Indium(I) iodide-catalyzed regio- and diastereoselective formal α-addition of an α-methylallylboronate to *N*-acylhydrazones†

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Indium(I) iodide was found to catalyze the formal α-addition of an α-methylallylboronate to various *N*-acylhydrazones, in the presence of an alcohol additive, to afford the corresponding *anti*-α-adducts with high regio- and diastereoselectivity in high yields.

Addition of allylic metal nucleophiles to C═N double bonds is one of the most important reactions to afford homoallylic amine derivatives, which can be useful synthetic building blocks as well as biologically active compounds,[1] and various allylmetal reagents have been used to perform these C–C bond formations.[2] When a substituted allylmetal nucleophile is used, the regioselectivity of this reaction emerges as an important issue since two types of products can be obtained: α-adduct and γ-adduct. Hence, regioselective formation of both α- and γ-adducts is desired with regard to improving efficiency and decreasing by-products. The ratio of α- to γ-adducts is known to depend on the nature of the allylmetal reagents used;[3] in this context, allylic boron and silicon nucleophiles are of particular importance since they readily form C–C bonds *via* a six-membered transition state, affording γ-adducts exclusively.[4]

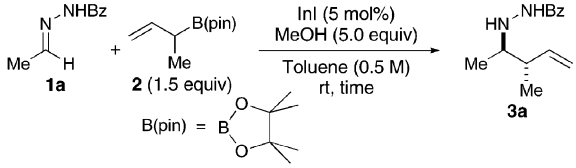
Recently, our group has uncovered enantioselective allylation of iminoesters catalyzed by a chiral zinc complex.[5] Interestingly, the products obtained indicated that the addition formally took place at the α-position of allylic boronates. It is quite rare for catalytic addition reactions of allylic boronates to imine derivatives to afford α-adducts regioselectively. Furthermore, this successful transformation provides the possibility of obtaining various homoallylamine products from α-substituted allylboronates,[4,6] which has not received so much attention. In two earlier reports, we have described as well the catalytic use[7] of indium(I) iodide for effective allylation of ketones[8] and *N*-acylhydrazones[9,10] with an allylboronate. On the basis of this concept involving two group 13 elements, we report here indium(I)-catalyzed additions of α-substituted allylic boronates to *N*-acylhydrazones. This reaction showed broad substrate generality and could afford formal α-adducts regioselectively with high *anti*-selectivity.

In an initial experiment, α-methylallylboronate **2** (1.5 equiv) reacted with acetaldehyde-derived *N*-benzoylhydrazone **1a** in dry toluene (0.5 M) in the presence of 5 mol% of indium(I) iodide[11] as a catalyst and 5 equiv of MeOH as an additive (Table 1). The reaction proceeded smoothly to afford the corresponding product in high yield. Surprisingly, the major product was revealed to be not the expected γ-adduct, but the α-adduct **3a** (entry 1). In contrast, the reaction in the absence of indium(I) iodide proceeded sluggishly and gave the γ-adduct predominantly. These results indicated that the indium(I) catalyst played a crucial role in achieving this unusual α-selectivity.

We next turned our attention to investigate the effect of alcohol additives and solvents (Table 2). An alcohol additive has already been suggested to be important for the activation of an allylboronate.[9] A clear trend was revealed; as the steric demand of alcohols was increased, the diastereoselectivities were substantially improved, although the reaction became more sluggish (entries 1–5). 2-Propanol was found to be the additive of choice to obtain the desired product with satisfactory diastereoselectivity (entry 4). Phenol and ethylene glycol were also tested, but resulted in lower yields and diastereoselectivities compared with 2-propanol (entries 6 and 7). The possibility that the alcohol might work as a proton source to activate the *N*-acylhydrazone seemed unlikely, because low reactivity and diastereoselectivity were observed when a more acidic alcohol was used (entry 8). As for the solvent, it was found that toluene gave better diastereoselectivity, although a low reaction rate was observed (entries 9 and 10).

