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Asymmetric nitroaldol reaction using nitromethane labeled with ^{11}C

Koichi Kato [a,b,*], Sven Åke Gustavsson [a,c], Bengt Långström [a,c,*]

[a] Department of Biochemistry and Organic Chemistry, Uppsala University, Box 576, SE753 23 Uppsala, Sweden
[b] Department of Molecular Probes, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan
[c] Uppsala Imanet, GE Healthcare, Box 967, SE751 05 Uppsala, Sweden

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ABSTRACT

Nitro[^{11}C]methane produced from [^{11}C]O_2 reacted with several aldehydes in the presence of chiral metal catalyst prepared from $LaLi_3${tris(binaphtoxide)}, *n*-BuLi, H_2O, and (*R*)-binaphtol. The molar ratios of La, Li, and binaphtol for effective catalysis in the ^{11}C-labeling were 1/4/4.5 and 1/4/6, respectively. The ^{11}C-nitroaldol products were obtained in 3–25% radiochemical yields with 39–51% ee within 20 min starting from the preparation of nitro[^{11}C]methane.

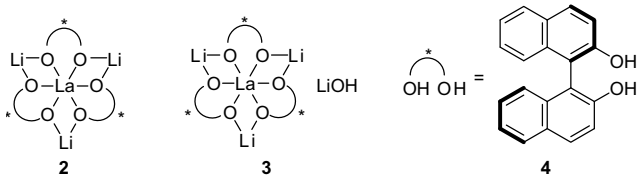
The positron-emitting radionuclide ^{11}C ($T_{1/2}$ = 20.3 min) which is frequently used to prepare tracers and compounds labeled by ^{11}C, can be utilized for in vivo imaging by positron emission tomography (PET). PET has been recognized as a useful tool for clinical diagnosis and the drug development process.[1] Several constraints are limiting the development of new ^{11}C-labeling methodology; rapid reaction under sub-micro molar scale, limited number of labeling precursors, and a need for remote-controlled system for radiation protection.[2]

Asymmetric labeling synthesis promoted by a chiral organometallic catalyst offers a new prospect for ^{11}C-labeling chemistry. The methodology needs to be further explored, especially considering the time constraints.[3] The chiral center often plays an important role in biological activity; therefore, asymmetric ^{11}C-labeling synthesis is sometimes required for precise PET analysis. Asymmetric ^{11}C-labeling syntheses have been carried out by enzymatic synthesis or using chiral handles;[4,5] however, these methods require a limited number of available substrates, resulting in no significant impact on further development. The recent progress in asymmetric catalysis by organometallics has shown exciting potential to solve such problems.[6] Although chemical and technical problems caused by the use of short-lived radioisotopes complicate asymmetric labeling synthesis, the use of an organometallic catalyst is attractive for ^{11}C-labeling synthesis and should be considered for further exploration.

We focused on the asymmetric nitroaldol reaction using [^{11}C]H_3NO_2 (**1**) as a model. Nitroaldol products can be transformed to β-amino alcohols,[7] which are structural elements of interesting biological compounds with potential to become valuable PET tracers. The asymmetric catalysts LLB (**2**) and LLB-II (**3**) (Fig. 1), developed by Shibasaki and co-workers, are binaphtol-modified La–Li bimetallic catalysts that are effective in the asymmetric nitroaldol reaction.[8,9] Catalysts **2** and **3** may be useful because they are prepared and used in the presence of water.[8a] Easy and reliable handling of the catalyst is crucial to minimize technical problems caused by the special conditions of radiolabeling, therefore, **2** and **3** were considered to be appropriate for ^{11}C-labeling. In this Letter, we describe asymmetric nitroaldol reactions using **1** in combination with the modification of **2** and **3** as a first attempt for use as an asymmetric catalyst for ^{11}C-labeling.

Including purification and formulation, the whole procedure should be rapid, aiming at less than 1 h; therefore, the actual ^{11}C-labeling is often terminated within 5 min in order to obtain a high radiochemical yield, considering the competing decay both of products and starting material.[2] Thus in syntheses using short-lived radionuclides, a higher reaction temperature is preferred in order to speed up reaction rates and obtain a higher radiochemical yield of the labeled product. The ^{11}C-labeling reactions performed in this paper proceeded at −10 °C and room temperature. Although −50 °C was employed as a reaction temperature to obtain high ee in Shibasaki's reports, there was a compromise between ee and radiochemical yield.

Cyclotron-produced [^{11}C]O_2 was immediately transformed into [^{11}C]H_3I via reduction by lithium aluminum hydride (LAH) and subsequent iodination by hydroiodic acid (HI). [^{11}C]H_3I was then converted to **1** via nitration by passing through a heated column



2 3 4

Figure 1. Structures of **2**, **3** and **4**.

