ORGANIC LETTERS

2008
Vol. 10, No. 5
737−740

Development of General Catalytic Allylation of Acylhydrazones with Pinacolyl Allylboronate Using an Indium(I) Catalyst

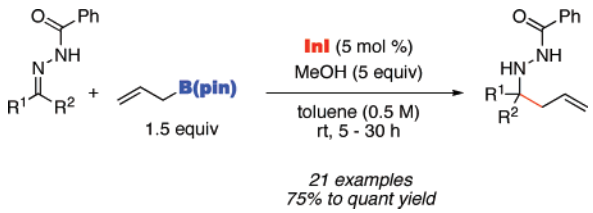
Uwe Schneider, I-Hon Chen, and Shū Kobayashi*

Department of Chemistry, School of Science and Graduate School of Pharmaceutical Sciences, The University of Tokyo, The HFRE Division, ERATO, Japan Science and Technology Agency (JST), Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

shu_kobayashi@chem.s.u-tokyo.ac.jp

Received November 14, 2007

ABSTRACT



Catalytic allylation of various acylhydrazones using a group 13 metal reagent (boron) in combination with a group 13 metal catalyst in its low-oxidation state (indium) has been developed. This operationally simple carbon–carbon bond-forming reaction displays remarkable substrate scope and functional group tolerance.

The development of innovative catalytic methods for efficient carbon−carbon bond formation is of high importance in modern organic synthesis.[1] In this context, the chemistry of indium in its low-oxidation state (I)[2] is still in its infancy;[3] only sporadic examples of its use as a *stoichiometric* reagent have been reported.[4] In addition, although organoindium compounds tolerate many functional groups and have a low toxicity, indium has been defined as a "rare metal";[5] thus the development of indium-*catalyzed* reactions becomes increasingly important. In an earlier report,[6] we disclosed a general catalytic allylation method for ketones through catalytic activation of an allylboronate with indium(I). To the best of our knowledge, this transformation represents the first catalytic synthetic method involving the use of a catalytic amount of indium(I). We subsequently aimed to extend this conceptually novel catalytic activation of a group 13 metal reagent (boron) with a group 13 metal catalyst in its low-oxidation state (indium) to imine derivatives as electrophiles.

The allylation of imine derivatives is an important carbon−carbon bond-forming transformation,[7] since the corresponding homoallylic amines and derivatives have proved to be extremely useful intermediates in natural products syntheses[8] and others.[9] Typical protocols for the allylation of imines involve the use of allylindium reagents generated in situ

(1) (a) *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*; Tsuji, J., Ed.; Wiley: Chichester, 2000. (b) *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, 2000.

(2) For recent reviews on the lower oxidation states of indium, see: (a) Tuck, D. G. *Chem. Soc. Rev.* **1993**, *22*, 269. (b) Pardoe, J. A. J.; Downs, A. J. *Chem. Rev.* **2007**, *107*, 2.

(3) In contrast, indium(III) derivatives are known to be commonly used in "catalytic" quantities as Lewis acid catalysts: Loh, T.-P.; Chua, G.-L. *Chem. Commun.* **2006**, 2739.

(4) For most significant examples, see: (a) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291. (b) Andrews, C. G.; Macdonald, C. L. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7453. (c) Cooper, B. F. T.; Andrews, C. G.; Macdonald, C. L. B. *J. Organomet. Chem.* **2007**, *692*, 2843. (d) Hill, M. S.; Hitchcock, P. B.; Pongtavornpinyo, R. *Inorg. Chem.* **2007**, *46*, 3783.

(5) *The Elements*, 3rd ed.; Emsley, J., Ed.; Oxford Press: Oxford, 1998.

(6) Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5909.

(7) For reviews on nucleophilic addition to imines, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (b) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651.

