

Palladium–Indium Iodide-Mediated Allylation and Propargylation of Glyoxylic Oxime Ether and Hydrazone: The Role of Water in Directing the Diastereoselective Allylation

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Abstract: Allylation and propargylation of glyoxylic oxime ether in the presence of a catalytic amount of palladium(0) complex and indium(I) iodide were studied. Excellent diastereoselectivities in allylation were achieved in the presence of water, although low diastereoselectivities were observed in the absence of water. Propargylation of glyoxylic oxime ether proceeded with good diastereoselectivities in the presence of LiBr or LiCl.

Indium-mediated allylation reactions have been of great importance from both economic and environmental points of view.¹ Recently, a new method for preparation of allylindium reagents via transient organopalladium intermediates has been studied by Araki et al.,² and then several successful examples of palladium–indium iodide-mediated allylation of aldehydes under new reaction conditions were reported by Grigg's group, Kang's group, and our group.³ Recently, the palladium–indium iodide-mediated propargylation of aldehydes was also studied by Marshall et al.⁴ However, the corresponding reaction of imine derivatives has not been widely studied;⁵ there-

SCHEME 1



TABLE 1.	Reaction	of	1A-	D	with	2a4
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entry	imine	conditions	time (h)	yield (%) ^b
1	1A	2a, Pd(PPh ₃) ₄	1	92
2	1B	2a , Pd(PPh ₃) ₄	10	nr (97)
3	1A	2a , BF ₃ •OEt ₂ , Pd(PPh ₃) ₄	3	nr (93)
4	1C	2a , Pd(PPh ₃) ₄	1	82
5	1D	2a , Pd(PPh ₃) ₄	10	nr (89)

^{*a*} Reactions were carried out with **1A–D** and **2a** in the presence of InI at 20 °C. ^{*b*} Isolated yields; yields in parentheses are for the recovered starting material.

fore, the allylation and propargylation of imine derivatives and its stereocontrol have been a subject of current interest. As a part of our program directed toward the development of indium-mediated reaction of imine derivatives,⁶ we recently reported the palladium-indium iodide-mediated regioselective allylation of glyoxylic oxime ether.⁷ In this study, the selective formation of α -adducts was observed in anhydrous THF, although the γ -adducts were formed in the presence of water. Herein, we now report the reactivity of glyoxylic imines, the effect of water in simple allylation, and diastereoselective propargylation.

We first investigated the reactivity of imines 1A-D toward an allylindium reagent (Scheme 1). The reaction of glyoxylic oxime ether 1A with allyl acetate 2a was carried out in the presence of Pd(PPh₃)₄ (0.05 equiv) and indium(I) iodide (2 equiv) in THF (Table 1, entry 1). As expected, glyoxylic oxime ether 1A exhibits a good reactivity to give the allylated product 3A in 92% yield after being stirred at 20 °C for 1 h, without formation of significant byproducts such as a reduced product. In contrast, allylation reaction of aldoxime ether 1B did not take place under similar reaction conditions, and 97% of starting compound 1B was recovered (entry 2). These results suggest that the reactivity of 1A is enhanced by the neighboring electron-withdrawing substituent. How-

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⁽¹⁾ For a recent review, see: Li, C. J.; Chan, T. H. Tetrahedron 1999, 55, 11149. For some examples of indium-mediated reaction, see: (a) Yang, Y.; Chan, T. H. J. Am. Chem. Soc. 2000, 122, 402. (b) Chan, T. H.; Yang, Y. J. Am. Chem. Soc. 1999, 121, 3228. (c) Paquette, L. A.; Rothhaar, R. R. J. Org. Chem. 1999, 64, 217. (d) Woo, S.; Sqires, N.; Fallis, A. G. Org. Lett. 1999, 1, 573. (e) Engstrom, G.; Morelli, M.; Palomo, C.; Mitzel, T. Tetrahedron Lett. 1999, 40, 5967. (f) Loh, T.-P.; Zhou, J. R. Tetrahedron Lett. 1999, 40, 9115. For examples of metallic indium-mediated allylation of imines, see: (g) Lu, W.; Chan, T. H. J. Org. Chem. 2001, 66, 3467. (h) Yanada, R.; Kaieda, A.; Takemoto, Y. J. Org. Chem. 2001, 66, 7516. (i) Lu, W.; Chan, T. H. J. Org. Chem. 2000, 65, 8589. (j) Chan, T. H.; Lu, W. Tetrahedron Lett. 1998, 39, 8605. (k) Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronichi, A. J. Org. Chem. 1994, 59, 7766. (l) Beuchet, P.; Marrec, N. L.; Mosset, P. Tetrahedron Lett. 1992, 33, 5959. (m) Lee, J. G.; Choi, K. I.; Pae, A. N.; Koh, H. Y.; Kang, Y.; Cho, Y. S. J. Chem. Soc., Perkin Trans. 1 2002, 1314.