* Corresponding authors. Tel.: +81 43 206 4042; fax: +81 206 3261 (K.K.); tel.: +46 18 66 6900; fax: +46 18 18 0932 (B.L.).
E-mail addresses: katok@nirs.go.jp (K. Kato), Bengt.Langstrom@biorg.uu.se (B. Långström).

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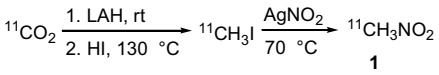
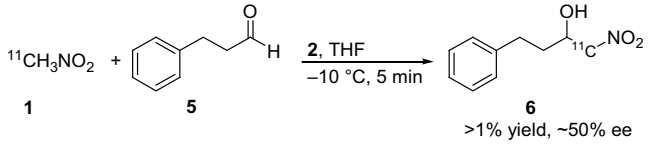


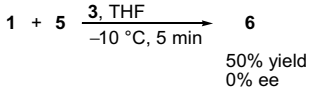
Figure 2. Preparation of **1**.

containing silver nitrite and dried potassium carbonate (Fig. 2).[10,11] Catalysts **2** and **3** with molar ratios of La, Li, and (*R*)-(+)-1,1′-bi-2-naphtol (**4**) of 1/3/3 and 1/4/3, respectively, were prepared in accordance with the literature by using La(O-*i*-Pr)$_3$, *n*-BuLi, and **4**.[8a] The reaction between **1** and 3-phenylpropanal (**5**) was selected to explore the feasibility of ^{11}C-labeling by an asymmetric nitroaldol reaction because the ee value of the reaction between CH_3NO_2 and **5** was high under the catalytic condition given in the literature (73% ee).[8b] The initial labeling reaction was carried out using **2**. The radioactivity of **1** using studies was 0.2–2 GBq. The mol amounts of **1** were uncertain, however, they could be estimated at less than 100 nM.[12] The reaction afforded **6** in approximately 50% ee, but radiochemical yield was less than 1% (Eq. 1).



(1)

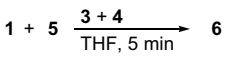
When the same reaction was carried out using **3**, the ^{11}C-labeling reaction provided **6** in 50% radiochemical yield (Eq. 2); however, product **6** was racemic (Eq. 2). In the literature, catalyst **3** afforded nitroaldol products in similar enantioselectivity and higher reactivity than **2** under catalytic conditions;[8a] however, the ^{11}C-labeling reaction mediated by **3** yielded a racemic mixture.



(2)

LDI-TOF MS analysis of a solution of **2** suggested that the solution contained mixtures of complexes comprising several molar ratios of Li, La, and **4**.[8c] We considered that there was equilibrium in the catalyst formation of **3**, and free LiOH resulted from the equilibrium at the higher reaction temperature employed for ^{11}C-labeling conditions. The resulting free LiOH can mediate nitroaldol reactions and cause problems with the racemic product. Thus, the effect of a further addition of **4** to a solution of **3** was investigated in order to force the equilibrium to form **3** with higher concentration and suppress the existence of free LiOH. Catalyst solutions with three different ratios of Li, La, and **4** were used to explore ee and the radiochemical yield of the reactions (Table 1). First, 1 mol equiv of **4** was added to **3** to form a molar ratio of 1/4/4 for Li, La, and **4** (catalyst **A**). In catalyst solution **A**, free LiOH was assumed to be consumed. The labeling reaction mediated by **A** afforded **6** in 15% ee at −10 °C (Table 1, entry 1). Compared to

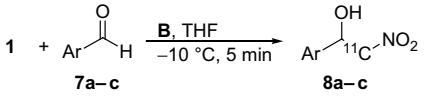
Table 1



Entry	Cat. No.	**4** (equiv)	La/Li/**4**	Temp (°C)	Yield[a,b] (%)	ee[b] (%)
1	**A**	1	1/4/4	−10	—	~15
2	**B**	1.5	1/4/4.5	−10	9	44
3	**B**	1.5	1/4/4.5	rt	29	9
4	**C**	3	1/4/6	rt	25	39

[a] Yields were decay-corrected radiochemical conversion.
[b] Determined by radio-HPLC.

Table 2



Entry	Ar	Product	Yield[a,b]	ee[b] (%)
1	C_6H_5 (**7a**)	**8a**	8	51
2	*p*-$NO_2C_6H_4$ (**7b**)	**8b**	12	41
3	*p*-$CH_3C_6H_4$ (**7c**)	**8c**	3	39

[a] Yields were decay-corrected radiochemical conversion.
[b] Determined by radio-HPLC.

