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

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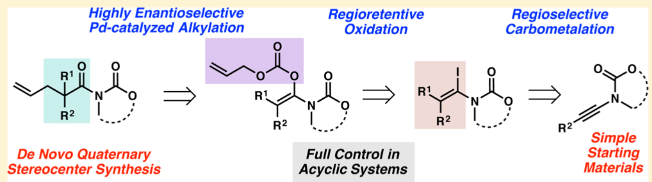
Supporting Information

**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 -retentive preparation of allyloxycarbonyl-trapped fully substituted stereodefined amide enolates and of a (2) enantioselective palladium-catalyzed decarboxylative allylic alkylation reaction using a novel bisphosphine 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;[1] however, only a select few provide general access to such molecular structures in an acyclic setting.[2] The prevailing majority of these methods heavily rely on the use of stereodefined trisubstituted alkenes as substrates for enantioselective allylic substitution,[3] conjugate addition,[4] or nucleophilic allylation reactions.[5]

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,[6] with several attractive strategies having been reported for the preparation of *β*,*β*-disubstituted enolates of esters[7] and amides[8] (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 regioretentive *in situ* oxidation reaction.[9] This approach proved to be successful in preparation of new compounds bearing quaternary carbon stereocenters using aldol, 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.[9d] Recent studies demonstrated efficient preparation of stereochemically defined acyclic fully substituted ketone enolates from simple vinyl carbamates in a single-pot operation (Scheme 1C).[10]

As most of the above-mentioned strategies relied on the use of chiral auxiliaries, the remaining challenge was development of catalytic enantioselective tranformations[11,12] 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,[13] especially those involving fully substituted cyclic allyl enol carbonates (Scheme 1D)[14] en route to the synthesis of complex natural products.[15] 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[16] as well as more recent applications in catalytic transformations.[17] 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

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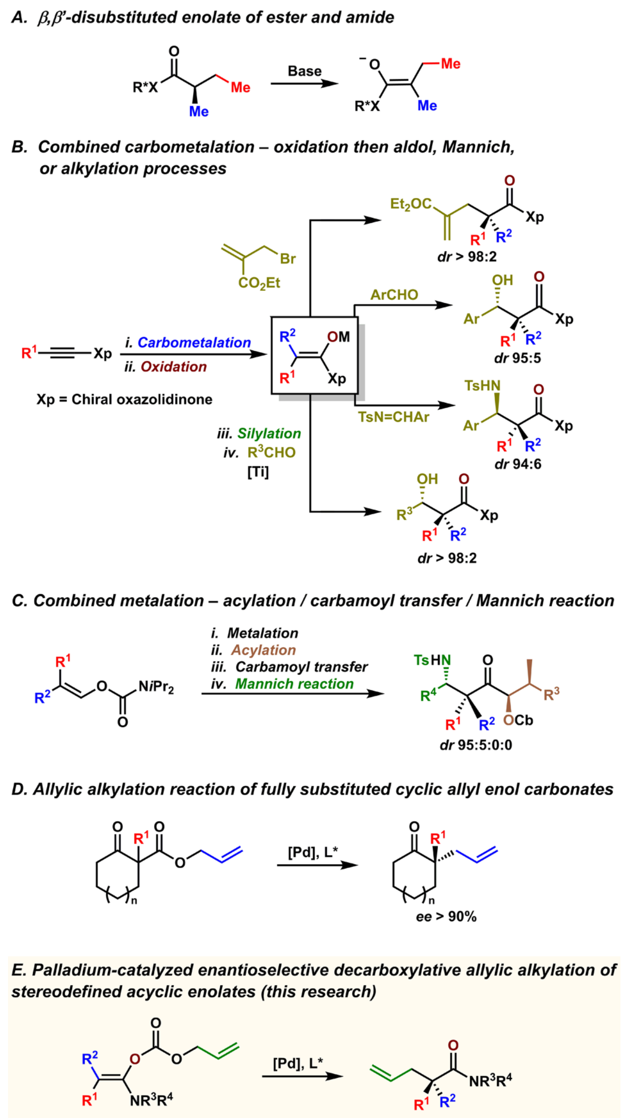
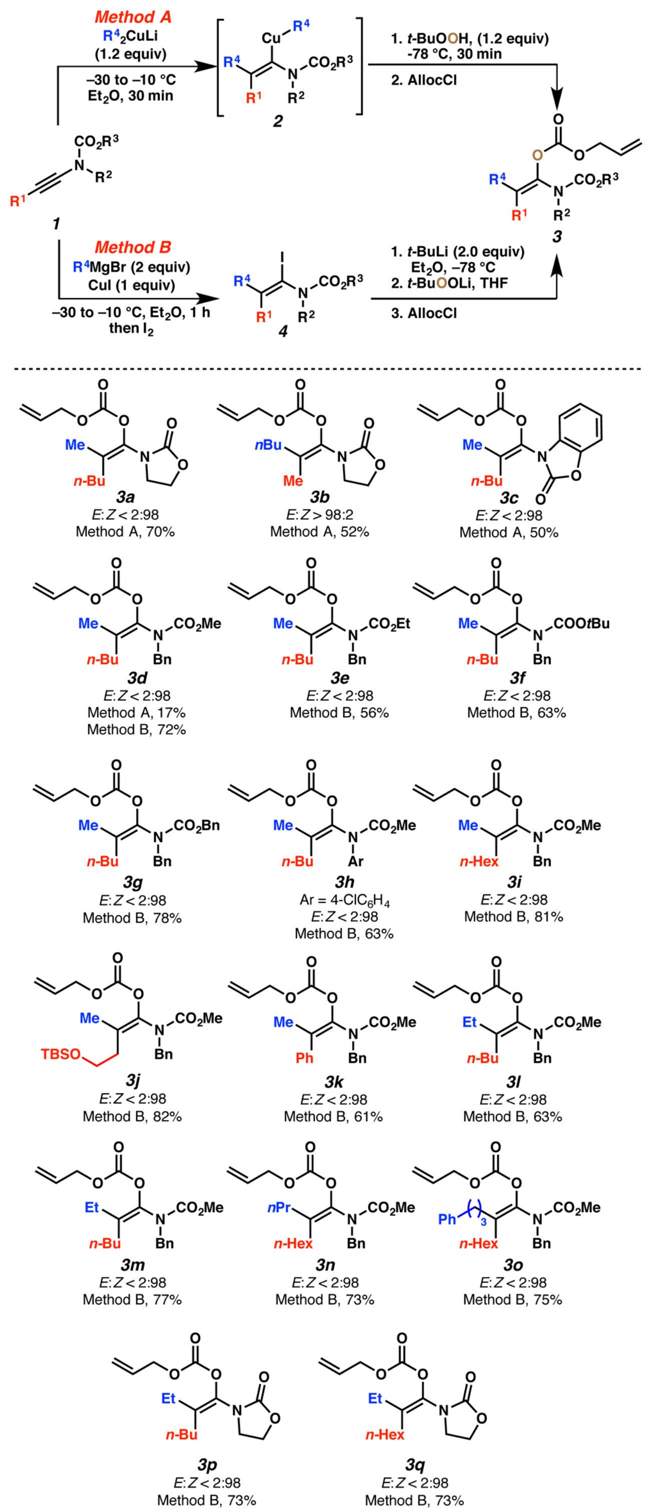
**Scheme 1. Preparation of Polysubstituted Enolates and Construction of Quaternary Stereocenters**




