopropanes, could also be coupled with ketones in a reaction where CuH would not be applicable.

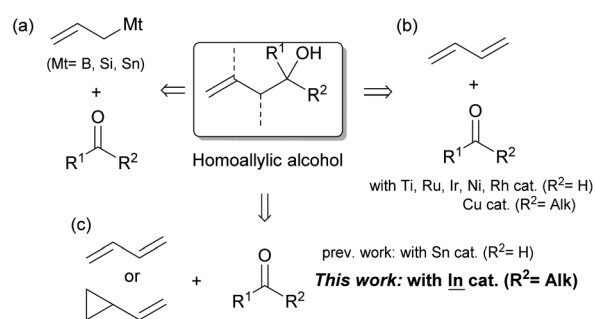
Homoallylic alcohols are useful building blocks in the synthesis of bioactive natural compounds and pharmaceuticals. For these syntheses, the preparation of tertiary compounds has remained challenging regardless of whether or not they are given asymmetrically.¹ The allylation of ketones with allylic reagents is a typical method for the preparation of these compounds (Scheme 1a).² This method, however, cannot avoid wasteful steps such as the transmetalation between Grignard reagents and B, Si or Sn sources and the reductive generation between allylic halides and low-valent metals. Although this method can be applied to highly stereocontrolled reactions, the wasteful steps are cumbersome and more practical reaction methods are required.

For this process, 1,3-dienes are an important industrial feedstock that is produced on a massive scale *via* either the cracking of ethylenes or the transformation of biomass. Easily available dienes have recently replaced the conventional allylation of aldehydes with the aid of transition metal catalysts (Scheme 1b).³ After the first application using a Ti catalyst by Gendre and Moïse,⁴ Krische has expanded the field with the introduction of Ru-catalyzed stereocontrolled reactions.⁵ Other transition metals such as Ni,⁶ Ir,⁷ and Rh⁸ have contributed to improvements in coupling. A recent adoption of ketones as viable substrates was achieved by Liu and Buchwald *via* proficient Cu–H chemistry.⁹ The scope of possible substrates could be expanded even further,¹⁰ however, particularly with the use of 1,3-dienes and ketones that possess a variety of functional groups.

Our group has explored the hydrostannylation¹¹ or indation¹² of unsaturated bonds in the preparation of reactive

organostannanes or indiums that could be applied to further transformations, although stoichiometric amounts of Sn or In sources must be added to the reaction systems. Recently, a transition metal-free reductive coupling of 1,3-dienes,¹³ or their derivatives such as vinyl cyclopropanes,¹⁴ with aldehydes catalyzed by Bu_2SnXH has been developed, but the method would not allow the use of ketones due to the low reactivity of the reaction intermediate, allylic stannanes (Scheme 1c). On the other hand, our group has already developed a process for the hydroindation of 1,3-dienes with a stoichiometric amount of InX_2H to give allylic indiums followed by the allylation of ketones.^{12b,12d} Herein, we report the catalytic coupling of 1,3-dienes or vinyl cyclopropanes with ketones through the generation of allylic indiums *via* the hydroindation of 1,3-dienes with a catalytic amount of InX_2H (Scheme 1c).

We initiated the optimization of the reaction conditions by combining 1,3-butadiene (**1a**) and acetophenone (**2a**) in a sealed test tube (Table 1). The gaseous diene **1a** was liquefied and weighed before addition to the reaction. Based on our previous reports, InCl_2OMe generated from $\text{InCl}_3/\text{NaOMe}$ and a silane were chosen as indium and hydride sources, respectively.¹³ The desired product **3aa** was obtained in a 92% yield as a mixture of



Scheme 1 Synthesis of homoallylic alcohols from allylation reagents with ketones.

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Table 1 Optimization of the reaction conditions^a

Entry	Silane	Solvent	Conditions	Yield (%) 3aa (syn : anti) ^b
1	MePhSiH ₂	THF	25 °C, 48 h	92 (80 : 20)
2			25 °C, 48 h w/o MeOH	42 (88 : 12)
3			25 °C, 24 h w/o MeOH	54 (76 : 24)
4	Et ₃ SiH	THF	25 °C, 24 h	12 ^c
5	Ph ₃ SiH	THF	25 °C, 24 h	0
6	Ph ₂ SiH ₂	THF	25 °C, 24 h	32 (83 : 17)
7	PhSiH ₃	THF	25 °C, 24 h	54 (83 : 17)
8	MePhSiH ₂	THF	60 °C, 3 h	92 (80 : 20)
9		MeCN		38 (80 : 20)
10		Et ₂ O		71 (76 : 42)
11		Toluene		9 ^c
12		THF	w/o NaOMe	Trace
13			w/o InCl ₃	0
14			With TEMPO (0.2 mmol)	0
15			With InCl ₂ OMe (0.1 mmol)	51 (78 : 22)

^a The yields were determined by ¹H NMR. ^b Stereochemistry, see: ref. 15. ^c dr could not be determined because of complex of the reaction mixture.

the diastereomers (entry 1). The yield was lowered either when no MeOH was used or when the reaction time was cut by half (entries 2 and 3). A screening of the silanes showed that MePhSiH₂ was the optimal hydride source (entries 4–7). We found that the reaction was finished in 3 h when the reaction temperature was raised to 60 °C (entry 8). Replacing the solvent with MeCN, Et₂O or toluene did not improve the reaction yield (entries 9–11). It was necessary to add NaOMe to the reaction system for a facile generation of InCl₂H (entry 12).¹⁶ It was important to add InCl₃ to the reaction (entry 13). A radical scavenger, TEMPO, suppressed the progress of the reaction, which implied that this reaction contains a radical process (entry 14). The reaction yield was decreased when the lower amount of the catalyst was employed (entry 15).

