Enantioselective Construction of Acyclic Quaternary Carbon Stereocenters: Palladium-Catalyzed Decarboxylative Allylic Alkylation of Fully Substituted Amide Enolates

Pavel Starkov,†‡§⊥ Jared T. Moore,‡⊥ Douglas C. Duquette,‡⊥ Brian M. Stoltz,‡⊥‡⊥ and Ilan Marek‡⊥⊥

†The Mallat Family Laboratory of Organic Chemistry, Schulich Faculty of Chemistry, and The Lise Meitner–Minerva Center for Computational Quantum Chemistry, Technion—Israel Institute of Technology, Technion City, Haifa 32000, Israel
‡Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

ABSTRACT: We report a divergent and modular protocol for the preparation of acyclic molecular frameworks containing newly created quaternary carbon stereocenters. Central to this approach is a sequence composed of a (1) regioselective and stereoretentive preparation of allyloxycarbonyl-trapped fully substituted stereodefined amide enolates and of a (2) enantioselective palladium-catalyzed decarboxylative allylic alkylation reaction using a novel biphosphine ligand.

1. INTRODUCTION

The quaternary carbon stereocenter is a structure that represents a minimalistic molecular framework with enhanced (bio)chemical stability and embedded propensity to encode directionality in the three-dimensional space. Over the past decade, several efficient approaches addressing de novo construction of cyclic quaternary carbon stereocenters have been developed,† however, only a select few provide general access to such molecular structures in an acyclic setting.‡ The prevailing majority of these methods heavily rely on the use of stereodefined trisubstituted alkynes as substrates for enantioselective allylic substitution,§ conjugate addition,⊥ or nucleophilic allylation reactions.†

An alternative strategy, with potentially a broader synthetic application, is enantioselective electrophilic functionalization of fully substituted acyclic enolates. In this context, regioselective formation of functionalized and fully substituted enolates is the center of renewed interest,‡ with several attractive strategies having been reported for the preparation of β,β-disubstituted enolates of esters⊥⊥ and amides,⊥⊥ albeit, largely using enantiomerically enriched α,α-disubstituted carbonyl derivatives (Scheme 1A).

The Marek group has previously reported a robust stereoselective approach to the formation of polysubstituted stereodefined acyclic enolates using a highly regioselective carbometalation of α-heterosubstituted alkynes followed by a regioselective in situ oxidation reaction.⊥⊥ This approach proved to be successful in preparation of new compounds bearing quaternary carbon stereocenters using aldon, Mannich, and allylic alkylation reactions, achieving good to excellent overall yields and exceptional diastereoselectivities (Scheme 1B). Additionally, a highly diastereoselective aldol reaction employing aliphatic aldehydes was possible using stereodefined fully substituted silyl ketene aminals and titanium-mediated Mukaiyama aldol-type reaction conditions.⊥⊥ Recent studies demonstrated efficient preparation of stereochemically defined acyclic fully substituted ketone enolates from simple vinyl carbamates in a single-pot operation (Scheme 1C).⊥⊥

As most of the above-mentioned strategies relied on the use of chiral auxiliaries, the remaining challenge was development of catalytic enantioselective transformations⊥⊥⊥ to establish acyclic quaternary carbon centers via electrophilic C-functionalization of fully substituted amide enolates. The Stoltz group has extensively contributed to the design of highly efficient catalysts for highly enantioselective allylic alkylation-type reactions,⊥⊥⊥ especially those involving fully substituted cyclic allyl enol carbonates (Scheme 1D)⊥⊥⊥ en route to the synthesis of complex natural products.⊥⊥⊥ We envisaged developing a unified carbometalation–enantioselective catalysis approach to access de novo quaternary carbon stereocenters. Our approach would involve implementing achiral acyclic amide enolates in combination with enantioselective palladium-catalyzed decarboxylative allylic alkylation technology (Scheme 1E).

Of special interest are the α-quaternary amide and imide derivatives that this outlined strategy would produce. Activated amides are among the most widely utilized carboxylic acid derivatives and have seen historical synthetic use⊥⊥⊥ as well as more recent applications in catalytic transformations.⊥⊥⊥ Additionally, we surmised that having the ability to tune the electronic and steric nature of the amido functionality would be critical for the success of the asymmetric catalysis. Thus, based

Received: April 22, 2017
Published: June 19, 2017

DOI: 10.1021/jacs.7b04086
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX
on our past experience with catalytic enantioselective allylic alkylations of lactam-derived enolates, we intentionally focused our studies on amido-type enolate chemistry. This supposition indeed proved to be true, as will be outlined below.

