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Lithium acetylides as alkynylating reagents for the enantioselective alkynylation of ketones catalyzed by lithium binaphtholate†

Kana Tanaka,[a] Kenji Kukita,[a] Tomonori Ichibakase,[a] Shunsuke Kotani[b] and Makoto Nakajima*[a]

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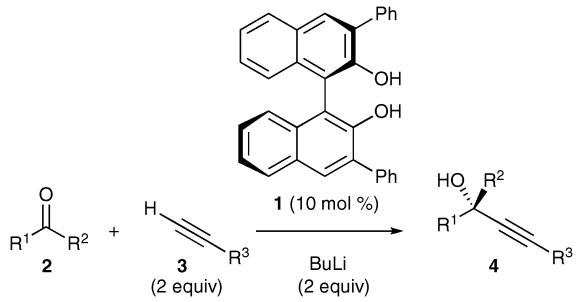
Chiral lithium binaphtholate effectively catalyzed the enantioselective alkynylation of ketones using lithium acetylide as an alkynylating agent. This is the first example of the catalytic enantioselective addition of lithium acetylide to carbonyl compounds without the aid of other metal sources.

Optically active propargylic alcohols are useful and versatile building blocks for the synthesis of a wide range of natural products and pharmaceuticals. The enantioselective alkynylation of carbonyl compounds is an important process for the preparation of chiral propargylic compounds. During this process, C–C bonds are formed with concomitant creation of a stereogenic center.[1]

The first enantioselective alkynylation of carbonyl compounds was reported by Mukaiyama *et al.*, who employed lithium acetylide as an alkynylating reagent using 4 equivalents of a chiral amino alkoxide ligand.[2] The catalytic process for the enantioselective alkynylation was developed by Niwa and Soai, who employed zinc acetylide as an alkynylating reagent with an amino alcohol as a catalyst.[3] Since then, several catalytic enantioselective alkynylations were reported using various metal acetylides, including *in situ* generation, in the presence of a variety of metal catalysts.[4–7] However, there is a limited number of successful reports for the alkynylation of ketones because of their low reactivities.[1c,e,f,8] We have previously reported the enantioselective alkynylation of aldehydes and ketones with trimethoxysilylalkyne[9] using lithium binaphtholate as a catalyst.[10] While investigating the reaction mechanism, we were surprised to find that a high enantioselectivity was observed in the reaction of lithium acetylide in the presence of catalytic amounts of lithium binaphtholate. In the literature,[2] excess amounts of the chiral ligand were required for the asymmetric addition of lithium acetylide to carbonyl compounds in order to achieve high enantioselectivities, because lithium acetylide is reactive toward the carbonyl compounds even in the absence of a catalyst. Here we report the first example of employing lithium acetylide in catalytic enantioselective alkynylation without the aid of other metals, using lithium binaphtholate as a catalyst.



(1)

First we investigated the alkynylation of benzaldehyde (**2a**) with lithium phenylacetylide, generated *in situ* from phenylacetylene (**3a**) and butyllithium in the presence of lithium diphenylbinaphtholate, *in situ* generated from the corresponding binaphthol (**1**) and butyllithium (eqn (1)) at 0 °C. No asymmetric induction was observed in toluene (89% yield, 1% ee), however, a significant enantioselectivity was observed in THF (85% yield, 33% ee). As the reaction proceeded in the absence of a catalyst, our result shows that the catalyst increased the reactivity of lithium acetylide toward the carbonyl carbon. In order to reduce the non-catalytic pathway, we then investigated the reaction of the less reactive substrate, acetophenone (**2b**).

Although no enantioselectivity was again observed in toluene (72% yield, 3% ee), good enantioselectivity was achieved in THF at 0 °C (67% yield, 76% ee). After screening the ligands and reaction conditions,[11,12] we found that the corresponding adduct was obtained in high chemical and optical yields at −78 °C using the catalyst prepared from **1** and BuLi (96% yield, 93% ee, Table 1, entry 1).

With the optimal conditions and catalyst in hand,[13] we next investigated the reaction of acetophenone (**2b**) with various acetylenes. Acetylenes **3b** or **3c** gave high selectivities (entries 2 and 3), but acetylene **3d** with a bulky substituent at the opposite side of the acetylene decreased the selectivity (entry 4). We then investigated the phenylethynylation of various ketones using phenylacetylene (**3a**) as an alkynylating reagent.