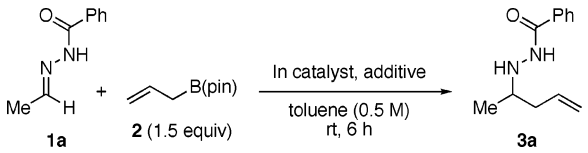
(8) For selected examples, see: (a) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (b) Kropf, J. E.; Meigh, I. C.; Bebbington, M. W. P.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 2046.

10.1021/ol702756k CCC: $40.75
Published on Web 02/07/2008

under Barbier-type conditions from the corresponding allyl halides.[10] More recently, these nucleophiles have been accessed through transmetallation of allylpalladium[11] and allylmercury[12] precursors. However, the major drawback of these methods is the use of more than stoichiometric amounts of indium metal or indium(I) halides. Moreover, other efficient allylation methods rely on toxic allylstannanes[13] or corrosive allylsilanes[14] and/or often require activated imine derivatives.[15] On the other hand, acylhydrazones[16] are readily available from the corresponding carbonyl compounds and offer superior stability compared to imines. Unfortunately, catalytic allylations of these electrophiles typically display very limited substrate generality.[17] We report here the general catalytic allylation of *N*-benzoylhydrazones with an allylboronate[18] in the presence of a catalytic amount of indium(I).

Our initial experiments were carried out in the reaction of acetaldehyde-derived acylhydrazone **1a** as a model substrate in dry toluene (0.5 M) at room temperature (Table 1). On the basis of our previous results,[6] we used commercially available pinacolyl allylboronate (**2**; 1.5 equiv) as a nucleophile and indium(I) iodide[19] (5 mol %) as a catalyst.

Table 1. Examination of the Indium(I)-Catalyzed Allylation of Model Hydrazone **1a** with Allylboronate **2**



entry	In catalyst (mol %)	additive (equiv)	yield (%)[a]
1	InI (5)		trace
2	InI (5)	MeOH (1)	40
3	InI (5)	MeOH (5)	99
4	InI (0.5)	MeOH (5)	93[b]
5		MeOH (5)	25
6	In(0) (5)	MeOH (5)	28
7	InI_3 (5)	MeOH (5)	62
8	In(0) (3.3) + InI_3 (1.7)	MeOH (5)	40

[a] Isolated yields after preparative thin-layer chromatography (silica gel). [b] Reaction time, 24 h.

The indium(I)-catalyzed reaction in dry toluene essentially did not proceed (entry 1), whereas in the presence of 1 equiv of methanol the desired homoallylic hydrazide **3a** was cleanly formed albeit in moderate yield (entry 2). However, the indium(I)-catalyzed allylation proceeded smoothly when 5 equiv of methanol were added under otherwise identical conditions (99% yield, entry 3). The significantly improved results in the presence of methanol may be ascribed to the increased solubility of hydrazone **1a**, which is virtually insoluble in toluene. Alternatively, methanol could play an important role in the activation of allylboronate **2**[20] or might promote the catalyst turnover as a proton source.[21] To our delight, further examination of catalyst loading revealed that use of as little as 0.5 mol % of indium(I) iodide gave the desired addition product in 93% isolated yield, after prolonged reaction time (24 h, entry 4). In contrast, the noncatalyzed transformation (in the absence of indium(I) iodide) was found to provide product **3a** in only 25% yield (entry 5). Various other solvents such as tetrahydrofuran, dimethoxyethane, 1,4-dioxane, *N*,*N*-dimethylformamide, acetonitrile, dimethyl sulfoxide, and water were investigated as well, but such solvents proved to be significantly less effective than the toluene−methanol system.[22,23] These truly remarkable catalytic results with indium(I) stand in sharp contrast to literature reports that require at least stoichiometric amounts of indium(I) reagents for indium-mediated Barbier-type[4a] and Reformatsky-type[24] reactions, metal-to-indium transmetallations,[11,12] or radical-generating reactions.[25]

(9) For selected examples of the use of homoallylic amines, see: (a) Agami, C.; Couty, F.; Evano, G. *Tetrahedron: Asymmetry* **2000**, *11*, 4639. (b) Schmidt, A. M.; Eilbracht, P. *J. Org. Chem.* **2005**, *70*, 5528. (c) Denhez, C.; Vasse, J.-L.; Harakat, D.; Szymoniak, J. *Tetrahedron: Asymmetry* **2007**, *18*, 424.