2. RESULTS AND DISCUSSION

2.1. Stereodefined Acyclic Enol Carbonates. Our first target was an efficient approach to stereodefined acyclic allyloxycarbonyl-protected polysubstituted amide enolates. Given the multiple potential challenges and pitfalls of our strategy, we purposely limited the scope of the study to substrates with the highest probability of success. For the formation of stereodefined acyclic allyloxycarbonyl-protected polysubstituted amide enolates, we envisioned that heteroatoms in proximity to the sites of reactivity could interfere with the regio- and stereoselectivity of the multistep organometallic process, and thus generally limited our exploration to alkyl and aryl substituted systems. To this end, we have developed two complementary methods. The initial method (Method A, Scheme 2) consists of a regioselective carbometalation reaction of ynecarbamates 1 using one equivalent of the Gilman reagent

a Conditions for each method are as follow. Method A: ynecarbamate (1.0 equiv), CuBr-DMS (1.0−1.2 equiv), RLi in hexanes or Et₂O (2.0−2.4 equiv), in Et₂O (ca. 0.1−0.5 M) at −30 to −10 °C for 0.5 h, then 5.5 M tBuOOH in decane (1.0−1.2 equiv) at −80 °C for 0.5 h, then AllocCl (2.5−4.0 equiv) at −80 to 23 °C for 1 h, then 1 M HCl. Method B: step 1, ynecarbamate (1.0 equiv), CuI (1.0 equiv), R₄MgBr in Et₂O (2.0 equiv), in Et₂O (ca. 0.1−0.5 M) at −30 to −10 °C for 1 h, then I₂ (2.0 equiv) in THF at −20 to 0 °C for 15 min, then sat. Na₂S₂O₃; step 2, vinyl iodide (1 equiv), tBuLi (2.0−2.1 equiv), in Et₂O
(0.1−0.3 M) at −80 °C for 15 min, then in situ prepared tBuOOLi (from ca. 5.5 M tBuOOH in decane (1.8−2.1 equiv) and MeLi in EtO (2.0−2.3 equiv), in THF at −80 °C for 0.5 h at −80 to −40 °C for 1 h, then AllocCl (4.0−5.0 equiv) at −50 to 23 °C for 1 h, then 1 M HCl.

(R4CuLi) to result in the formation of nonsymmetric vinyl alkyl cuprate species 2.18 Upon treatment with a single equivalent of tert-butyl hydroperoxide (t-BuOOH), a selective protonation of the residual R4 moiety of 2 occurs to give a reactive heterocuprate intermediate.9 It subsequently undergoes an intramolecular S2,2 reaction (1,2-metallate rearrangement) to provide the desired stereodefined copper(1) enolate. The final electrophilic trapping by allyl chloroformate (AllocCl) gives allyloxyformyl-protected polysubstituted amide enolate 3. Method A is effective for substrates bearing cyclic carbamates such as 2-oxazolidinone and 2-benzoxazolinone (3a−3c) but is much less efficient for acyclic carbamates. In the latter case of acyclic nycarbonate-derived products (e.g., 3d), the regioselectivity of the carbometalation reaction is poor and therefore, the overall efficiency of preparation of our desired allyloxyformyl-protected polysubstituted amide enolates 3 was less than optimal. As an alternative, a copper-promoted carbomagnesi nation reaction using Normant-type reagent (RMgBr/Cul in a 2:1 ratio)18 proved to be highly regioselective in diethyl ether as solvent. Trapping of the resulting vinyl magnesium species with molecular iodine leads to the formation of fully substituted vinyl iodide 4 in excellent yields as a single constitutional isomer (Method B, Scheme 2). The vinyl iodide is then directly converted to the corresponding vinyl lithium species by iodine−lithium exchange and regioretentively oxidized with an externally prepared oxenoid19 (t-BuOOLi). The resulting stereodefined fully substituted enolate is then reacted with AllocCl to deliver well-diversified products 3d−3q in excellent yields as single isomers as shown in Scheme 2.

