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Enantioselective alkynylation of ketones with trimethoxysilylalkynes using lithium binaphtholate as a catalyst

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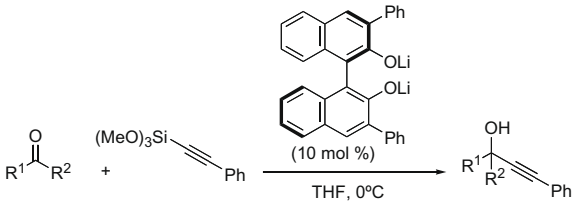
ABSTRACT

Chiral lithium 3,3′-diphenylbinaphtholate successfully catalyzed the alkynylation of ketone with trimethoxysilylalkyne, affording chiral tertiary propargylic alcohols in high chemical yields and high enantioselectivities. The present reaction could be extended to the alkynylation of acetylpyridine, which afforded a biologically active pyridyl propargylic alcohol in good enantioselectivity.

Chiral tertiary propargylic alcohols are important building blocks for the synthesis of biologically active compounds.[1] The enantioselective alkynylation of ketones is one of the most reliable methods for the synthesis of these compounds.[2] The alkynylation of aldehydes has been widely investigated,[3] however, there is a limited number of successful reports for the alkynylation of ketones because of their low reactivities.[4] Since the first report on the enantioselective alkynylation of ketones using an amino alcohol as a catalyst, alkynylzinc compounds[5] were most frequently used as intermediates for the alkynylations of ketones.[6–9]



(1)

Trialkoxysilylalkynes developed by Scheidt represent a novel class of alkynyl nucleophiles that react with carbonyl compounds.[10] Upon activation with alkoxide bases they form hypervalent silicates[11] that react with carbonyl compounds. The reactivity of the trialkoxysilylalkynes is sufficiently high to promote a nucleophilic addition to ketones in high yields. We have already reported that trimethoxysilyl enol ethers were activated by dilithium salts of binaphthols to react with aldehydes affording aldol adducts in high chemical yields and high enantioselectivities.[12] In our pursuit to develop a new enantioselective reaction of trimethoxysilyl compounds, herein we report the alkynylation of ketones with trimethoxysilylalkynes catalyzed by dilithium salts of binaphthol derivatives.

We initially investigated the alkynylation of acetophenone with trimethoxy(phenylethynyl)silane.[13] The dilithium salt of unsubstituted binaphthol[14] was found to promote the alkynylation in THF at rt, albeit in low chemical yield and enantioselectivity (24% yield, 10% ee). Screening of binaphthol derivatives revealed that the introduction of phenyl groups to 3 and 3′-positions of the binaphthol catalyst dramatically increased both the chemical yield and enantioselectivity.[15]

After slight modification to optimize the reaction conditions, we investigated the alkynylation of various ketones using dilithium salt of 3,3′-diphenylbinaphthol (Eq. 1) and the results are shown in Table 1.[16] Similar enantioselectivities and chemical yields were obtained with 4′-substituted acetophenones (entries 1–5). Propiophenone gave decreased selectivity (entry 6) and isobutyrophenone gave almost racemic product (entry 7), which suggests that the selectivity of the reaction decreases with increasing bulkiness of the aliphatic group on the acetophenone derivatives. Aliphatic ketones gave better chemical yield than acetophenone, but with

Table 1
Enantioselective alkynylation of ketone (R^1COR^2) with trimethoxy(phenyethynyl)silane catalyzed by dilithium diphenylbinaphtholate[a]

Entry	R^1, R^2	Yield[b] (%)	ee %[c]
1[d]	Ph, Me	64 (81)	82 (82)
2	4-$MeOC_6H_4$, Me	61	81
3	4-$NO_2C_6H_4$, Me	71	72
4	4-FC_6H_4, Me	67	79
5	4-$CF_3C_6H_4$, Me	63	75
6	Ph, Et	77	61
7	Ph, ^{i}Pr	65	8
8	$PhCH_2CH_2$, Me	92	41
9	^{c}Hex, Me	74	52
10	^{t}Bu, Me	64	43

[a] Silylalkyne 1.5 equiv, catalyst 10 mol %. See representative procedure in Ref. 16.
[b] Isolated yields.
[c] Determined with chiral HPLC (Daicel chiralcel OD-H).
[d] Data in parentheses: silylalkyne 3 equiv.

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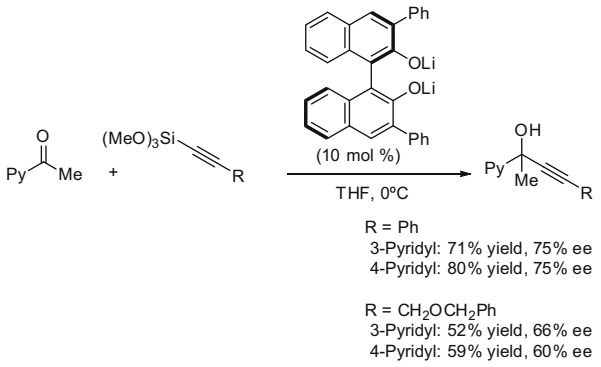

Scheme 1.

lower selectivities (entries 8–10). Increasing the number of equivalents of alkyne provided a better chemical yield with no reduction of selectivity (entry 1).

A number of pyridyl propargylic alcohol derivatives are known to have interesting biological activities.[17] However, there are no successful results for the enantioselective alkynylation of acetylpyridines because the basic nitrogen atoms in the pyridine moiety deactivate the chiral Lewis acid catalysts. Because our catalyst is basic, we thought that our protocol could be applied to the alkynylation of acetylpyridine. The addition of phenylethyne or benzyloxypropyne to acetylpyridine gave the corresponding alcohols in good chemical yield and enantioselectivity (Scheme 1). These results represent the highest chemical yields and enantioselectivities reported to date for the alkynylation of acetylpyridines.[18]

Herein we reported the first example of an enantioselective alkynylation of ketones with trialkoxysilylalkyne catalyzed by chiral bases. These results demonstrate the synthetic utility of our catalytic system for the synthesis of optically active tertiary propargylic alcohols as building blocks for biologically active compounds.[19] Further studies to design to enhance the enantioselectivity and to explore the reaction mechanism are in progress and will be reported in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.084.

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15. 3,3′-Dimethyl-, dichloro-, dibromobinaphthol, or mono lithium salt of the binaphthol derivatives gave lower yields and/or enantioselectivities.
16. *Representative experimental procedure*: *n*-BuLi (0.16 M in hexane, 0.58 mL, 0.094 mmol) was added to a solution of (*R*)-3,3′-diphenylbinaphthol (21 mg, 0.047 mmol) in THF (3 mL) at 0 °C under Ar atmosphere. Trimethoxy-(phenylethynyl)silane (156 mg, 0.71 mmol) was added to the mixture in one portion, and then a solution of acetophenone (56 mg, 0.47 mmol) in THF (0.5 mL) was added over 3 h at the same temperature. After stirring for another 1 h, the reaction was quenched with tetrabutylammonium fluoride (1.0 M in THF, 4 mL). The mixture was stirred for 0.5 h and extracted with EtOAc. The organic layer was washed with water and brine successively. Drying over sodium sulfate and concentration followed by silica gel column chromatography afforded the alcohol (67 mg, 64%) as a colorless oil.
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19. 3-Phenyl-1-(3-pyridyl)-2-propyn-1-ol has an antifungal activity, see Ref. 17a.