JOC*Note*

Organometallic Reactions in Aqueous Media: Indium-Promoted Additions to 2-Pyridyl and Glyoxylic Acid Oxime Ethers

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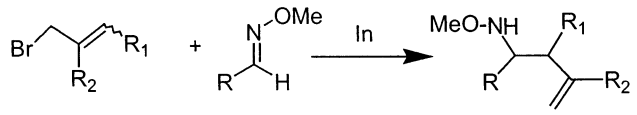
Abstract: Oxime ethers derived from 2-pyridinecarboxaldehyde and glyoxylic acid can be effectively allylated in water with five differently functionalized allylic bromides promoted by indium. When the metal is positioned in close proximity of flanking heteroatomic centers, chelation by In is indeed operative and affects both reactivity and stereochemistry. Stereochemical assignments in the addition products were based on X-ray crystallographic measurements and spectral correlations.

Indium-mediated reactions have gained increasing popularity over the past decade as a useful tool in organic synthesis under environmentally benign conditions.[1] A particularly important synthetic development involves the reaction of allylindium with carbonyl compounds under aqueous conditions with the major aim of forming new carbon−carbon bonds in a stereoselective fashion.[2] Although the allylation of imines, to give the corresponding homoallylic amines, could be considered an important transformation, no applications of indium-mediated Barbier-type reactions in aqueous media have been reported for a long time and only a few papers dealing with the allylation in organic solvents such as THF and DMF have appeared so far.[3] This could be attributed to the well-established lower electrophilicity of aldimines compared with that of the corresponding carbonyl compounds[4] and to their propensity to undergo hydrolysis and to give homocoupling products.[5] Only very recently[6] sulfonimines, derived from aryl and non enolizable aliphatic aldehydes, turned out to be the reagents of choice to overcome successfully the drawbacks associated with the fragility and low reactivity of the C=N moiety in aqueous media. Regarding the indium-mediated allylation of other C=N containing systems, a procedure has been reported[7] for tosyl/aryl hydrazones and aldonitrones in a DMF−H_2O system that generates homoallylic nitrogen compounds.

SCHEME 1



Our continuing interest in indium-promoted reactions[8] prompted us to focus on the allylation of oxime ethers, an almost unexplored area of indium-mediated reactions.[9] Besides imines, oximes and oxime ethers are in fact attractive starting materials[10] for the synthesis of amino compounds because the N−O bond of alkoxyamines is much easier to cleave than the amine C−N bond or the hydrazine N−N bond.[11] The synthesis of alkoxy amines by addition of classical organometallic reagents to the C−N double bond of oxime ethers is, however, plagued by the propensity for proton abstraction α to the C−N double bond, by the lability of the N−O bond, and by the poor electrophilicity of the oxime ethers.[12] Some of the difficulties described above can be avoided by using organocerium reagents generated by Li → Ce or Mg → Ce transmetalation.[13]

Reportedly,[14] additions to oximes are facilitated by prior protection of the oxime oxygen. Considering this we initially chose the methyl moiety as the protecting group to oxygen. Barbier-type allylation of a number of oxime ethers mediated by indium was examined (Scheme 1).

We started investigating the reaction of the *O*-methyl oxime of benzaldehyde (Ph-CH=N-OMe) with allylbromide and indium, but even after prolonged reaction times and excess of reagents only the starting material was recovered. Recent studies have provided convincing evidence that chelation control between indium and oxygen can indeed operate under aqueous conditions. Furthermore the chelation of nitrogen to indium detected in the 2-PyCHO 1,2-addition of allylindium reagents in water has been assumed by Paquette[15] to provide a

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(6) (a) Lu, W.; Chan, T. H. *J. Org. Chem*. **2000**, *65*, 8589. (b) Lu, W.; Chan, T. H. *J. Org. Chem*. **2001**, *66*, 3467.