Next, the substrate scope for *N*-acylhydrazones using α-methylallylboronate **2** was examined in the presence of 5 mol% of the indium(I) catalyst (Table 3). Although a slight amount of γ-adduct was observed in several entries, the

Table 1 Addition of an α-methylallylboronate to an *N*-acylhydrazone



Entry	InI	Time/h	Yield (%)	α : γ	*syn* : *anti*
1	+	6	87	92 : 8	16 : 84
2	–	36	36	13 : 87	16 : 84

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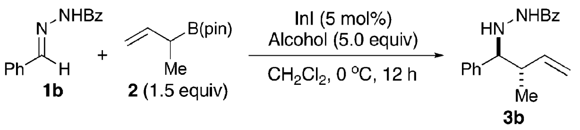
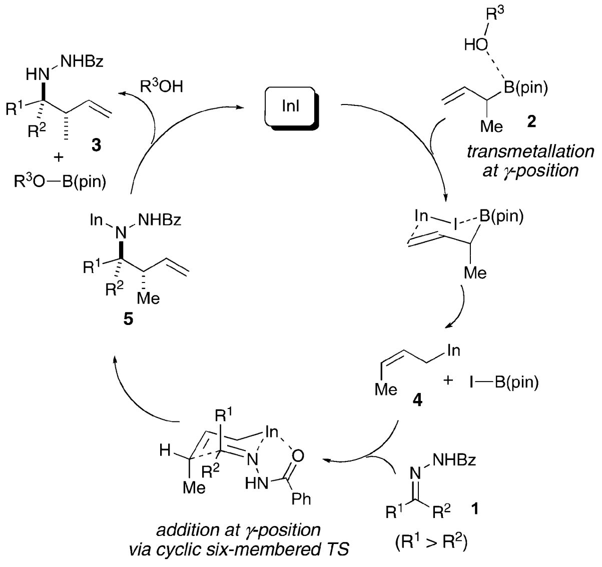
Table 2 Effect of alcohols and solvents



Entry	Alcohol	Yield (%)	α : γ	*syn* : *anti*
1	—	9	>99 : <1	7 : 93
2	MeOH	57	>99 : <1	13 : 87
3	EtOH	86	>99 : <1	12 : 88
4	*i*-PrOH	29	>99 : <1	3 : 97
5	*t*-BuOH	8	>99 : <1	<1 : >99
6	PhOH	20	>99 : <1	15 : 85
7	$HOCH_2CH_2OH$	25	>99 : <1	33 : 67
8	HFIP[c]	17	>99 : <1	18 : 82
9[a]	MeOH	96	>99 : <1	37 : 63
10[ab]	MeOH	23	>99 : <1	20 : 80

[a] Reaction was conducted at rt. [b] Toluene was used as a solvent. [c] HFIP = hexafluoroisopropanol.



Scheme 1 Assumed catalytic cycle.

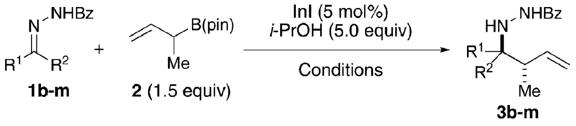
reactions were highly regio- and diastereoselective to afford *anti*-α-adducts[12] in all cases. Since aliphatic imines generally suffer from poor stability,[2,9,10] successful transformation of stable aliphatic hydrazones is particularly noteworthy (entries 1–4). Concerning aromatic hydrazones, both electron-donating and electron-withdrawing groups on the aromatic ring did not markedly affect the reaction rate and selectivity (entries 5–8). Moreover, α,β-unsaturated substrates reacted smoothly to afford the desired 1,2-adducts in high yields (entries 9 and 10). Furthermore, glyoxylate- and pyruvate-derived hydrazones were found to be excellent substrates (entries 11 and 12).