⁽²⁾ Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. Org. Lett. **2000**, *2*, 847.

^{(3) (}a) Anwar, U.; Grigg, R.; Rasparini, M.; Savic, V.; Sridharan, V. Chem. Commun. **2000**, 645. (b) Anwar, U.; Grigg, R.; Sridharan, V. Chem. Commun. **2000**, 933. (c) Kang, S.-K.; Lee, S.-W.; Jung, J.; Lim, Y. J. Org. Chem. **2002**, 67, 4376. We reported InI-Pd(0)-promoted metalation and addition of chiral 2-vinylaziridines. See: (d) Takemoto, Y.; Anzai, M.; Yanada, R.; Fujii, N.; Ohno, H.; Ibuka, T. *Tetrahedron Lett.* **2001**, 42, 1725. (e) Anzai, M.; Yanada, R.; Fujii, N.; Ohno, H.; Ibuka, T.; Takemoto, Y. *Tetrahedron* **2002**, 58, 5231.

^{(4) (}a) Marshall, J. A.; Grant, C. M. J. Org. Chem. 1999, 64, 696.
(b) Marshall, J. A.; Grant, C. M. J. Org. Chem. 1999, 64, 8214. (c) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. Org. Lett. 2001, 3, 3369.

⁽⁵⁾ Cooper, I. R.; Grigg, R.; MacLachlan, W. S.; Thornton-Pett, M.; Sridharan, V. *Chem. Commun.* **2002**, 1372.

⁽⁶⁾ For indium-mediated radical reaction of imine derivatives, see: (a) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131. (b) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454. (c) Yanada, R.; Nishimori, N.; Matsumura, A.; Fujii, N.; Takemoto, Y. *Tetrahedron Lett.* **2002**, *43*, 4585.

⁽⁷⁾ Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. J. Org. Chem. 2003, 68, 6745.

SCHEME 2



ever, the reaction of **1A** did not proceed in the presence of $BF_3 \cdot OEt_2$ and starting compound **1A** was recovered (entry 3), because the reaction would proceed via the sixmembered ring transition state between the allylic indium reagent and the C=N bond of **1A**. The reaction of glyoxylic hydrazone **1C** having a benzoylamino group also proceeded smoothly to afford the desired allylated product **3C** in 82% yield (entry 4). In contrast, the reaction of glyoxylic hydrazone **1D** having a diphenylamino group did not proceed, probably because the basic diphenylamino group on **1D** would suppress the formation of the six-membered ring transition state (entry 5). These results suggest that the formation of six-membered ring transition state is also an important point for successful allylation of imine derivatives.

We next examined the reaction of Oppolzer's camphorsultam derivative of glyoxylic oxime ether **4**, which has shown excellent reactivity in our previous work on radical reactions (Scheme 2).⁸ Recently, we have observed that the palladium—indium iodide-mediated reaction of glyoxylic oxime ether **4** with monosubstituted allyl acetates or carbonates afforded either the γ -adducts or the α -adducts by change of the reaction conditions.⁷ Thus, we expected that the study on allylation using unsubstituted allyl reagents would lead to informative suggestions regarding the reaction pathway.

At first, we studied the allylation in anhydrous THF by using several allylic reagents 2a-f (Table 2). The reaction of **4** with allyl acetate **2a** (2 equiv) in the presence of Pd(PPh₃)₄ (0.05 equiv) and indium(I) iodide (2 equiv) proceeded smoothly at 20 °C to give 89% yield of the desired product **5** with 62% de (entry 1). Additionally, the diastereoselectivity of **5** was shown to be dependent on the reaction time; thus, the prolonged reaction led to lower selectivity (entries 1–3). To our surprise, the low diastereoselectivities were also observed in the reaction using allylic reagents **2b**–**f** in anhydrous THF (entries 4–8). In our previous studies on metallic indium(0)-mediated reaction of **4** in aqueous media, the desired product **5** was obtained with 90% de.^{6b} In contrast to indium(0)-mediated allylation,^{6b} the indium iodide-