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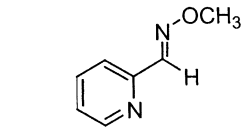
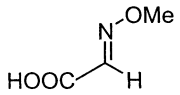
suitable mean for activation, delivery of the allyl residue, and control of stereochemistry. On these grounds we selected 2-pyridincarboxaldoxime-methyl ether (2-Py-CH=N-OMe) (**I**) and glyoxylic acid methoxime (**II**) as external chelators in which a combined enhanced electrophilic character and an additional chelation site might result in a beneficial effect on the reactivity. The five allylic bromides **1**−**5** served as reaction partners.



I



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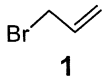
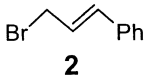
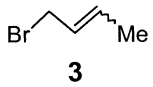


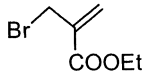
1



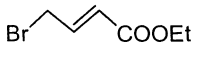
2



3



4

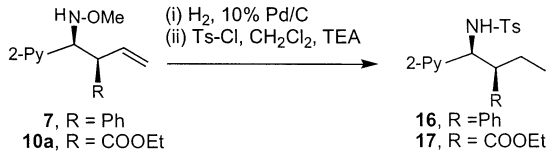


5

The indium-mediated Barbier type reaction of **I** with activated halides **1**−**5** was examined (Table 1). The reactions could be smoothly carried out in pure water, whereas the use of aqueous mixed solvents (see entries 2 and 3) led to a remarkable lowering of the yields, in line with the general picture provided by literature data. Moving from THF to water would decrease stability of the allylindium[2c] with increase of reactivity toward the incoming electrophile and would increase the hydrophobic effect, well-known[16] for playing a favorable role on the reactivity in many instances. Both of these factors might account for the observed trend. Unless otherwise stated all allylation reactions were allowed to proceed for several hours (see Experimental Section) at room temperature. Throughout 1:1:1.1 or 1:2:2 ratios between oxime ether, indium, and halide were used, because in the presence of a larger excess of reagents, overallylation (see entry 7) occurred.

The expected products were formed in satisfactory to very good yields, and no side reaction products were observed with the only exception of the allylation with **4**, which even under the optimized conditions led (entry 8) to a residual formation of minor amounts (ca. 10%) of the bisallylated derivative. Moreover the indium-mediated allylation of oxime ethers occurred with excellent regioselectivity when cinnamyl (**2**) and crotyl bromide (**3**) or bromocrotonate (**5**) were used. The γ-allylation products were obtained exclusively from the allylation, and no α-products were found, in line with the regioselectivity observed for indium-mediated allylation of carbonyl compounds[17] and imines.[6] Interestingly, the reaction of

SCHEME 2



7, R = Ph
10a, R = COOEt

16, R =Ph
17, R = COOEt

1 with 3-Py-CH=N-OMe and 4-Py-CH=N-OMe performed under standard conditions was unsuccessful, the starting materials being recovered even after prolonged reaction times.

The level of diastereoselectivity of the processes listed in Table 1 lies in the range of 52−98%. Whereas the reaction of **I** and **II** with bromides **2** and **5** resulted highly stereoselective (entries 5, 9, 11, 14), for the crotyl bromide (**3**) the stereoselectivity was strongly diminished (entries 6 and 12), in agreement with the previously reported reaction of this allylic bromide with carbonyl compounds.[18] The assignment of the relative configuration to the highly prevailing diastereoisomer **7** as the *syn* adduct (entry 5) was done on the strength of X-ray crystallographic analysis after hydrogenolysis of **7** and conversion into the corresponding sulfonamide **16** (Scheme 2).[19]

In adduct **10a** the methine vinylic proton appeared characteristically[15] at higher field (δ 5.67) than the counterpart (δ 5.74) in its epimer **10b** obtained by treatment of **7** with $NaBH_3CN$,[20] thus allowing distinction between the 1,2-*syn* and 1,2-*anti* diastereoisomers. The stereochemical assignment of **10a** as the *syn* adduct (entry 9) was ultimately corroborated by solid-state structural studies on the sulfonamido derivative **17** obtained as before.[19]

