N,N′-(1S)-[1,1′-Binaphthalene]-2,2′-diylbis-(2S,2′S)-pyrrolidine-2-carboxamide

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Abstract

[891496-34-7] C₃₀H₃₀N₄O₂ (MW 478.24)


InChIKey = FYTHJMKJYUTERE-UBXIPSODCL

(used as a catalyst and as a ligand in enantioselective synthesis of aldol products and cyanosilylation of ketones, respectively)

Alternate Names: (S₆)-2,2′-bis[(2S)-pyrrolidin-2-ylcarbonyl]amino]-1,1′-binaphthale, (S)-Binam-l-Pro.

Physical Data: mp 230 °C; [α]D²⁰ = −108.0° (c = 1, MeOH).

Solubility: soluble in most polar organic solvents; insoluble in hexane, ether, and
water.

*Form Supplied in:* not commercially available. Prepared from \((S_a)-2,2'\text{-diamino}-1,1'\text{-binaphthalene}\) and protected \(l\)-proline, both commercially available.

*Analysis of Reagent Purity:* elemental analysis, NMR, HRMS, and X-ray structure.

*Preparative Methods:* the reagent can be prepared by coupling \((S_a)-2,2'\text{-diamino}-1,1'\text{-binaphthalene}\) with the mixed anhydride obtained from \(l\)-Boc-proline and isobutyryl or ethyl chloroformate or by direct coupling of Boc-\(l\)-proline with \((S_a)-2,2'\text{-diamino}-1,1'\text{-binaphthalene (Binam)}\) mediated by 1-ethyl-3-(3-methylamino)propyl)carbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) or \(N,N'\text{-dicyclohexylcarbodiimide (DCC)}\) and 4-(dimethylamino)pyridine (DMAP). The coupled intermediate was deprotected by using TFA. Alternatively, the reagent can be prepared by coupling \((S_a)-2,2'\text{-diamino}-1,1'\text{-binaphthalene}\) with the acyl chloride derived from Fmoc-\(l\)-proline, and deprotection with piperidine.

*Purification:* by column chromatography and/or recrystallization from \(CH_2Cl_2/hexane\) or \(CHCl_3/ether\).

*Handling, Storage, and Precaution:* the reagent is stable for months when stored in air at room temperature.

Enantioselective Cyanosilylation of Ketones

The generation of chiral quaternary stereocenters is a challenging task, with the addition of trimethylsilyl cyanide (TMSCN) to ketones being one of the most successful examples.\(^1\) \((S)\text{-Binam-}l\text{-Pro was used as a ligand for the enantioselective addition of TMSCN to acetophenone (eq 1). The catalytic complex obtained by reaction with titanium tetra isopropoxide gave the O-TMS cyanohydrin with 47% yield and 33% ee. Better results (up to 90% yield and 94% ee) were obtained under similar reaction conditions using the bisamide derived from 1,2-diphenylethane-1,2-diamine and proline.}\(^2\)

\[
\text{Ph}^\text{C} + \text{TMSCN} \xrightarrow{(S)\text{-Binam-}l\text{-Pro (20 mol %)}} \text{OTMS} \;
\begin{array}{c}
\text{Ti(OPr}_3\text{)}_4 \text{(20 mol %)} \\
\text{CH}_2\text{Cl}_2, 0 \text{ C, 60 h}
\end{array}
\]

0.2 M 1.5 equiv 47%, 33% ee

Enantioselective Direct Aldol Reaction

The use of organocatalytic methods\(^3\) for the enantioselective direct aldol reaction\(^4\)
has reached its maturity allowing the synthesis of chiral molecules with high atom efficiency.\textsuperscript{5} (S)-Binam-L-Pro was first used as an organocatalyst in the intermolecular direct aldol reaction of aromatic aldehydes and alkyl or cyclic ketones using two different protocols.\textsuperscript{6} Whereas in one protocol the mixture of 1,4-dioxane/ketone (4:1) at 4 °C were the best reaction conditions, giving the corresponding aldols with 9–79\% yield and 50–88\% ee's (eq 2),\textsuperscript{6a} DMF/water (1:1) at 0 °C or DMF at 25 °C afforded better results in the second instance (52–99\% yield, 78–95\% ee).\textsuperscript{6b} Under the latter reaction conditions, the use of l-proline as catalyst afforded the racemic product.

\begin{equation}
\begin{array}{c}
\text{O} + \text{R}^1\text{CH} = \overset{\text{(S)-Binam-L-Pro}}{\text{\textbullet}} (10 \text{ mol } \%)
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{1,4-dioxane/acetone (4:1, v/v), 4 °C, 68 h}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{9–79\% yield, 50–88\% ee}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{R}^1 = \text{C}_6\text{F}_5, \text{4-CNCl}_2\text{H}_4, \text{4-CF}_2\text{C}_6\text{H}_4,
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{2,6-Cl}_2\text{C}_6\text{H}_3, \text{2-CIC}_6\text{H}_4, \text{4-CIC}_6\text{H}_4,
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{4-BrC}_6\text{H}_4, \text{Ph, } \beta-\text{napthyl}
\end{array}
\end{equation}