2.2. Asymmetric Pd-Catalyzed Decarboxylative Allylic Alkylation. With a library of acyclic substrates 3 in hand, we evaluated the enantioselective palladium-catalyzed decarboxylative allylic alkylation (Table 1). Initially, the enantionic excess was determined directly by using the decarboxylative allylic alkylation reaction products 5 (on chiral SFC and HPLC); however, we opted to include an additional olefin metathesis step that results in products 6, which were more easily separable and gave a greater UV signal strength on chiral SFC. We first examined a subset of solvents using the two PHOX ligands (L1 and L2), known to achieve excellent enantioselectivities for the palladium-catalyzed asymmetric allylic alkylation of cyclic ketones. Surprisingly, for acyclic substrates 3a−3d, neither of these ligands achieved satisfactory level of enantiodiscrimination (for the full list of solvents and detailed results, see Table S1 in Supporting Information). The first promising results were obtained with C2-symmetric bisphosphines ligands L3−L5 in THF (Table 1, entries 1−5, and Table S2 in the Supporting Information).20 Increasing the bulk around the phosphine (L5), which has been shown to have had a positive impact on alkylation of trisubstituted amide enolates with stilbene-derived diamine-linked P,P-ligands21 inhibited the reaction with our fully substituted enolates 3a and 3d (Table 1, entries 6 and 20). Interestingly, when the two alkyl groups (R1 and R2) on the stereodefined acyclic allyloxyformyl polysubstituted amide enolate were permuted (cf. 3a and 3b), opposite enantiomers were obtained in lower enantiomeric excess (Table 1, cf. entries 3 and 7 vs entries 4 and 8). These observations suggest that the enolate geometry is likely conserved through the course of the reaction and that the highest enantioselectivities are obtained when the smallest substituent is syn to the allyloxyformyl group. Slightly better enantiodiscrimination was observed when EtOAc was used as solvent instead of THF (Table 1, entries 8 and 9). Benzoxazolidinone 3c21 performed unsatisfactorily when compared to the parent oxazolidinone 3a (Table 1, cf. entries 2 and 10 and entries 4 and 11). Far better enantioselectivities

Table 1. Evaluation of Ligands for Palladium-Catalyzed DAA of Acyclic Allyloxyformyl Polysubstituted Amide Enolates

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>solvent</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>L4</td>
<td>THF</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>L4</td>
<td>THF</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>L4</td>
<td>THF</td>
<td>−70</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>L4</td>
<td>THF</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>L7</td>
<td>THF</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>3a</td>
<td>L3</td>
<td>THF</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>3b</td>
<td>L3</td>
<td>THF</td>
<td>46</td>
</tr>
<tr>
<td>8</td>
<td>3b</td>
<td>L6</td>
<td>THF</td>
<td>−30</td>
</tr>
<tr>
<td>9</td>
<td>3b</td>
<td>L6</td>
<td>EtOAc</td>
<td>−36</td>
</tr>
<tr>
<td>10</td>
<td>3c</td>
<td>L4</td>
<td>THF</td>
<td>32</td>
</tr>
<tr>
<td>11</td>
<td>3c</td>
<td>L6</td>
<td>THF</td>
<td>50</td>
</tr>
<tr>
<td>12</td>
<td>3d</td>
<td>L4</td>
<td>THF</td>
<td>72</td>
</tr>
<tr>
<td>13</td>
<td>3d</td>
<td>L4</td>
<td>THF</td>
<td>74</td>
</tr>
<tr>
<td>14</td>
<td>3d</td>
<td>L4</td>
<td>THF</td>
<td>−60</td>
</tr>
<tr>
<td>15</td>
<td>3d</td>
<td>L6</td>
<td>EtOAc</td>
<td>−68</td>
</tr>
<tr>
<td>16</td>
<td>3d</td>
<td>L6</td>
<td>THF</td>
<td>86</td>
</tr>
<tr>
<td>17</td>
<td>3d</td>
<td>L6</td>
<td>EtOAc</td>
<td>84</td>
</tr>
<tr>
<td>18</td>
<td>3d</td>
<td>L7</td>
<td>THF</td>
<td>86</td>
</tr>
<tr>
<td>19</td>
<td>3d</td>
<td>L7</td>
<td>EtOAc</td>
<td>94</td>
</tr>
<tr>
<td>20</td>
<td>3d</td>
<td>L6</td>
<td>THF</td>
<td>NR</td>
</tr>
</tbody>
</table>
were finally achieved with acyclic carbamate 3d using C2-
symmetric bisphosphine ligands L3−L7 (Table 1, entries 12−
18) to reach an excellent enantiomeric excess of 94% with the
novel electron-deficient ligand L7 and EtOAc as solvent (Table
1, entry 19). Using these optimized conditions, we decreased
the catalyst loading to 4 mol% of Pd(dba)2 and ligand L7
loading to 7 mol% in EtOAc with no loss in enantiodiscrimi-
nation.

With an optimal asymmetric reaction protocol in hand, we
initiated an investigation into the scope of the enantioselective
alkylation. The nature of the R2 substituent and R3 of the
acyclic carbamate substrate was probed by measuring the
enantioselectivity of the reaction as shown in Scheme 3A.

Scheme 3. Access to All-Carbon Quaternary Stereocenters in
Unbiased Acyclic Systems with Alloc-Trapped Enolates

Gratifyingly, the scope of the reaction process appears to be
fairly broad with respect to the R3 substituent on the carbamate
group (COOR3), where R3 = Me, Et, t-Bu, and Bn, 3d−3g,
respectively) and produced reaction products 6d−6g of
uniformly high enantiomeric excesses. Additionally, changing
the R1 substituent from N-benzyl to N-4-chlorophenyl
produced α-quaternary amide 6h in 90% ee.