In the reaction between **I** and **3** (entry 6) the diastereomeric mixture of adducts **8a** and **8b** was amenable to chromatographic separation and distinction between the two diastereoisomers was achieved by high-field ^{1}H NMR analysis. The stereochemical assignment based on the sequence of the methine vinylic proton chemical shifts (**8a** δ 5.68; **8b** δ 5.81) and on their correlation with an array of analogues including **10a** and **10b** and with those trends established earlier[15] made it possible again again to identify the major constituent **8a** as the 1,2-*syn* adduct. Regarding the reaction between **II** and **3** (entry 12), the assignment of the *syn* configuration to **13a**, the major constituent of the diastereomeric mixture, was done after hydrogenation with Pd on charcoal, which led to alloisoleucine as the main product.[21] By analogy and taking into consideration the trend previously observed in the case of adducts **8** and **7**, the *syn* diastereoselectivity could be suggested for **12** as well. Finally for **15** (entry 14) the

(15) Paquette, L. A.; Rothhaar, R. R. *J. Org. Chem.* **1999**, *64*, 217.
(16) (a) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1993**, 741. (b) Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Schomer, W. W. *J. Org. Chem.* **1997**, *62*, 4293.

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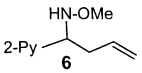
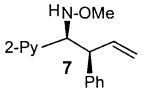
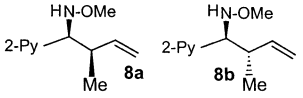
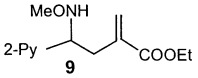
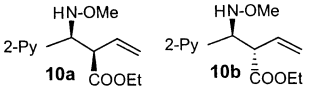
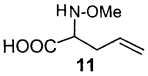
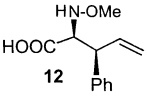
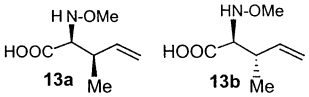
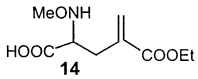
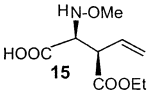
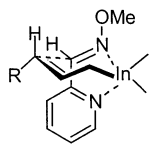
(18) Ho, D. S.-C.; Sim, K. Y.; Loh, T.-P. *Synlett* **1996**, 263.
(19) CCDC 197104 and CCDC 197103 contain the supplementary crystallographic data for compound **16** and **17,** respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033. E-mail: deposit@ccdc.cam.ac.uk).
(20) Attempts at performing the epimerization with NaH led to double bond isomerization, whereas when $NaBH_4$ or BH_3 was employed simultaneous epimerization and double bond reduction took place. Only when $NaBH_3CN$ was used did a clean epimerization of the carbon α to the ester moiety occur.
(21) Lloyd-Williams, P.; Monerris, P.; Gonzales, I.; Jou, G.; Giralt, E. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1969.

TABLE 1. Indium-Mediated Allylation Reaction of Oxime Ethers in Aqueous Media

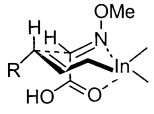
Entry	Oxime Ether	Allylic Bromide	Solvent	Ratio[a]	Product	Yield%[b]	*Syn/anti*
1	**I**	**1**	H_2O	1 : 2 : 5		70	
2	**I**	**1**	H_2O/DMF[c]	1 : 2 : 5	 **6**	20	
3	**I**	**1**	H_2O/THF[d]	1 : 2 : 5		40	
4	**I**	**1**	H_2O	1 : 1 : 1.1		70	
5	**I**	**2**	H_2O	1 : 2 : 2	 **7**	60	> 99 : 1
6	**I**	**3**	H_2O	1 : 2 : 2	 **8a** **8b**	75	76 : 24
7	**I**	**4**	H_2O	1 : 2 : 5	 **9**	e	
8	**I**	**4**	H_2O	1 : 1 : 1.1		67	
9	**I**	**5**	H_2O	1 : 2 : 2	 **10a** **10b**	96	> 99 : 1
10	**II**	**1**	H_2O	1 : 1 : 1.1	 **11**	65	
11	**II**	**2**	H_2O	1 : 2 : 2	 **12**	57	> 99 : 1
12	**II**	**3**	H_2O	1 : 2 : 2	 **13a** **13b**	70	80 : 20
13	**II**	**4**	H_2O	1 : 1 : 1.1	 **14**	58	
14	**II**	**5**	H_2O	1 : 2 : 2	 **15**	70	> 99 : 1