**Scheme 2. Preparation of Stereodefined Acyclic Allyloxycarbonyl Polysubstituted Amide Enolates 3**




[a]Conditions for each method are as follow. Method A: ynecarbamate (1.0 equiv), CuBr·DMS (1.0−1.2 equiv), $R^4$Li in hexanes or $Et_2O$ (2.0−2.4 equiv), in $Et_2O$ (ca. 0.1−0.5 M) at −30 to −10 °C for 0.5 h, then ca. 5.5 M *t*BuOOH 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), $R^4$ MgBr in $Et_2O$ (2.0 equiv), in $Et_2O$ (ca. 0.1−0.5 M) at −30 to −10 °C for 1 h, then $I_2$ (2.0 equiv) in THF at −20 to 0 °C for 15 min, then sat. $Na_2S_2O_3$; step 2, vinyl iodide (1 equiv), *t*BuLi (2.0−2.1 equiv), in $Et_2O$

on our past experience with catalytic enantioselective allylic alkylations of lactam-derived enolates, we intentionally focused our studies on amido-type enolate chemistry.[14b,d] 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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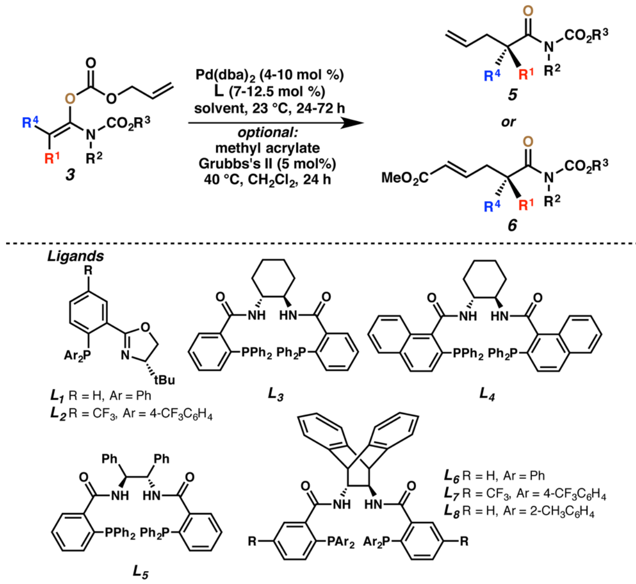
**Scheme 2. continued**

(0.1−0.3 M) at −80 °C for 15 min, then *in situ* prepared *t*BuOOLi [from ca. 5.5 M *t*BuOOH in decane (1.8−2.1 equiv) and MeLi in $Et_2O$ (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.