An assumed catalytic cycle as well as a transition state for formal α-addition with *anti*-selectivity is shown in Scheme 1. The catalytic cycle is initiated by boron-to-indium transmetallation at the γ-position of an allylic boronate to generate (*Z*)-crotylindium (**4**); an alcohol may accelerate this transmetallation. This (*Z*)-configured indium species **4** reacted then with an acylhydrazone *via* a cyclic six-membered transition state[3g,12] to afford *anti*-crotylated adduct **5**, which was protonated to give the product **3**[13] accompanied by regeneration of indium(I) iodide.[14] Thus, two γ-additions give the formal α-addition product.[15]

Finally, it was confirmed that the InI-catalyzed regio- and diastereoselective addition reaction could be applied to a ketone. When acetophenone (**6**) was used as an electrophile, addition of α-methylallylboronate **2** took place in high yield with complete α-selectivity and high diastereoselectivity (Scheme 2). In this case, the *syn*-adduct **7** was obtained predominantly.[16]

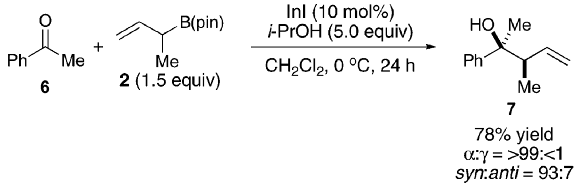
In summary, we have discovered that indium(I)-catalyzed addition of an α-methylallylboronate to *N*-acylhydrazones proceeded smoothly to give formal α-adducts with high

Table 3 Substrate scope for InI-catalyzed formal α-addition of α-methylallylboronate **2** to *N*-acylhydrazones **1**



Entry	R^1	R^2	Conditions	Product	Yield (%)	α : γ	*syn* : *anti*
1	$PhCH_2CH_2$	H	Toluene, rt, 48 h	**3c**	85	97 : 3	5 : 95
2	*n*-C_7H_{15}	H	Toluene, rt, 48 h	**3d**	94	96 : 4	8 : 92
3	*c*-Hex	H	Toluene, rt, 24 h	**3e**	97	94 : 6	7 : 93
4[a]	*t*-Bu	H	CH_2Cl_2, 0 °C, 48 h	**3f**	88	95 : 5	3 : 97
5[b]	Ph	H	CH_2Cl_2, 0 °C, 24 h	**3b**	97	99 : 1	6 : 94
6	4-$MeOC_6H_4$	H	CH_2Cl_2, 0 °C, 24 h	**3g**	98	>99 : <1	9 : 91
7	4-ClC_6H_4	H	CH_2Cl_2, 0 °C, 24 h	**3h**	96	>99 : <1	4 : 96
8	2-$MeOC_6H_4$	H	CH_2Cl_2, −20 °C, 72 h	**3i**	75	>99 : <1	6 : 94
9	$CH_2{=}CH$	H	CH_2Cl_2, 0 °C, 36 h	**3j**	85	>99 : <1	9 : 91
10	$PhC{\equiv}C$	H	CH_2Cl_2, 0 °C, 36 h	**3k**	99	>99 : <1	5 : 95
11	EtO_2C	H	CH_2Cl_2, 0 °C, 12 h	**3l**	98	>99 : <1	2 : 98
12	MeO_2C	Me	CH_2Cl_2, 0 °C, 72 h	**3m**	95	91 : 9	8 : 92[c]

[a] MeOH was used instead of *i*-PrOH. [b] 10 mol% of InI was used. [c] Tentatively assigned.



Scheme 2 InI-catalyzed formal α-addition of α-methylallylboronate **2** to ketone **6**.

anti-selectivity. A catalytic cycle and a six-membered transition state involving two γ-additions are proposed. Moreover, this unusual regioselectivity was also observed when a ketone was used as an electrophile. Further mechanistic investigations on this catalytic activation of a group 13 metal reagent (boron) with the same group 13 metal in its low-oxidation state (indium) and its application to asymmetric catalysis are now in progress.

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