[a] **I** or **II**/indium/allylic bromide. [b] Isolated yields. [c] H_2O/DMF = 1:3. [d] H_2O/THF = 1:1. [e] The bis-allylation product was isolated in 53% yield.

value of the methine vinylic proton (δ 6.00) appeared similar to the value obtained (δ 6.00−5.90) for the *syn* isomer in the allylation of glyoxylic aldehyde.[15]



A



B

The heavily favored *syn* diastereoselectivities can be explained in terms of the adherence by **I** and **II** to transition states where the indium atom coordinates to chelation sites. Concerning the competitive involvement of intermolecular versus intramolecular modes of chelation, the presence of two proximal binding sites to indium conforms the expectation based on the chelated transition states **A** and **B**, in line with Paquette findings in the allylation reaction of 2-pyridinecarboxaldehyde and glyoxylic acid.[15] The formation of a single diastereomeric

product (entries 5, 9, 11, 14) further attests on the other hand to the powerful chelating ability of indium even in aqueous media. In the present circumstances, complexation of indium reagent to **I** is thought to foster adoption of a chair conformation as in **A** in order to maximize the level of the two *N*-indium interactions.[2d] A mechanistic model in which the indium atom coordinates simultaneously to the oxime-ether nitrogen and to the carbonyl is also viable for the reaction of the allylic bromides with the glyoxylic acid **II**. Chelation in this fashion simultaneously activates the oxime ether toward nucleophilic attack and locks the allylic bromide, giving rise to a chair conformation of the transition state **B**. A revealing piece of information that emerges from this study lies in the unreactivity of 3-Py-CH=N-OMe and 4-Py-CH=N-OMe relative to **I** toward allylic bromides, which contrasts with what has been previously found for the corresponding aldehydes.[15] This ordering is not accommodated by a key role of electron withdrawal as the unique factor responsible for the reactivity of **I**, since direct competition would invariably be biased in the same direction for the three oxime-ethers. Rather it appears that, besides exerting a control only on the stereochemical outcome, the intramolecular chelation of indium to the pyridine nitrogen does indeed operate in water and is sufficiently favorable to override the poor electrophilicity of the C=N-OMe moiety, leading to smooth reactivity and good stereochemical control.

In summary, the indium-mediated reaction with a range of allylic bromides of 2-pyridyl and glyoxylic oxime ethers in water discloses a novel reaction potential of these poorly electrophilic systems for the synthesis of compounds of interest as precursors of various types of amino acids. Though high yielding and highly stereoselective, the effectiveness of these reactions is subject to several constrains such as the need of good chelation sites and optimized structural features in the starting oxime ethers.

Experimental Section

General Methods. All reagents were obtained from commercial suppliers and were used without further purification. Light petroleum ether refers to the fraction with boiling range 40−60 °C. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200 and 300 MHz and 75 and 50 MHz, respectively. Chemical shifts are reported in the δ scale relative to an internal reference of TMS (0 ppm). The coupling constants (J) values are given in Hz. Mass spectra (MS) were obtained at an ionizing voltage of 70 eV (EI-MS) or with an electrospray ionization source (ESI-MS). All the ESI-MS spectra were performed using MeOH as the solvent. The originality of all compounds was checked by a CAS online structure search. Oximes **I**[22] and **II**[23] were prepared following literature procedures.