When 2-butanone was used as precursor, the reaction took place nearly exclusively at the methyl position, to give the \textit{iso}-isomer preferentially (eq 3). These conditions permitted the recovery by acidic-basic extraction and reuse of catalyst without any detrimental effect on the obtained yields and enantioselectivities during three additional cycles.\textsuperscript{6b} Alternatively, CHCl\textsubscript{3}/ketone (1:1) at -27 °C gave the corresponding aldols with 35–98\% yield and 68–95\% ee.\textsuperscript{7}

\begin{equation}
\begin{array}{c}
\text{O} + \text{R}^1\text{CH} = \overset{\text{(S)-Binam-L-Pro}}{\text{\textbullet}} (10 \text{ mol } \%)
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{DMF/H}_2\text{O, 0 °C}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{or DMF, 25 °C, 1.5–11 d}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{53–99\%, 65–96\% ee}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{98–99\%, de 60–82\%, 90–92\% ee}
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{R}^1 = \text{4-NO}_2\text{C}_6\text{H}_4, \text{2-NO}_2\text{C}_6\text{H}_4, \text{2-CIC}_6\text{H}_4, \text{Ph, C}_6\text{H}_{11}, (\text{CH}_3)_2\text{CH}
\end{array}
\end{equation}
Under similar conditions, (S)-Binam-l-Pro was used as catalyst in the reaction between \(\alpha\)-alkoxy ketones \(R^1 = \text{OH, OMe, OBn, OTBDMS}\) and aromatic aldehydes (eq 4) to give mainly the anti/syn-regioisomer mixture, with small amounts of corresponding iso-regioisomer being formed. The diastereoselectivity was dependent on the nature of \(R^1\) group, with the anti-regioisomer obtained as the main product. The enantioselectivity of the process ranged from 73 to 99%. For the case of \(\alpha\)-hydroxyacetone \(R^1 = \text{OH}\), the best conditions employed DMSO at 25 °C, affording mainly the anti-isomer with 85% ee. These results are comparable in terms of regio- and diastereoselectivities to those obtained with l-proline, with the advantage that (S)-Binam-l-Pro prolinamide could be recovered when DMF was used as solvent.8

\[
\begin{align*}
\text{R}^1 = \text{OH, OMe, OBn, OTBDMS} & \quad + \quad \begin{array}{c}
\text{R}^2 = 4-\text{NO}_2, 3-\text{NO}_2, 2-\text{NO}_2, 2-\text{Cl}
\end{array} \\
\text{(S)-Binam-l-Pro} & \quad \text{(10 mol \%)} \\
& \quad \text{DMF; 0 °C, 1–4 d} \\
& \quad \text{or DMSO, 25 °C, 1 d}
\end{align*}
\]

The reaction rate was highly increased by the addition of catalytic amounts of carboxylic acids, with benzoic acid giving the best results. For instance, using 20 mol % benzoic acid in the reaction between acyclic and cyclic alkyl ketones with 4-nitrobenzaldehyde in DMF:H\(_2\)O, the reaction time was reduced from 3 d to only 1.5 h, maintaining the enantioselectivity. This procedure enabled reactions at −20 °C with enhanced enantioselectivity (86–99%). Using benzoic acid as cocatalyst allowed the reaction to be conducted in water without addition of DMF.9 The combination of (S)-Binam-l-Pro (10 mol %) and benzoic acid (20 mol %) in either DMF or pure water permitted the use of less reactive ketones such as \(\alpha\)-(methylsulfanyl)acetone,
giving mainly the iso-isomer with an excellent 93% ee (eq 5). α-Alkoxy ketones give similar yields, regio-, diastereo-, and enantioselectivities to those achieved in the absence of acid, but in shorter reaction times (3-24 h).

\[
\begin{array}{c}
\text{O} \\
\text{SMe} \\
\text{H} \\
\text{O}_2\text{N} \\
\text{C} \\
\text{H} \\
\text{O} \\
\text{SMe}
\end{array}
\xrightarrow{(S)-\text{Binam-L-Pro} \\
(10 \text{ mol } \%)}
\begin{array}{c}
\text{OH} \\
\text{C} \\
\text{H} \\
\text{O} \\
\text{SMe}
\end{array}
\xrightarrow{\text{H}_2\text{O}, 0 \degree \text{C}, 21 \text{ h}}
\begin{array}{c}
\text{OH} \\
\text{C} \\
\text{H} \\
\text{O} \\
\text{SMe}
\end{array}
\]

(5)

89%, 1:8 rr, 93% ee

Other carboxylic acids can be used as cocatalyst. For instance, using acetic acid (10 mol %) as cocatalyst in toluene at -40 °C, the aldol products were obtained in 45-91% yield, 40-96% de, and 67-95% ee but longer reaction times being required (2-3 d). Using a micellar agent stearic acid (20 mol %) as cocatalyst in water at 2 °C permitted reduction of the amount of nucleophilic ketone to 3 equiv, providing 61-99% yield and 58-93% ee in only 12 h.

Using benzoic acid as cocatalyst, α-chloroacetone mainly produces the anti-isomer in moderate yields, but high diastereo- and enantioselectivities. These aldol products were easily converted into chiral (3R,4S)-trans-epoxides by treatment with triethylamine (eq 6).
A further improvement involved the use of solvent-free conditions. Thus, mixing the reagents by simple magnetic stirring allowed reduction of nucleophile to only 2 equiv, catalyst loading of 5 mol %, and in some cases reduced reaction time. The aldol reaction between cycloalkyl, alkyl, and α-functionalized ketones with aldehydes gave the expected aldol products with similar yields, regio-, diastereo-, and enantioselectivities to those obtained in solution. Furthermore, aldehydes can also be used as nucleophiles providing, after in situ reduction of the aldol products, chiral 1,3-diols with moderate to good enantioselectivities mainly as anti-isomers (eq 7).

**Enantioselective Mannich Addition**

A single example of the use of (S)-Binam-l-Pro (10 mol %) as catalyst for this type of transformation has been reported. Thus, the multicomponent Mannich reaction between 4-nitrobenzaldehyde, 4-methoxyaniline, and acetone afforded the corresponding β-amino ketone with 51% ee at 25 °C (eq 8).
Bibliography