(10) (a) Loh, T.-P.; Ho, D. S.-C.; Xu, K.-C.; Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865. (b) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823. (c) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464. For related reviews on the use of indium in organic synthesis, see: (d) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (e) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959.

(11) (a) Cooper, I. R.; Grigg, R.; MacLachlan, W. S.; Sridharan, V.; Thornton-Pett, M. *Tetrahedron Lett.* **2003**, *44*, 403. (b) Fontana, G.; Lubineau, A.; Scherrmann, M.-C. *Org. Biomol. Chem.* **2005**, *3*, 1375.

(12) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.

(13) (a) Nakamura, H.; Nakamura, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4242. (b) Gastner, T.; Ishitani, H.; Akiyama, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1896. (c) Fernandes, R. A.; Stimac, A.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 14133.

(14) (a) Nakamura, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 2614. (b) Hamada, T.; Manabe, K.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 3927. (c) Kobayashi, S.; Ogawa, C.; Konishi, H.; Sugiura, M. *J. Am. Chem. Soc.* **2003**, *125*, 6610. (d) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596. (e) Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735. (f) Ding, H.; Friestad, G. K. *Synthesis* **2004**, 2216. (g) Ogawa, C.; Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 6491. (h) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686.

(15) (a) Ferraris, D.; Dudding, T.; Young, B.; Drury, W. J., III; Lectka, T. *J. Org. Chem.* **1999**, *64*, 2168. (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. (c) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10.

(16) (a) Oyamada, H.; Kobayashi, S. *Synlett* **1998**, 249. (b) Sugiura, M.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5176.

(17) For the use of more than a stoichiometric amount of indium metal in enantioselective or diastereoselective allylations of acylhydrazones: (a) Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741. (b) Cook, G. R.; Kargbo, R.; Maity, B. *Org. Lett.* **2005**, *7*, 2767. (c) Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315. (d) Kargbo, R.; Takahashi, Y.; Bhor, S.; Cook, G. R.; Lloyd-Jones, G. C.; Shepperson, I. R. *J. Am. Chem. Soc.* **2007**, *129*, 3846.

(18) For selected examples of the use of allylboron reagents in additions to C=N bonds, see: (a) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, 1382. (b) Sebelius, S.; Szabó, K. J. *Eur. J. Org. Chem.* **2005**, 2539. (c) Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, 5551. (d) Ramachandran, P. V.; Burghardt, T. E. *Pure Appl. Chem.* **2006**, *78*, 1397. (e) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, Kanai, K. M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687. (f) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398.

(19) Anhydrous indium(I) iodide powder (99.999%; Aldrich) was selected for its higher thermodynamic stability compared with other indium(I) halides.

(20) Methanol as a Lewis base could coordinate to the Lewis acidic boron atom of allylboronate **2** to generate the corresponding allylborate; this species might be activated for catalytic boron-to-indium transmetallation.

(21) Methanol could be necessary for the hydrolysis of the assumed *N*−metal bond in the initially formed reaction product.

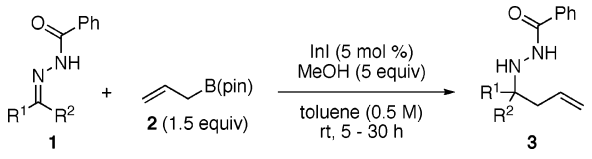
(22) It is noted that indium(I) iodide proved to be unstable in solvents such as DME, DMF, DMSO, and water; this redox-disproportionation process (formation of indium metal) is visible.

(23) After submission of our manuscript, the formation of a neutral indium sub-halide cluster from indium(I) iodide in the presence of TMEDA in toluene was reported: Green, S. P.; Jones, C.; Stasch, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8618.