TABLE 2. Reaction of 4 with 2a-f^a

entry	reagent	solvent	time (h)	yield (%) ^b	de (%) ^c
1	2a (2 equiv)	THF	0.25	89	62
2	2a (2 equiv)	THF	1	89	31
3	2a (2 equiv)	THF	3	91	20
4	2b (2 equiv)	THF	1	89	37
5	2c (1.2 equiv)	THF	1	93	35
6	2d (2 equiv)	THF	1	91	42
7	2e (1.2 equiv)	THF	1	83	45
8	2f (1.2 equiv)	THF	1	78	36
9	2a (2 equiv)	THF-H ₂ O (10:1)	0.25	88	92
10	2a (2 equiv)	$THF - H_2O(10:1)$	1	91	91
11	2a (2 equiv)	$THF - H_2O(10:1)$	20	95	91
12	2b (1.2 equiv)	$THF - H_2O(10:1)$	1	96	92
13	2c (2 equiv)	$THF - H_2O(10:1)$	1	95	94
14	2d (2 equiv)	$THF - H_2O(10:1)$	1	96	91
15	2e (1.2 equiv)	$THF - H_2O(10:1)$	1	90	93
16	2f (1.2 equiv)	$THF - H_2O(10:1)$	1	90	92

^{*a*} Reactions were carried out with **4** and **2a**–**f** in the presence of Pd(PPh₃)₄ and InI at 20 °C. ^{*b*} Isolated yields. ^{*c*} Diastereoselectivities of the product were determined by ¹H NMR analysis of the diastereomeric mixture obtained after rough purification of chromatography.

mediated allylation of oxime ether **4** with allyl halides 2c, 2e, and 2f did not proceed in the absence of the palladium catalyst. Additionally, we observed the effect of water on regioselectivity in reaction of 4 using monosubstituted allylic reagents.7 Therefore, we next investigated the effect of water on the allyaltion reaction (entries 9-16). As expected, in the presence of water, the desired product 5 was obtained from allyl acetate 2a (2 equiv) in 88% yield with 92%, after being stirred at 20 °C for 0.25 h (entry 9). Prolonged reaction in THF- $H_2O(10:1, v/v)$ did not lead to lower selectivity, and good diastereoselectivity was observed after being stirred at 20 °C even for 20 h (entries 9-11). These diastereoselectivities are comparable to that obtained by metallic indium-mediated reaction reported in our previous work.^{6b} The absolute configuration of major product was assigned to be S by comparison with authentic spectral data. 6b,9 The replacement of allyl acetate 2a with other allylic reagents 2b-f led to similar chemical yields and selectivities (entries 12-16).

Although the precise reason for the effect of water was unclear, these observations would be explained by the reversibility of allylation reaction (Scheme 3). Under the anhydrous reaction conditions, the prolonged reaction would allow reversibility between oxime ether **4** and the adduct **B**, giving isomers (*S*)-**5** and (*R*)-**5** having thermodynamically similar stability with low diastereoselectivities. In contrast, water suppresses the reversibility as a result of the quick trapping reaction of the branched adduct **B** with H_2O ; therefore, the product (*S*)-**5** was kinetically formed via a stable six-membered ring transition state **A** having lower energy. The reversibility in

⁽⁸⁾ We reported radical addition to glyoxylic oxime ether. See: Miyabe, H.; Ushiro, C.; Ueda, M.; Yamakawa, K.; Naito, T. J. Org. Chem. **2000**, 65, 176.

⁽⁹⁾ Zinc-mediated allylation reaction of glyoxylic oxime ether was reported by Hanessian's group. They also reported a potential route to amino acids. The allylglycine derivative can be prepared from product **5** through selective cleavage of the N–O bond using Mo(CO)₆ and the hydrolysis of sultam auxiliary by treatment with aqueous LiOH. See: (a) Hanessian, S.; Yang, R.-Y. *Tetrahedron Lett.* **1996**, *37*, 5273. (b) Hanessian, S.; Bernstein, N.; Yang, R.-Y.; Maguire, R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1437. (c) Hanessian, S.; Lu, P.-P.; Sanceau, J.-Y.; Chemla, P.; Gohda, K.; Fonne-Pfister, R.; Prade, L.; Cowan-Jacob, S. W. *Angew. Chem., Int. Ed.* **1999**, *38*, 3160.