With the optimal reaction conditions in hand (Table 1, entry 8), the scope of the ketones was investigated (Table 2). Electron-deficient substitution on the phenyl ring had a small effect on the reaction yield, but an electron-rich substitution decreased it appreciably (entries 2–6). The efficiency was also attenuated by steric hindrance around the C=O moiety of propiophenone (**2g**) and butyrophenone (**2h**) (entries 7 and 8). α -Cyano and -bromo acetophenone **2i** and **2j**, respectively, reacted sufficiently (entries 9 and 10). The tolerance to reduction of the C–Br bond by InX₂H under reductive conditions is a characteristic of coupling (entries 3 and 10).¹⁷ On the other hand, α -methoxy one was unsatisfactory as a reactant probably due to chelation between the OMe and C=O groups with the catalyst that would have

promoted a reduction in the ketone **2k** (entry 11). β -Keto ester **2l** was a good partner even though a similar chelation involving two C=O groups could have happened (entry 12). Both acyclic and cyclic aliphatic ketones were allylated (entries 13–14). Other aromatic rings such as naphthalenes were introduced into the products **3ao** and **3ap** (entries 15 and 16).

Reductive coupling was then applied to other dienes (Scheme 2). In the case of isoprene (**1b**), two different products, **3ba** and **3ba'**, were formed even though the reaction was very slow (eqn (1)). The regioselectivity derived from the different structures of the allylic indiums. To our delight, diene **1c** made it possible to establish contiguous quaternary C–C bonds with ketones **2a–2c** (eqn (2)). To date, construction of contiguous quaternary C–C bonds with a catalyst remains a challenging task in organic synthesis,¹⁸ and the task has never been realized by the same type of reductive coupling that is catalyzed by transition metal catalysts.

Our proposal of the reaction mechanism is described in Scheme 3. Initially, prepared InCl₂(OMe) is reduced by MePhSiH₂ to give HInCl₂. The indium radical is formed in the presence of tiny amounts of O₂ and adds to diene **1a**.¹⁷ The stable allylic radical **A** extracts hydrogen from InCl₂H to afford allylic indium **B**, which regenerates the indium radical. Following the allylation of ketone **2**, the generated indium alkoxide **3'** is protonated by CH₃OH to give the product **3** and InCl₂(OMe). The reaction mechanism was investigated using a deuterated silane, Ph₂SiD₂ (Scheme 4). We found that the



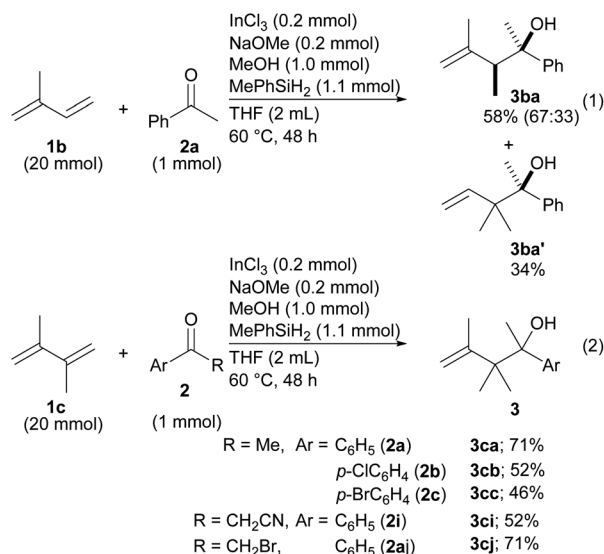
Table 2 Scope of ketones^a

Entry	R ¹	R ²	Ketone	Product	Yield (%) (dr)
1	C ₆ H ₅	Me	2a	3aa	92 (80 : 20)
2	<i>p</i> -ClC ₆ H ₄		2b	3ab	83 (79 : 21)
3	<i>p</i> -BrC ₆ H ₄		2c	3ac	88 (80 : 20)
4	<i>p</i> -CNC ₆ H ₄		2d	3ad	79 (79 : 21)
5	<i>p</i> -MeC ₆ H ₄		2e	3ae	53 (75 : 25)
6	<i>p</i> -OMeC ₆ H ₄		2f	3af	58 (75 : 25)
7	C ₆ H ₅	Et	2g	3ag	69 (84 : 16)
8		ⁿ Pr	2h	3ah	66 (84 : 16)
9		CH ₂ CN	2i	3ai	75 (82 : 18)
10		CH ₂ Br	2j	3aj	74 (84 : 16)
11		CH ₂ OMe	2k	3ak	22 (80 : 20)
12		CH ₂ CO ₂ Et	2l	3al	59 (80 : 20)
13 ^b	PhCH ₂ CH ₂ -(CH ₂) ₅ -	Me	2m	3am	73 (57 : 43)
14			2n	3an	75
15	1-Np	Me	2o	3ao	77 (75 : 25)
16	2-Np	Me	2p	3ap	80 (76 : 24)