Next, we turned our attention to control experiments because indium(I) is known to be prone to redox-disproportionation under certain conditions, thereby generating indium metal and indium(III) in a molar ratio of 2:1.[2] If this is the case in our current system, indium metal might activate **1a** and/or **2** through single electron transfer, whereas indium(III) might activate **1a** and/or **2** as a Lewis acid. However, independent use of either indium metal or indium(III) iodide proved to be less effective than indium(I) (entries 6 and 7). This trend also holds true for the combined use of indium(0) (3.3 mol %) and indium(III) iodide (1.7 mol %) in a molar ratio of 2:1 (40% yield, entry 8). These experiments demonstrate that indium(I) is by far the most effective catalyst tested and partially support the idea that indium(I) might be the real catalyst in our system.

We then investigated the substrate generality for the allylation of acylhydrazones **1** with pinacolyl allylboronate (**2**) by using 5 mol % of indium(I) iodide under optimized conditions (Table 2). Gratifyingly, it was found that the reaction displayed excellent generality, with various primary, secondary, and tertiary aliphatic aldehyde-derived hydrazones being transformed into the corresponding homoallylic hydrazides **3** in excellent yields (entries 1−8). It is noted that α,β-unsaturated substrates underwent exclusive 1,2-addition (entries 9−11). Moreover, various aromatic hydrazones including a heterocycle were shown to be smoothly allylated with **2** by using the indium(I) catalyst system (entries 12−18). Additionally, ketone-derived hydrazones were also converted into the corresponding tertiary homoallylic hydrazides in high yields (entries 19−21). Importantly, functional groups such as silyloxy, methoxy, chloro, dimethylamino, pyridine, and ester were compatible under the mild conditions of this operationally simple indium(I)-catalyzed carbon−carbon bond formation.[26]

Table 2. Substrate Scope for the Indium(I) Iodide Catalyzed Allylation of Hydrazones **1** with Allylboronate **2**



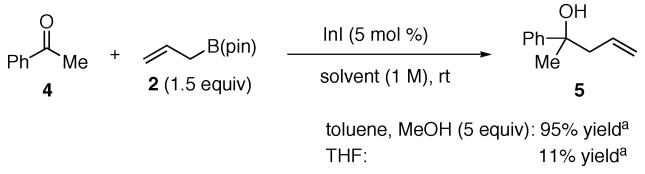
entry	hydrazone	R^1	R^2	yield (%)[a]
1	**1a**	Me	H	99
2	**1b**	*n*-pent	H	93
3	**1c**	Ph-CH_2-CH_2	H	99
4	**1d**	TBSO-CH_2-CH_2	H	96
5	**1e**	*i*-Pr-CH_2	H	97
6	**1f**	*i*-Pr	H	99
7	**1g**	*c*-hex	H	93
8	**1h**	*t*-Bu	H	93
9	**1i**	CH_2=CH	H	82
10	**1j**	(*E*)-Ph-CH=CH	H	78
11	**1k**	Ph-C≡C	H	quant
12	**1l**	Ph	H	91
13	**1m**	4-Cl-C_6H_4	H	96
14	**1n**	4-MeO-C_6H_4	H	98
15	**1o**	2-MeO-C_6H_4	H	98
16	**1p**	4-NMe_2-C_6H_4	H	75
17	**1q**	1-naphthyl	H	91
18	**1r**	3-pyridyl	H	86
19	**1s**	-$(CH_2)_5$-		87
20	**1t**	Me	Me	80
21	**1u**	CO_2Me	Me	89

[a] Isolated yields after preparative thin-layer chromatography (silica gel).

