C-C Coupling

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Direct Carbon–Carbon Bond Formation from Alcohols and Active Methylenes, Alkoxyketones, or Indoles Catalyzed by Indium Trichloride**

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To construct C–C bonds, coupling reactions between reactive nucleophiles such as organometallic compounds (R'M) and halides or a related species (RX) are undoubtedly a useful process. The species RX and R'M are often prepared from alcohols (ROH) and active methylenes (R'H), respectively. However, the coupling reaction intrinsically produces a salt (MX) alongside the desired product (R–R'). The direct

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reaction between ROH and R'H would be an ideal process for C–C bond formation because preparation of the reactive materials would not be required and only H_2O would be generated as a side product (Figure 1). This process would





significantly save energy during multistep transformations and separation of the product from the salt. Thus, a catalyst for the reaction is required that activates either ROH or R'H and has low oxophilicity and insensitivity to water.

The Tsuji-Trost coupling reaction between allylic acetate or its derivatives with a carbanion derived from active methylenes^[1] is an important synthetic tool. Recently, direct use of allylic alcohols and active methylenes for the Tsuji-Trost-type reactions has been intensively studied using palladium complexes in the presence of a base or acid cocatalyst.^[2,3] Copper(I) can accelerate the reaction in the absence of a cocatalyst but an equimolar amount is required.^[4] Although the catalytic reaction using a cobalt species was reported,^[5] active methylenes were limited to β diketones or keto esters, while diesters, which display a much lower reactivity owing to lower acidity (enolizable ability), could not be used. Those reactions based on transition-metal chemistry involve only allylic alcohols because the key intermediates are a π -allylic species. In this context, expansion of substrates for this type of reaction to a wide range of active methylenes and other classes of alcohols is desired.

Catalytic activation of alcohols is generally difficult because of the inefficient leaving-group ability of the hydroxy group. We have been studying catalytic activation with silyl nucleophiles and found that indium catalysts are quite effective.^[6] We now report the indium-catalyzed reaction of allylic and benzylic alcohols with various active methylenes, alkoxyketones, and indoles, in the absence of a cocatalyst/ activator.

First, we examined the reaction of the allylic alcohol **1a** with diethyl malonate **2a** using various catalysts (Table 1). Neither a palladium catalyst nor HCl gave the product (entries 1 and 2). Gratifyingly, InCl₃ was found to act as a catalyst to give **3aa** in 52 % yield (entry 3, Table 1). InBr₃ also led to formation of the product (entry 4), while no products were observed using In(OAc)₃, In(OH)₃, In(acac)₃ (acac = acetylacetonate), or In as a catalyst. Other Group 13 Lewis acids such as BF₃·OEt₂, AlCl₃, and GaCl₃ gave lower yields (entries 5–7, Table 1). When Sc(OTf)₃ was used as a catalyst, the product was contaminated with that of a redox side reaction (entry 8).^[7] A large-scale synthesis of **3aa** was successful using InCl₃ without the need for a solvent



	Ph Ph E OH 1a	tO CEt	catalyst (5 mol%) toluene 80 °C, 3 h	Ph Ph EtO Ph O O (+ H ₂ O)	OEt 3aa
Entry	Catalyst	Yield [%]	Entry	Catalyst	Yield [%]
1	[Pd(PPh ₃) ₄]	0	5	BF ₃ ·OEt ₂	0
2	HCI ^[b]	0	6	AICI ₃	6
3	InCl₃	52 (49) ^[c]	7	GaCl₃	18
4	InBr ₂	45	8	Sc(OTf)	25 ^[d]

[a] All reactions were performed using **1a** (1 mmol), **2a** (1 mmol), and catalyst (0.05 mmol) in toluene (2 mL). OTf=trifluoromethanesulfonate. [b] HCl in dioxane. [c] Isolated yield (8.6 g) after distillation from a synthesis performed on a large scale (50 mmol scale, 15 h). [d] PhCOCH₂CHPhCH(CO₂Et)₂ was obtained in 25% alongside the desired product **3aa** (25%).

(entry 3, Table 1). The product was easily isolated by distillation as there was no contamination by salt side-products.

