PALLADIUM-CATALYZED DECARBOXYLATIVE AND DECARBONYLATIVE TRANSFORMATIONS IN THE SYNTHESIS OF FINE AND COMMODITY CHEMICALS

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ABSTRACT

Decarboxylation and decarbonylation are important reactions in synthetic organic chemistry, transforming readily available carboxylic acids and their derivatives into various products through loss of carbon dioxide or carbon monoxide. In the past few decades, palladium-catalyzed decarboxylative and decarbonylative reactions experienced tremendous growth due to the excellent catalytic activity of palladium. Development of new reactions in this category for fine and commodity chemical synthesis continues to draw attention from the chemistry community.

The Stoltz laboratory has established a palladium-catalyzed enantioselective decarboxylative allylic alkylation of β-keto esters for the synthesis of α-quaternary ketones since 2005. Recently, we extended this chemistry to lactams due to the ubiquity and importance of nitrogen-containing heterocycles. A wide variety of α-quaternary and tetrasubstituted α-tertiary lactams were obtained in excellent yields and exceptional enantioselectivities using our palladium-catalyzed decarboxylative allylic alkylation chemistry. Enantioenriched α-quaternary carbonyl compounds are versatile building blocks that can be further elaborated to intercept synthetic intermediates en route to many classical natural products. Thus our chemistry enables catalytic asymmetric formal synthesis of these complex molecules.

In addition to fine chemicals, we became interested in commodity chemical synthesis using renewable feedstocks. In collaboration with the Grubbs group, we developed a palladium-catalyzed decarbonylative dehydration reaction that converts abundant and inexpensive fatty acids into value-added linear alpha olefins. The chemistry proceeds under relatively mild conditions, requires very low catalyst loading, tolerates a variety of functional groups, and is easily performed on a large scale. An additional advantage of this chemistry is that it provides access to expensive odd-numbered alpha olefins.

Finally, combining features of both projects, we applied a small-scale decarbonylative dehydration reaction to the synthesis of α-vinyl carbonyl compounds. Direct α-vinylation is challenging, and asymmetric vinylations are rare. Taking advantage of our decarbonylative dehydration chemistry, we were able to transform enantioenriched δ-oxocarboxylic acids into quaternary α-vinyl carbonyl compounds in good yields with complete retention of stereochemistry. Our explorations culminated in the catalytic enantioselective total synthesis of (–)-aspewentin B, a terpenoid natural product featuring a quaternary α-vinyl ketone. Both decarboxylative and decarbonylative chemistries found application in the late stage of the total synthesis.

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LIST OF ABBREVIATIONS

Å	Ångstrom
$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl
atm	atmosphere
BBN	borabicyclononane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
i-Bu	*iso*-butyl
t-Bu	*tert*-Butyl
Bz	benzoyl
c	concentration for specific rotation measurements
°C	degrees Celsius
calc'd	calculated
cat	catalytic
Cbz	carbobenzyloxy
CCDC	Cambridge Crystallographic Data Centre
CI	chemical ionization
Cy	cyclohexyl
d	doublet

D	deuterium
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
e.g.	for example (Latin “exempli gratia”)
equiv	equivalent
ESI	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
GC	gas chromatography
h	hour(s)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectroscopy
Hz	hertz
i.e.	that is (Latin “id est”)
IR	infrared (spectroscopy)
J	coupling constant

λ	wavelength
L	liter
LDA	lithium diisopropylamide
LiHMDS	lithium hexamethyldisilazide
lit.	literature value
m	multiplet; milli
m	meta
m/z	mass to charge ratio
M	metal; molar; molecular ion
Me	methyl
MHz	megahertz
μ	micro
min	minute(s)
MM	mixed method
mol	mole(s)
mp	melting point
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
N	normal
nbd	norbornadiene
NMP	*N*-methylpyrrolidone
NMR	nuclear magnetic resonance
[O]	oxidation
o	ortho
p	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution

PHOX	phosphinooxazoline
p*Ka*	p*K* for association of an acid
pmdba	bis(4-methoxybenzylidene)acetone
ppm	parts per million
i-Pr	isopropyl
Py	pyridine
q	quartet
ref	reference
R_f	retention factor
s	singlet or strong or selectivity factor
sat.	saturated
SFC	supercritical fluid chromatography
t	triplet
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium difluorotriphenylsilicate
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yloxy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl
TOF	time-of-flight
Tol	tolyl
TON	turnover number
t_R	retention time
Ts	*p*-toluenesulfonyl (tosyl)