the enantioselectivity of the ^{11}C-labeling reaction obtained by **A** and **2**, catalyst **A** might not suppress the racemic reaction completely; therefore, the following catalyst solution was prepared by adding 1.5 mol equiv of **4** to **3**, forming a molar ratio of La, Li, and **4** of 1/4/4.5 (catalyst **B**). The labeling reaction mediated by **B** afforded **6** in 44% ee (entry 2) at −10 °C. Under ^{11}C-labeling conditions, **B** gave similar ee of the product as **2** and higher radiochemical yield (9%).[13,14] Stoichiometric reaction using cat **B** for CH_3NO_2 was carried out in the presence of 3 mol equiv of **5** at −10 °C. The reaction gave non-labeled **6** in 69% yield and 39% ee for 20 h.[15] When the ^{11}C-labeling reaction mediated by **B** was carried out at room temperature, the reaction afforded **6** in higher radiochemical yield (29%), but in lower enantioselectivity (9% ee, entry 3). When 3 mol equiv of **4** was added to **3**, a molar ratio of La, Li, and **4** of 1/4/6 of the catalyst solution (catalyst **C**) was obtained. The ^{11}C-labeling reaction mediated by **C** afforded **6** in similar enantioselectivity (39%) and higher radiochemical yield (25%) as **B** at room temperature.

The reactions between **1** and benzaldehyde (**7a**) or other aromatic aldehydes **7b**, **7c** were also explored. In the literature, the ee value of the reaction between CH_3NO_2 and **7a** was moderate (approximately 40% ee) under the catalytic condition using **2**;[16] however, ^{11}C-labeled nitroaldol products derived from aromatic aldehydes are interesting as PET tracers.[7b] All ^{11}C-labeling reactions were carried out by catalyst solution **B** at −10 °C. The ^{11}C-labeling reaction for **7a** afforded **8a** in 51% ee at −10 °C (Table 2, entry 1). The ee value of **8a** was higher than the reported ee value of the catalytic condition at −40 °C even though a higher reaction temperature was employed for ^{11}C-labeling reaction. The molar amount of **7a** to **1** may play an important role in the ee value of **8a**. Excess CH_3NO_2 to aldehyde was usually used under catalytic conditions; however, a minute amount of **1** could be used under the ^{11}C-labeling conditions presented here. The undesired side reaction might be suppressed in the reaction between **1** and **7a**, affording **8a** in higher ee than the reaction performed under catalytic conditions. The ^{11}C-labeling reactions for **7b**, **7c** afforded **8b** and **8c** in 41% ee and 39% ee, respectively. No significant difference was observed for ee values of **8b** and **8c** (entries 2 and 3).

In summary, we investigated the asymmetric nitroaldol reaction for **1** and several aldehydes. Enantioselective ^{11}C-labeling mediated by organometallic catalysts was performed and the ee values of products were moderate but this is a first step to fuse organometallic asymmetric catalysis and radiolabeling synthesis. Recently, several environmentally friendly catalysts have been developed, allowing reactions to be performed in the presence of water,[17] and some of these catalysts will further support the progress of radiolabeling chemistry and PET tracer development.

Acknowledgment

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12. The specific activity of **1** was not determined, but it could be considered to have similar value as $[^{11}C]H_3I$ (around or higher than 37 GBq/μmol) due to no isotope contamination during nitration reaction.
13. *Typical procedure of asymmetric nitroaldol reaction:* $[^{11}C]$Carbon dioxide was produced by the $^{14}N[p,\alpha]^{11}C$ nuclear reaction using a nitrogen gas target containing 0.05% oxygen bombarded with 17 MeV protons. $[^{11}C]$Carbon dioxide was reduced by 0.2 M $LiAlH_4$ solution in THF (500 μL), and thereafter THF was evaporated. To the residue, a 54% HI aqueous solution (1 mL) was added and the mixture was heated at 130 °C to give $[^{11}C]H_3I$ in the gas phase. **1** was prepared by passing $[^{11}C]H_3I$ through a column filled with silver nitrite at 70 °C and dried potassium carbonate. **1** was trapped in a 0.03 M catalyst solution in THF (300 μL). The reaction mixture was placed in a cooling bath and 5 μL of the aldehyde was added. After 5 min, a saturated solution of aqueous ammonium chloride (100 μL) was added to quench the reaction mixture. The contents of the vial were diluted and the formed product was purified by semi-preparative HPLC.
14. Catalyst solution of **B** was prepared as below. To a solution of **4** (856 mg, 3 mmol) in THF (13 mL) a 1.6 M solution of *n*-BuLi (1.25 mL, 2 mmol) in hexane was added at 0 °C. Soon a clear solution was changed to suspension, then a 0.2 M solution of La(O-*i*-Pr)$_3$ (2.5 mL, 0.5 mmol) in THF was added at room temperature. After mixture was stirred overnight, water (9 μL, 0.5 mmol) was added and the resulting catalyst solution was stored at room temperature.
15. ^{1}H NMR was measured for a mixture of **4** and non-labeled **6**. Non-labeled **6** was detected by GC and HPLC in the mixture. Yield was determined by HPLC using methyl 4-chlorocinnamate as an internal standard. Ee was determined by HPLC using CHIRALPAK AD-H (DAICEL).
16. Shibasaki et al. reported that using other lanthanide metal for catalysts gave corresponding nitroaldol product in good ee for this reaction. Details are described in Ref. 8d.
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