($R^4{}_2CuLi$) 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 $R^4$ moiety of **2** occurs to give a reactive heterocuprate intermediate.[9] It subsequently undergoes an intramolecular $S_N2$ reaction (1,2-metalate rearrangement) to provide the desired stereodefined copper(I) enolate. The final electrophilic trapping by allyl chloroformate (AllocCl) gives allyloxycarbonyl-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 ynecarbamate-derived products (e.g., **3d**), the regioselectivity of the carbometalation reaction is poor and therefore, the overall efficiency of preparation of our desired allyloxycarbonyl-protected polysubstituted amide enolates **3** was less than optimal. As an alternative, a copper-promoted carbomagnesiation reaction using Normant-type reagent (RMgBr/CuI 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 oxenoid[19] (*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 enantiomeric 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 ($L_1$ and $L_2$), known to achieve excellent enantioselectivities for the palladium-catalyzed asymmetric 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 $C_2$-symmetric bisphosphines ligands $L_3$−$L_7$ in THF (Table 1, entries 1−5, and Table S2 in the Supporting Information).[20] Increasing the bulk around the phosphine ($L_8$), which has been shown to have had a positive impact on allylation of trisubstituted amide enolates with stilbene-derived diamine-linked *P,P*-ligands,[21] inhibited the reaction with our fully substituted enolates **3a** and **3d** (Table 1, entries 6 and 20). Interestingly, when the two alkyl groups ($R^1$ and $R^4$) on the stereodefined acyclic allyloxycarbonyl polysubstituted amide enolate were permutated (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 allyloxycarbonyl group. Slightly better enantiodiscrimination was observed when EtOAc was used as solvent instead of THF (Table 1, entries 8 and 9). Benzoxazolidinone **3c**[21] 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 Allyloxycarbonyl Polysubstituted Amide Enolates 3**[a]




| entry | substrate | ligand | solvent | ee |
|---|---|---|---|---|
| 1 | **3a** | $L_3$ | THF | 64 |
| 2 | **3a** | $L_4$ | THF | 76 |
| 3 | **3a** | $L_5$ | THF | −70 |
| 4 | **3a** | $L_6$ | THF | 70 |
| 5 | **3a** | $L_7$ | THF | 70 |
| 6 | **3a** | $L_8$ | THF | NR |
| 7 | **3b** | $L_5$ | THF | 46 |
| 8 | **3b** | $L_6$ | THF | −30 |
| 9 | **3b** | $L_6$ | EtOAc | −36 |
| 10 | **3c** | $L_4$ | THF | 32 |
| 11 | **3c** | $L_6$ | THF | 50 |
| 12 | **3d** | $L_3$ | THF | 72 |
| 13 | **3d** | $L_4$ | THF | 74 |
| 14 | **3d** | $L_5$ | THF | −60 |
| 15 | **3d** | $L_5$ | EtOAc | −68 |
| 16 | **3d** | $L_6$ | THF | 86 |
| 17 | **3d** | $L_6$ | EtOAc | 84 |
| 18 | **3d** | $L_7$ | THF | 86 |
| *19* | ***3d*** | $L_7$ | *EtOAc* | *94* |
| 20 | **3d** | $L_8$ | THF | NR |