General Procedure for the Indium-Mediated Allylation of Oxime Ethers I and II. Indium powder and the allylic bromide (**1**−**5**, see Table 1) were added at room temperature to 2.5 mL of water. After the mixture was stirred for 0.5 h at room temperature, the oxime-*O*-methyl ether (1.0 mmol) **I** or **II** was added. The reaction mixture was stirred at room temperature until disappearance of the starting oxime and then quenched with a saturated aqueous NH_4Cl solution (10 mL). The obtained suspension was stirred for 1 h, and then the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by chromatography on silica gel.

2-[1-(Methoxyamino)-3-butenyl]pyridine (6). Following the general procedure (entry 4, Table 1), starting from oxime **I** and allyl bromide **1**, the title compound was obtained after 24 h in 70% yield as a yellow oil after chromatography on silica gel (light petroleum/Et_2O 1/1): ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.59 (d, 1H, J = 4.1 Hz), 7.69−7.60 (m, 1H), 7.30 (d, 1H, J = 7.8 Hz), 7.21−7.14 (m, 1H), 6.30 (br s, 1H), 5.75 (m, 1H, irradiating at δ 2.49 dd, J = 16.9, 10.1 Hz), 5.08 (m, 1H, irradiating at δ 2.49 dd, J = 10.0, 2.0 Hz), 5.07 (m, 1H, irradiating at δ 2.49 dd, J = 17.1, 2.0 Hz), 4.20 (apparent triplet, 1H, irradiating at δ 2.49 s), 3.48 (s, 3H), 2.49 (apparent triplet, 2H, irradiating at δ 4.18 d, J = 7.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 161.2, 149.6, 136.4, 134.6, 122.6, 122.4, 117.8, 65.5, 62.1, 37.5; EI-MS (*m*/*e*) 145 (3.6), 137 (100), 130 (4.5), 117 (16.4), 106 (22.0), 79 (44), 65 (21.8), 52 (7.3). Anal. Calcd for $C_{10}H_{14}N_2O$: C, 67.39; H, 7.92; N, 15.72. Found: C, 67.11; H, 8.02; N, 15.85.

2-(Methoxyamino)-4-pentenoic Acid (11). Following the general procedure (entry 10, Table 1), starting from oxime **II** and allyl bromide **1**, the title compound was obtained after 24 h in 65% yield as a colorless thick oil, after chromatography on silica gel (Et_2O/MeOH 9/1): ^{1}H NMR (200 MHz, acetone-d_6) δ 8.1−7.8 (br s, 2H), 5.97 (m, 1H, irradiating at δ 2.58 dd, J = 17.2, 10.2 Hz), 5.23 (m, 1H, irradiating at δ 2.58 dd, J = 17.2, 2.0 Hz), 5.11 (m, 1H, irradiating at δ 2.58 dd, J = 10.2, 2.0 Hz), 4.1−4.0 (m, 1H), 3.58 (s, 3H), 2.62−2.40 (m, 2H); ^{13}C NMR (50 MHz, acetone-d_6) δ 171.8, 135.8, 117.8, 65.1, 63.8, 33.7; EI-MS (*m*/*e*) 104 (56.09), 100 (19.64), 86 (67.52), 68 (23.34), 58 (57.49), 45 (17.94), 41 (100), 39 (65.04). Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64; N, 9.65. Found: C, 50.01; H, 7.50; N, 9.80.

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Supporting Information Available: Experimental procedures and characterizations for compounds **7**, **8a**,**b**, **9**, **10a**, **12**, **13a**,**b**, **14**, **15**, ethyl 2-{2-[2-(ethoxycarbonyl)-2-propenyl]-(methoxy)amino}-2-(2-pyridinyl)ethyl]acrylate (**9′**), *syn*-2-(1-amino-2-phenyl-butyl)pyridine, *syn*-2-(1-ammino-2-ethoxycarbonyl-butyl)pyridine, **10b**, **16**, and **17**. ORTEP diagrams and X-ray data for compounds **16** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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