SCHEME 4



allylation reaction of imines using other allylmetals has been observed.¹⁰⁻¹² Recently, a new mechanism involving [3,3]-sigmatropic rearrangement was also proposed by T.-P. Loh et al.¹³

We next investigated propargylation of glyoxylic oxime ether 4 in anhydrous THF (Scheme 4). Among several propargylic alcohol derivatives evaluated (6a-c), mesylate 6a was the most effective for propargylation of oxime ether 4. The palladium-indium iodide-mediated reaction of 4 with mesylate 6a proceeded slowly to give the propargylated product 7 in 67% yield as a major product, accompanied with 14% of starting compound 4 (Table 3, entry 2), although no reaction took place in the absence of palladium catalyst (entry 1). Several palladium catalysts and additives were investigated (entries 3-9). Although the use of HMPA led to a low yield (entry 3),⁴ the reaction was found to proceed smoothly in the presence of LiBr or LiCl as an additive (entries 4-7).¹⁴ The reaction of **4** in the presence of Pd(dppf)Cl₂ and LiBr proceeded smoothly to give the major product 7 in 73% yield, after being stirred at 20 °C for 15 h (entry 5). $Pd(OAc)_2 \cdot PPh_3$ also served as an effective catalyst (entry

(10) Crossover experiment was performed. See: Supporting Information.

(12) Isomerization of indium reagents via the allylic rearrangement of indium atom was reported. See: Hirashita, T.; Hayahi, Y. Mitsui, K.; Araki, S. *J. Org. Chem.* **2003**, *68*, 1309.

(13) (a) Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. J. Am. Chem. Soc. 2003, 125, 2958. (b) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. Tetrahedron Lett. 2001, 42, 8705.

(14) Lee, K.; Seomoon, D.; Lee, P. H. Angew. Chem., Int. Ed. 2002, 41, 3901.

1 6a ^a
i 6a

entry	catalyst	additive	time (h)	yield (%) b
1	none	none	20	nr (78)
2	Pd(PPh ₃) ₄	none	50	67 (14)
3	Pd(PPh ₃) ₄	HMPA	20	20
4	Pd(PPh ₃) ₄	LiBr	25	75
5	Pd(dppf)Cl ₂	LiBr	15	73
6	Pd(OAc) ₂ ·PPh ₃	LiBr	15	78
7	Pd(dppf)Cl ₂	LiCl	15	72
8	Pd(dppf)Cl ₂	LiI	15	58
9	none	LiBr	20	trace

^{*a*} Reactions were carried out with **4** and **6a** in the presence of InI in THF at 20 °C. ^{*b*} Isolated yields of major product; yields in parentheses are for the recovered starting material.

SCHEME 5



6).¹⁵ Although the exact diastereoselectivities of the product could not determined by ¹H NMR analysis of the diastereomeric mixture, the combined yields of other diastereoisomers were less than 7%. The absolute configuration at the newly formed stereocenter of **7** was determined by X-ray analysis.¹⁶

We finally investigated the palladium—indium iodidemediated reaction of **4** with mesylate **8** (Scheme 5). The reaction of **4** with **8** (2 equiv) in the presence of Pd(dppf)-Cl₂, LiCl, and indium(I) iodide proceeded smoothly to give 44% yield of the propargylic product **9** with 90% de and 17% yield of the allenic product **10** with 90% de. These results indicated that the interconversion of allenic isomer **B** and propargylic isomer **C** would lead to the propargylic product **9** and the allenic product **10**, respectively.

In conclusion, we have demonstrated that the palladium—indium iodide-mediated allylation and propargylation of glyoxylic oxime ether afforded allylated and propargylated products. As the important effect of water on diastereoselectivity, the allylated products were kinetically formed with excellent diastereoselectivities in

^{(11) (}a) Yanagisawa, A.; Ogasawara, K.; Yasue, K.; Yamamoto, H. J. Chem. Soc., Chem. Commun. **1996**, 367. (b) Miginiac, L.; Mauzé, B. Bull. Soc. Chim. Fr. **1968**, 4674. (c) Mauzé, B.; Miginiac, L. Bull. Soc. Chim. Fr. **1973**, 1832. (d) Mauzé, B.; Miginiac, L. Bull. Soc. Chim. Fr. **1973**, 1838. (e) Mauzé, B.; Miginiac, L. Bull. Soc. Chim. Fr. **1973**, 1082.

 ⁽¹⁵⁾ Oppolzer, W.; Flachsmann, F. *Tetrahedron Lett.* **1998**, *39*, 5019.
 (16) X-ray analysis of **7** and a rationalized stereochemical feature for propargylation are provided in Supporting Information.

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the presence of water. In contrast, propargylation proceeded with good diastereoselectivities in anhydrous THF.

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Supporting Information Available: Experimental procedure and characterization data for all obtained compounds, ¹H and ¹³C NMR spectrum of all obtained compounds, crossover experiment, X-ray crystal data of 7, and rationalized stereochemical feature for propargylation. This material is available free of charge via the Internet at http://pubs.acs.org.

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