[a] *Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Kumamoto, Japan. E-mail: nakajima@gpo.kumamoto-u.ac.jp; Fax: +81 96 362 7692; Tel: +81 96 371 4680*
[b] *Priority Organization for Innovation and Excellence, Kumamoto University, 5-1 Oe-honmachi, Kumamoto, Japan*

† Electronic supplementary information (ESI) available: Experimental details for the enantioselective alkynylation and determination of absolute configurations of **4ca**, **4fa**, and **4ga**, spectroscopic data for new compounds, and HPLC data for the alkynylated products. See DOI: 10.1039/c1cc10734h

Table 1 Enantioselective alkynylation of ketones catalyzed by Li salt of **1**

Entry	Ketone (R^1, R^2)	Alkyne (R^3)	Product	%Yield[a]	%ee[b,c]
1	**2b** (Ph, Me)	**3a** (Ph)	**4ba**	96	93
2	**2b** (Ph, Me)	**3b** (Bu)	**4bb**	89	87
3	**2b** (Ph, Me)	**3c** ($BnOCH_2$)	**4bc**	97	86
4	**2b** (Ph, Me)	**3d** (^{t}Bu)	**4bd**	88	55
5	**2c** (Ph, Et)	**3a** (Ph)	**4ca**	93	73
6	**2d** (Ph, iPr)	**3a** (Ph)	**4da**	99	7
7	**2e** (^{c}Hex, Me)	**3a** (Ph)	**4ea**	91	57
8	**2f** ($PhCH_2CH_2$, Me)	**3a** (Ph)	**4fa**	99	39
9	**2g** (4-MeC_6H_4, Me)	**3a** (Ph)	**4ga**	93	88
10	**2h** (4-$MeOC_6H_4$, Me)	**3a** (Ph)	**4ha**	95	92
11	**2i** (3,4,5-$(MeO)_3C_6H_2$, Me)	**3a** (Ph)	**4ia**	93	92
12	**2j** (4-FC_6H_4, Me)	**3a** (Ph)	**4ja**	89	91
13	**2k** (2-Naph, Me)	**3a** (Ph)	**4ka**	94	85
14	**2l** (3-Py, Me)	**3a** (Ph)	**4la**	96	87

[a] Isolated yields. For the reaction conditions, see ref. 13. [b] Determined by chiral HPLC. [c] For the absolute configurations of the product, see ref. 14.

Propiophenone **2c** gave a decreased selectivity (entry 5), and isobutyrophenone **2d** gave an almost racemic product (entry 6), suggesting that the bulkiness of the aliphatic group has an inferior effect on selectivity. Aliphatic ketones **2e** and **2f** gave lower selectivities than acetophenone, but again the difference of steric bulkiness between the two substituents around ketone plays an important role in enantiocontrol (entries 7 and 8). An electron-donating or -deficient substituent on the benzene ring of acetophenone did not affect the selectivity. Most acetophenone derivatives gave results similar to that of acetophenone itself (entries 9–13).

Our protocol could be applied to the asymmetric synthesis of bioactive compounds. Using the above conditions, the reaction of 3-acetylpyridine **2l** and phenylacetylene **3a** gave the product **4la**, which has antifungal activity,[15] in high chemical and optical yields. These yields were the highest of those reported for the enantioselective alkynylation of acetylpyridines.

In summary, we have developed an enantioselective alkynylation of ketones using lithium acetylide in the presence of chiral lithium binaphtholate as a catalyst. This is the first example of catalytic enantioselective addition of lithium acetylide to carbonyl compounds without the aid of other metal sources. Studies on the mechanism as well as the design of chiral catalysts to further enhance enantioselectivity are currently in progress.

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13 The representative procedure for the enantioselective alkynylation: under an Ar atmosphere, BuLi (1.65 M in hexane, 0.57 mL, 0.94 mmol) was added to the solution of binaphthol **1** (20.7 mg, 0.047 mmol) and phenylacetylene (**3a**) (0.10 mL, 0.94 mmol) in THF (1.3 mL) at −78 °C. To the mixture, acetophenone (**2b**) (56 mg, 0.47 mmol) in THF (0.5 mL) was added dropwise at the same temperature and the solution was stirred for 12 h. The reaction was quenched with NH_4Cl sat. aq. and the mixture was extracted by AcOEt. The organic layer was washed with $NaHCO_3$ and brine. After drying over Na_2SO_4, the solvent was removed and the residue was purified by silica gel column chromatography (hexane/CH_2Cl_2 = 1/1), affording **4ba** (100 mg, 96%) as an oil. The ee was determined by chiral HPLC (Daicel OD-H) to be 93% ee.

14 The absolute configuration of **4ba** was determined by comparison of $[\alpha]_D$ data with ref. 9*b*. The absolute configurations of **4ca**, **4fa**, and **4ga** were determined by the derivatization to the known methyl esters *via* reduction to olefin and the following ozonolysis.

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