DEVELOPMENT OF A METHOD FOR THE COPPER-CATALYZED ASYMMETRIC PROPARGYLATION OF OXIME ESTERS

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ABSTRACT

Alkynes represent a significant motif in natural products and pharmaceutical drugs, and the wide variety of reactions they can undergo makes them a handy tool in total synthesis. They can be introduced readily in various manners, including via propargylations of ketones and aldehydes. However, one reaction that remains to be examined is the propargylation of oximes to give a propargyl hydroxylamine. Current enantioselective propargylations of oximes typically require a chiral auxiliary and/or rare metals such as palladium or indium. Having an enantioselective propargylation of oximes which could use an external ligand and more commonly available metals would facilitate use of the product in total synthesis, as well as potentially as an unnatural amino acid. Unusual amino acids including alkynes are desirable for their use in copper(I)-catalyzed azide-alkyne [3+2] dipolar cycloadditions, a common bioorthogonal reaction.

Herein, the development of a copper-catalyzed propargylation of oxime esters is described. Initial efforts to induce enantioselectivity using a zinc nucleophile-based system proved fruitless. Although some Lewis acids could raise the yield, the enantioselectivity remained very low. Therefore, new reaction conditions using a boronate nucleophile were investigated. The use of a copper catalyst with a diphosphine ligand gave the desired product in high enantioselectivity, albeit low yield.

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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
app	apparent
aq	aqueous
Ar	aryl group
BBD	borabicyclodecane
BIBOP	(2*R*,2'*R*,3*R*,3'*R*)-3,3'-di-*tert*-butyl-2,2',3,3'-tetrahydro-2,2'-**bib**enzo[*d*][1,3]**o**xa**p**hosphole
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1'-bi-2-naphthol
BiOX	bi-oxazoline
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Box	bis(oxazoline)
BPE	1,2-bis(phospholano)ethane
br	broad
BTFM	bis(3,5-trifluoromethylphenyl)
Bu	butyl
^{i}Bu	*iso*-butyl
^{n}Bu	butyl or *norm*-butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl

^{13}C	carbon-13 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAM	ceric ammonium molybdate
Cbz	benzyloxycarbonyl
cm	centimeter(s)
cm^{-1}	wavenumber(s)
comp	complex
conc.	concentrated
conv.	conversion
Cy	cyclohexyl
d	doublet
d	dextrorotatory
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
de	diastereomeric excess
DIPEA	*N*,*N*-diisopropylethylamine (Hunig's base)
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMS	dimethylsulfide
dr	diastereomeric ratio

EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
E^+	electrophile
E	trans (entgegen) olefin geometry
e.g.	for example (Latin: *exempli gratia*)
EI	electron ionization
eq	equation
equiv	equivalence(s)
er	enantiomeric ratio
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
h	hour(s)
^1H	proton
^2H	deuterium
HFIP	hexafluoroisopropanol
HMPA	hexamethylphosphoramide
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IC_{50}	half maximal inhibitory concentration (50%)

IR	infrared spectroscopy
J	coupling constant
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
m	multiplet or meter(s)
M	molar or molecular ion or metal
m	meta
μ	micro
Me	methyl
MeCN	acetonitrile (CH_3CN)
MEK	methyl ethyl ketone
Mes	mesityl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
μM	micromolar
mol	mole(s)
MS	molecular sieves
m/z	mass-to-charge ratio
NMR	nuclear magnetic resonance

Nu^-	nucleophile
o	ortho
OTf	trifluoromethanesulfonate
p	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
ppm	parts per million
Pr	propyl
^{c}Pr	cyclopropyl
^{i}Pr	isopropyl
^{n}Pr	propyl or *norm*-propyl
py	pyridine
Pyox	pyridinyl oxazoline
pyr	pyridine
q	quartet
Quinox	quinolinyl oxazoline
R	alkyl group
R	rectus
ref	reference
R_f	retention factor
rt	room temperature
s	singlet or seconds
S	sinister

sat.	saturated
SFC	supercritical fluid chromatography
t	triplet
TADDOL	(−)-*trans*-α,α′-(2,2-Dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol)
TBS	*tert*-butyldimethylsilyl
temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	tolyl
Ts	*para*-toluenesulfonyl (tosyl)
UAA	unnatural or unusual amino acid
UV	ultraviolet
W	watts
X	anionic ligand or halide
Xyl	xylyl
Z	cis (zusammen) olefin geometry