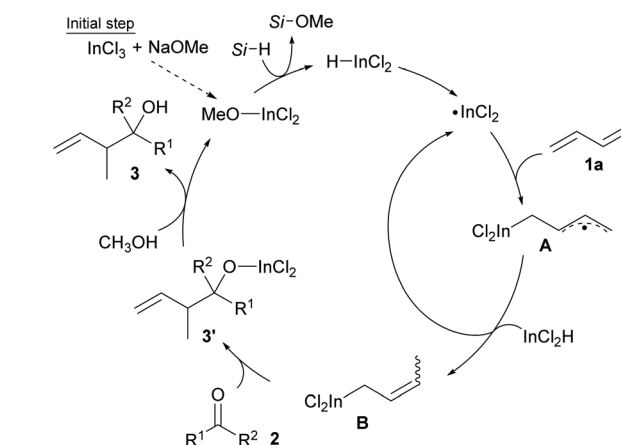
^a The yields were determined by ¹H NMR. ^b Reaction time was 24 h.

product **3aa-CH₂D** was afforded without any other deuterated compound. The product **3aa-CH₂D** is formed from δ -deuterated intermediate **B-d₁** as shown in Scheme 4. Further investigation on the reaction mechanism is ongoing in our laboratory.

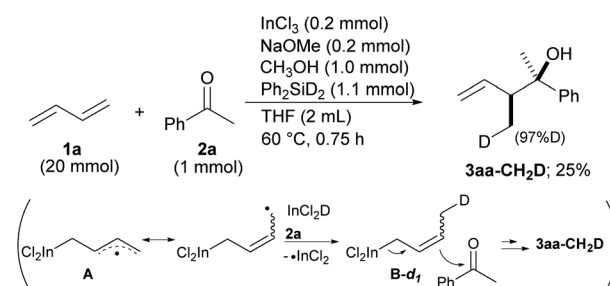
Finally, vinyl cyclopropane **4**, a diene derivative, was tested for reductive coupling with ketones.¹⁹ The desired product **5a** was produced in the presence of a radical initiator, V-70L, even

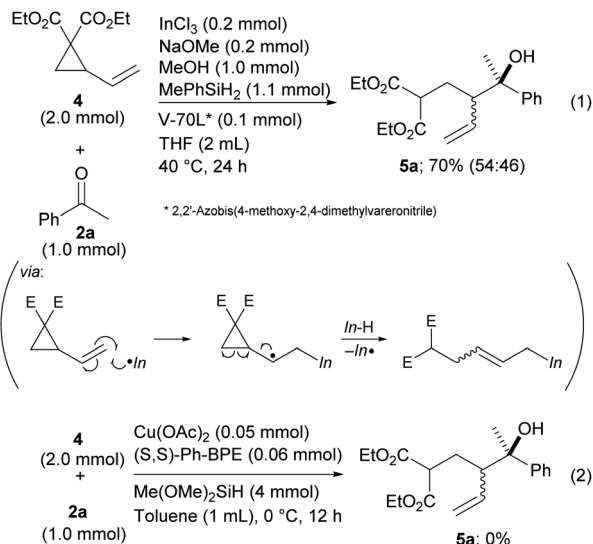


Scheme 2 Application of substituted 1,3-butadienes to the coupling.



Scheme 3 A plausible catalytic cycle.

Scheme 4 Deuterated experiments of allylation of ketone **2a**.



Scheme 5 Coupling of vinyl cyclopropanes with ketones.

though diastereoselectivity was not achieved (Scheme 5, eqn (1)). This could have been caused by low *E/Z* selectivity of the allylic indiums. The seminal work developed by Buchwald that was related to a Cu–H catalyzed reaction did not allow the use of vinyl cyclopropane as a reactant because their method has no process for a radical opening of the cyclopropane ring (Scheme 5, eqn (2)).⁹ Our method expands the scope of the dienes by allowing use of their derivatives.

In summary, we developed a process whereby the reductive coupling of 1,3-dienes with various ketones could be sufficiently catalyzed by HInCl_2 . This approach allowed the introduction of functional groups into homoallylic alcohols, which generated sequential $\text{C}_{\text{tert}}\text{--C}_{\text{tert}}$ bonds with expansion to vinyl cyclopropane 4. Application to an asymmetric version of the coupling and improvement of the diastereoselectivity are underway.

Conflicts of interest

There are no conflicts to declare.

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