[a]Conditions: polysubstituted amide (1.0 equiv), $Pd(dba)_2$ (4−10 mol %), ligand (7−12.5 mol%) in solvent (0.17 M) at 25 °C for 24−72 h in glovebox. Filtration through silica plug, optionally followed by methyl acrylate (10 equiv), Grubbs second generation catalyst (5 mol %) in $CH_2Cl_2$ (0.03 M) at 40 °C for 24 h in glovebox. For details of individual experiments, see Supporting Information. NR = no reaction.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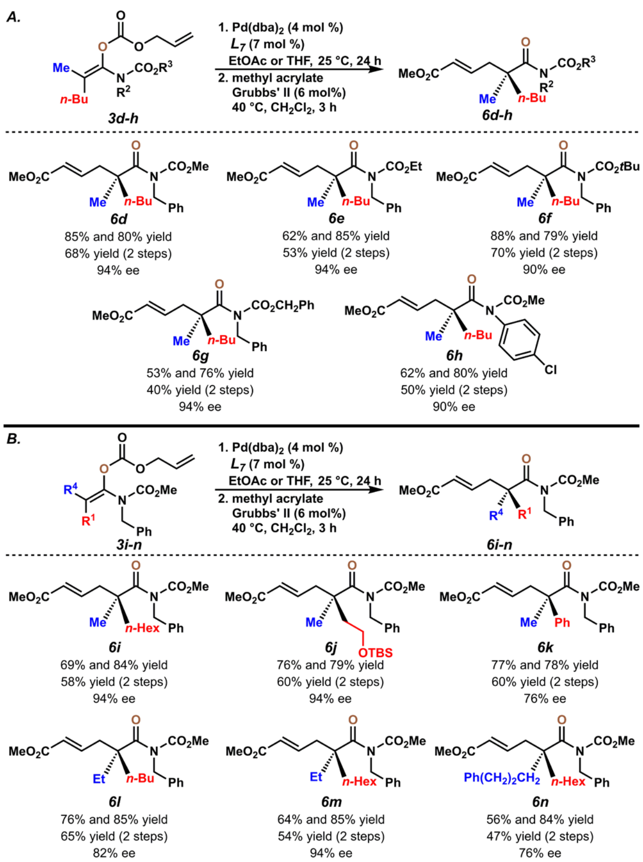
were finally achieved with acyclic carbamate **3d** using $C_2$-symmetric bisphosphine ligands **L**$_3$–**L**$_7$ (Table 1, entries 12–18) to reach an excellent enantiomeric excess of 94% with the novel electron-deficient ligand **L**$_7$ and EtOAc as solvent (Table 1, entry 19). Using these optimized conditions, we decreased the catalyst loading to 4 mol% of Pd(dba)$_2$ and ligand **L**$_7$ loading to 7 mol% in EtOAc with no loss in enantiodiscrimination.

With an optimal asymmetric reaction protocol in hand, we initiated an investigation into the scope of the enantioselective alkylation. The nature of the *N*-substituents R$^2$ and R$^3$ 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**[a]



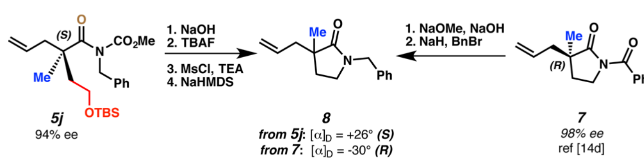

[a]Conditions: polysubstituted amide (1.0 equiv), Pd(dba)$_2$ (4 mol%), ligand (7 mol%) in solvent (0.17 M) at 20 °C for 24 h in glovebox. Purification (preparative TLC) followed by methyl acrylate (10 equiv), Grubbs second generation catalyst (6 mol%) in CH$_2$Cl$_2$ (0.03 M) at 40 °C for 3 h in glovebox. Yields are given for the individual steps along with the overall two-step yield.

Gratifyingly, the scope of the reaction process appears to be fairly broad with respect to the R$^3$ substituent on the carbamate group (COOR$^3$, where R$^3$ = Me, Et, *t*-Bu, and Bn, **3d**–**3g**, respectively) and produced reaction products **6d**–**6g** of uniformly high enantiomeric excesses. Additionally, changing the R$^2$ substituent from *N*-benzyl to *N*-4-chlorophenyl produced $\alpha$-quaternary amide **6h** in 90% ee.

We then turned our attention to altering the substituents at the $\alpha$-carbon (Scheme 3B, i.e., R$^1$ and R$^4$). Changing the R$^1$ substituent from a butyl group (**6d**, 94% ee) to a hexyl or CH$_2$CH$_2$OTBS group did not alter the enantioselectivity of the acyclic quaternary carbon center (94% ee for **6i** and **6j**, Scheme 3B). However, when the R$^1$ substituent is an aromatic group, the enantiodiscrimination is moderately lower (76% ee for **6k**). To a certain extent, replacing the R$^4$ substituent with an ethyl group was well tolerated (82% and 94% ee for **6l** and **6m**, respectively), while introduction of a bulkier (CH$_2$)$_3$Ph 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 protonation,[23] $\beta$-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

**Scheme 4. Determination of Absolute Stereochemistry**




easily accessible cyclic product resulting from simple manipulations 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 stereodefined amide enolates with the enantioselective catalytic decarboxylative allylic alkylation reaction employing a novel electronically perturbed $C_2$ symmetrical bisphosphine ligand. Finally, while the full synthetic utility of the enantioenriched $\alpha$-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

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Experimental procedures and characterization data (PDF)

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### Notes

The authors declare no competing financial interest.

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