We then explored the generality of the InCl₃-catalyzed reaction by varying the alcohol and active methylene substrates (Table 2). The reaction of allylic alcohol 1a with active methylenes 2a-c including diesters, keto esters, and diketones smoothly proceeded to give the corresponding alkylated products (entries 1-3, Table 2). The primary allylic alcohol 1b afforded a regioisomeric mixture (entry 4). The cyclic allylic alcohol 1c gave the desired product 3cc in high vield (entry 6, Table 2). Interestingly, the benzylic alcohols 1d and 1e were applicable in this system as electrophiles (entries 7-11, Table 2),^[8] while such benzylic species are not suitable in the Tsuji–Trost reaction based on π -allyl chemistry.^[9] When simple monoketones such as acetophenone or propiophenone were used as nucleophiles, no desired product was obtained. Surprisingly, the reaction using α -methoxyketone 2d gave the alkylated product 3ad (entry 12, Table 2). Higher loadings of 2 improved the yield for the reactions that initially gave low yields (entries 5 and 13). In all cases, selective monoalkylation was accomplished without dialkylation.^[3] Thus, the present system has potential for a wide range of nucleophiles and electrophiles.

Scheme 1 shows plausible pathways for the $InCl_3$ -catalyzed reaction,^[10] with the most probable being a direct path through alkylation of indium-activated alcohol.^[6] We also



Scheme 1. Plausible reaction courses for the catalyzed reaction.

propose paths A and B from the observation of bis(diphenylmethyl) ether **4d** by NMR spectroscopy during the formation of **3dc** in the InCl₃-catalyzed reaction of **1d** with **2c**. A dimeric ether **4** could be an intermediate of the reaction Table 2: InCl₃-catalyzed direct reaction of 1 with 2.^[a]



[a] The reactions were performed with alcohols (1 mmol), nucleophile (1.0 mmol), and $InCl_3$ (5 mol%) in toluene (2 mL) at 80 °C for 15 h. **2a**: $R^1 = OEt$; $R^2 = OEt$; 2b: $R^1 = Me$, $R^2 = OEt$; 2c: $R^1 = Me$, $R^2 = Me$. [b] Mixture of diastereomers (55:45) [c] Enol-type compound is involved. [d] 2c (5 mmol). [e] Dichloroethane was used as solvent. [f] Mixture of diastereomers (ca. 1:1). [g] 2d (2 mmol).

that proceeds in two steps: A) dimerization and B) alkylation. A catalyst that accelerates both steps is necessary to complete the reaction.

Paths A and B were independently examined with $InCl_3$ or other Lewis acids (Scheme 2). While both reactions



Scheme 2. Effect of the catalyst on paths A and B.

corresponding to paths A and B were catalyzed by $InCl_3$ and $BF_3 \cdot OEt_2$, $InCl_3$ showed significant activity for alkylation relative to $BF_3 \cdot OEt_2$. Furthermore, $BF_3 \cdot OEt_2$ showed no catalytic activity for the alkylation step in the presence of H_2O , in contrast to the effective activity of $InCl_3$. Interestingly, $InCl_3$ -catalyzed reaction of **4d** with **2c** is faster in the presence of H_2O than in its absence, as reflected by the yields of **3dc** (59% and 39%, respectively; 80°C, 3 min). An interaction between $InCl_3$ and the active methylenes is possible,^[11] even though our NMR study did not show any evidence for this. Although the exact reaction mechanism is not known at this stage, the activation of alcohols through two possible pathways (Scheme 1) and that of active methylenes by $InCl_3$ leads to effective C-C bond formation.

The modification of indoles^[12] is an important subject, and some reports have recently appeared in which equimolar promoters^[13] or transition-metal catalysts were used.^[14,15] Application of the present strategy to indoles gave 3-alkylated products in high yield and with high selectivity using allylic or benzylic alcohols (Scheme 3). No regioisomers through N- or 2-alkylation were obtained. Tamaru and co-workers recently reported the Pd-catalyzed reaction of allylic alcohol with indoles in the presence of Et₃B.^[16] Although N-methylindole (5b) was not a good substrate therein, in our system 5b gave the alkylated products 6b or 7b in high vields.

In summary, we have developed a mild and direct process for C–C bond formation from alcohols and

active methylenes, alkoxyketones, or indoles in the presence of an indium catalyst, with the formation of water only as a side product. This reaction can be carried out in a very simple operation, by just mixing the substrates with InCl₃, followed



Scheme 3. InCl₃-catalyzed alkylation of indoles.

by extraction and/or distillation. This method is energy-saving and "green" and provides a straightforward and practical route to alkylated compounds.

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