With the aim to shed light on the reaction mechanism, various control experiments were performed. ^{1}H and ^{11}B NMR spectroscopic analysis of allylboronate **2** in dry toluene-d_8 (0.75 M) in the presence of indium(I) iodide (100 mol %) and dry methanol-d_3 (3.33 equiv) indicated the remarkably clean transformation of **2** into a single species, allylindium(I),[27,28] within 3 h at room temperature (see Supporting Information, NMR experiment A). The identical species was independently generated under Barbier-type conditions from allyl bromide and indium metal (100 mol %) in the same deuterated solvent system (see Supporting Information, NMR experiment B). In addition, the Barbier-type allylation of **1a** with allyl bromide and a stoichiometric amount of indium(0) resulted in the smooth generation of **3a** as well (93% yield). Finally, ^{1}H and ^{11}B NMR monitoring of the indium(I) iodide catalyzed allylation of **1a** with **2** revealed the direct formation of product **3a**. On the basis of these control experiments, although some unclear points still remain, we surmise that the active species in our reaction system might be allylindium(I), generated in situ from **2** through catalytic boron-to-indium transmetallation.[29] In this context, it is noted that in the absence of methanol-d_3, allylboronate **2** proved to be stable in the presence of indium(I) iodide in toluene-d_8 at room temperature (see Supporting Information, NMR experiment C); this observation is consistent with the poor allylation result for **1a** in toluene as a sole solvent (trace yield; cf. Table 1, entry 1). Thus, methanol likely plays a key role in the present mechanistic scenario, through enabling the in situ formation of the catalytically active species from **2** and indium(I) iodide.[20]

In an additional experiment, we examined the indium(I)-catalyzed allylation of acetophenone (**4**) with **2** in the present toluene−methanol system at room temperature (Scheme 1). Importantly, we found that the reaction proceeded smoothly,

Scheme 1. Remarkable Solvent Effect in the Indium(I) Iodide Catalyzed Allylation of Acetophenone (**4**) with Allylboronate **2**



[a] Isolated yields after preparative thin-layer chromatography (silica gel).

(24) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4475.

(25) Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2006**, *47*, 2859.

providing the desired product **5** in 95% yield after 12 h. On the other hand, compound **5** was formed in only 11% yield after 24 h at room temperature when dry THF was used as a solvent.[30] The excellent allylation result under our newly developed, milder reaction conditions constitutes a substantial advance compared with our earlier report.[6,31]

(26) It is noted that in the absence of indium(I) iodide isolated yields for several exemplified products (**3h**, **3l**, **3o**, **3r**, **3t**) did not exceed 15%.

(27) ^{1}H NMR (toluene-d_8, 400 MHz): δ = 1.53−1.55 (m, 2H), 4.86−4.97 (m, 1H), 5.62−5.73 (m, 2H) (see Supporting Information, charts 8 and 10).

(28) Allylindium(I) has been previously reported: see refs 11b and 12.

(29) This selective transmetallation process was detected as well with ^{11}B NMR analysis, which unambiguously shows that the boron is stripped off the allylic moiety (shift of the initial boron signal at ~32 to ~21 ppm and ~17 ppm; see Supporting Information, NMR experiment A).

(30) This poor allylation result is consistent with the observation that allylboronate **2** is relatively stable in the presence of indium(I) iodide in dry THF-d_8 at room temperature; only a sluggish, non-selective boron-to-indium transmetallation occurs (see Supporting Information, NMR experiment D).

(31) Indeed, in our earlier report on indium(I)-catalyzed ketone allylation, heating to 40 °C and longer reaction times were required for full conversion of ketone substrates.

In summary, we have developed highly efficient catalytic allylation of *N*-benzoylhydrazones using a group 13 metal reagent (boron) with a group 13 metal catalyst in its low-oxidation state (indium). This transformation displays both broad substrate scope and high functional group tolerance. Importantly, the present toluene−methanol system proved to be significantly more effective for ketone allylation than the previously reported one.[6] Further mechanistic studies and the application to asymmetric catalysis are ongoing in our laboratories.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from Japan Society of the Promotion of Sciences (JSPS).

Supporting Information Available: Experimental Section and related spectra for the reported reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702756K