We then turned our attention to altering the substituents at
the α-carbon (Scheme 3B, i.e., R1 and R3). Changing the R1
substituent from a butyl group (6d, 94% ee) to a hexyl or
CH3CH2OTBS group did not alter the enantioselectivity of the
acyclic quaternary carbon center (94% ee for 6i and 6j, Scheme
3B). However, when the R1 substituent is an aromatic group,
the enantiodiscrimination is moderated lower (76% ee for 6k).
To a certain extent, replacing the R1 substituent with an ethyl
group was well tolerated (82% and 94% ee for 6l and 6m,
respectively), while introduction of a bulkier (CH2)3Ph group
resulted in diminished enantiomeric excess (76% ee for 6n).
In general, there is a reasonable amount of functional group
tolerance as well as structural flexibility at every variable
position in the new combined method. In certain cases the
chemical yields of the Pd-catalyzed allylic alkylation are
somewhat modest. This is likely due to a combination of steric
congestion and the opportunity for palladium-enolates to
proceed through multiple catalytic pathways (inner sphere
versus outer sphere alkylation chemistry),22 some of which do
not productively lead to the desired product (e.g., enolate
protonation23 β-hydride elimination,24 etc.).

To determine the absolute configuration of the newly formed
quaternary carbon stereocenters in acyclic compounds 5 and 6
(Scheme 4), we compared the optical rotation of lactam 8, an
easily accessible cyclic product resulting from simple manipu-
lations of 5j with a previously characterized derivative obtained
by enantioselective decarboxylative allylic alkylation of cyclic
allyl enol carbonate 7 (see Supporting Information for further
details).14d As a result of this chemical structural correlation, we
determined that the absolute stereochemistry of acyclic
derivative 5j is S. All other acyclic amide products resulting
from our new asymmetric alkylation reaction are assigned in
Scheme 3 by analogy.

3. CONCLUSION

In conclusion, we have developed a robust method for the
preparation of versatile molecular backbones containing a
newly created quaternary carbon stereocenter in unbiased
acyclic systems. This was accomplished by the unique
combination of easily accessible, fully substituted stereo-defined
amide enolates with the enantioselective catalytic decarbox-
ylative allylic alkylation reaction employing a novel electroni-
cally perturbed C2 symmetrical bisphosphine ligand. Finally,
while the full synthetic utility of the enantoienriched α-
quaternary amides prepared has yet to be realized, one can
 glean the implications of this chemistry from both past
literature applications of these subunits as well as the simple
sequence employed to determine absolute stereochemistry,
resulting in the preparation of lactam 8 (Scheme 4). Efforts to
exploit this new technology on the context of multistep
synthetic chemistry will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the
ACS Publications website at DOI: 10.1021/jacs.7b04086.
Experimental procedures and characterization data (PDF)

AUTHOR INFORMATION

Corresponding Authors
stoltz@caltech.edu
chilamm@tx.technion.ac.il

ORCID

Pavel Starkov: 0000-0003-1421-4731
Brian M. Stoltz: 0000-0001-9837-1528
Ilan Marek: 0000-0001-9154-2320

Present Address
§P.S.: Department of Chemistry and Biotechnology, Tallinn University of Technology, Tallinn 12618, Estonia

Author Contributions
†P.S. and J.T.M. contributed equally.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the Israel Science Foundation administrated by the Israel Academy of Sciences and Humanities (140/12), the Fund for Promotion of Research at the Technion, the NIH-NIGMS (R01GM116304), and the NSF (predoctoral research fellowship to D.C.D., No. DGE-1144469). Research reported in this publication was supported by the NIH-NIGMS under Award Number F32GM116304 (postdoctoral fellowship to J.T.M.). I.M. is holder of the Sir Michael and Lady Sobell Academic Chair (Technion). Dr. Mona Shahgholi (Caltech) and Naseem Torian (Caltech) are thanked for mass spectrometry assistance. Dr. Scott Virgil (Caltech) is thanked for instrumentation assistance and helpful discussions.

REFERENCES


(3) For recent reviews, see:  
(c) Trost, B. M. Tetrahedron 2015, 71, 5708.  
(c) Numajiri, Y.; Pritchett, B. P.; Chiyoda, K.; Stoltz, B. M. J. Am. Chem. Soc. 2015, 137, 1040.  
(d) Ling, T.; Rivas, F. Tetrahedron 2016, 72, 6729.  
(c) Snieckus, V. Chem. Rev. 1990, 90, 879.  
(17) (a) Topczewski, J. J.; Cabrera, P. J.; Saper, N. I.; Sanford, M. S. Nature 2016, 531, 220.  