JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

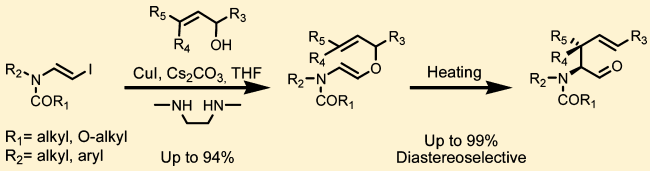
Synthesis of γ,δ-Unsaturated α-Aminoaldehydes Using a Copper-Catalyzed Vinylation Reaction Followed by a Claisen Rearrangement

Simon Ricard, Gabriel F. Sanapo, Neel Rahem, and Benoit Daoust*

Département de Chimie, Biochimie et Physique, Université du Québec à Trois-Rivières, Trois-Rivières, Québec G9A 5H7, Canada

Supporting Information

ABSTRACT: A new method to synthesize γ,δ-unsaturated α-nitrogenated aldehydes in very good yields is described herein. This method involves a copper-coupling reaction between β-iodoenamide derivatives and allylic alcohols to generate β-allyloxyenamide derivatives. The latter, when heated, undergo a Claisen rearrangement and form γ,δ-unsaturated α-nitrogenated aldehydes.



INTRODUCTION

Amino acids are peptide building blocks. Though synthetic peptides made from natural amino acids are recognized as therapeutic agents, their use as drugs is limited by (i) rapid protease degradation and (ii) fast renal excretion. Consequently, peptides built from non-natural amino acids, which are less prone to degradation and excretion, represent a promising avenue for the drug development industry. Preparation of non-natural amino acids and their precursors is thus an essential endeavor.[1]

α-Nitrogenated aldehydes are versatile non-natural amino acid precursors.[2] These functionalized aldehydes are indeed easily transformed into amino acids which, upon oligomerization, can lead to synthetic peptides.[2a,3] In addition, α-nitrogenated aldehydes are key chiral intermediates and can be transformed into useful 1,2-amino alcohols.[4]

Our synthetic strategy to produce non-natural amino acid precursors (**6**) is presented in Scheme 1. This three-step sequence involves two copper-coupling reactions (steps 1 and 2) and a stereoselective Claisen rearrangement (step 3). Step 1 of this sequence (copper-catalyzed C−N bond formation between nitrogenated compounds **1** and (*E*)-diiodoethene **2** to form β-iodoenamides **3**) has been previously published.[5] Steps 2 (copper coupling between vinyl iodides **3** and allylic alcohols **4** to form β-allyloxyenamide **5**) and 3 (stereoselective rearrangement leading to **6**) are the object of the present publication.

RESULTS AND DISCUSSION

Copper Coupling between Vinyl Iodides 3 and Allylic Alcohols 4. Cross-coupling reactions allowing the formation of C−N and C−O bonds represent important tools to prepare various chemical entities.[6] The first reported examples for producing such bonds are the Ullmann[7] and Goldberg[8] copper-coupling reactions. Both reactions suffer from harsh reaction conditions (high temperatures, use of strong bases, stoichiometric amounts of copper, and extended reaction times). Almost a century later, Hartwig[9] and Buchwald[10] circumvented these difficulties by introducing palladium-catalyzed carbon-heteroatom bond-forming reactions. Unfortunately, these reactions also exhibit disadvantages, mainly due to some Pd drawbacks such as high cost and toxicity limiting large-scale applications,[11] air and moisture sensitivity,[12] and low tolerance for nitrogen-containing functional groups.[12]

Cu-catalyzed C−N and C−O bond-forming processes received assistance with the use of chelating ligands (e.g., DMEDA, 1,10-phenanthroline), allowing for lower temperatures and shorter reaction times along with the possibility of using non- or low-polar solvents. Cu-coupling reactions between aromatic partners (anilines/phenols and aryl halides) have been the subject of many studies.[13] However, research work involving nonaromatic partners is much more recent and scarce. For example, Pan,[14] Jiang,[15] Shen,[16] and Lam[17] have demonstrated over the past decade that Cu-catalyzed amide vinylation between aliphatic amides and vinyl monoiodides or vinylmonoboronic acids was possible under mild conditions. As discussed earlier, we published in 2008 the first examples of intermolecular copper couplings between secondary amide derivatives and vinyl diiodide **2** (Scheme 1, step 1).[5] We showed that lactams and oxazolidinones can couple with diiodide **2**, leading to β-iodoenamides **3** in moderate to high yields with complete stereocontrol. We were also the first to report a copper-induced amide vinylation of an acyclic secondary amide (*N*-phenylacetamide) with an excellent yield (90%, **3a**, R_1 = Me and R_2 = Ph).[18]

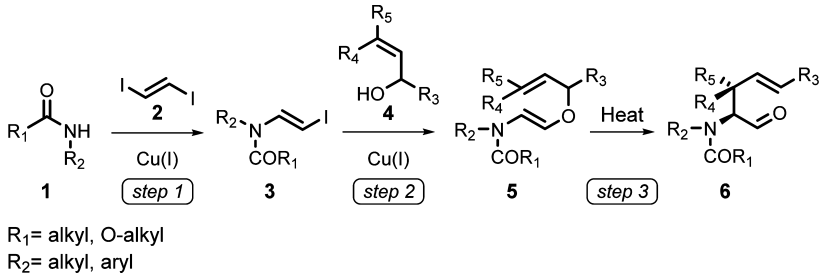
We recently tried to extend our reaction to acyclic primary amides (**1**, R_2 = H) but were unsuccessful in isolating the desired β-iodoenamides (**3**, R_2 = H) (unpublished results, 2015). Jiang's group[19] published an intramolecular version of the copper coupling between lactams and a vinyl diiodide moiety.

Cu-catalyzed C−O bond formation between nonaromatic partners has been even less studied. As far as we know, Buchwald's research group was the only one to show that Cu-coupling involving aliphatic alcohols and vinyl monoiodides can lead to allyl vinyl ethers with high yields.[20]

Received: March 22, 2016
Published: May 25, 2016

DOI: 10.1021/acs.joc.6b00512
J. Org. Chem. 2016, 81, 5066−5073

Scheme 1. General Strategy for the Synthesis of α-Nitrogenated Aldehydes 6



As previously mentioned, our synthetic strategy to produce **6** involves a Cu-catalyzed C−O bond forming cross-coupling reaction between β-iodoenamides **3** and allylic alcohols **4** (Scheme 1, step 2). We undertook this work using similar reaction conditions to those used for the transformation of amide derivatives **1** to β-iodoenamides **3** (i.e., CuI, DMEDA, Cs_2CO_3, and THF at 55 °C) (Scheme 1, step 1).[5] This facilitated manipulations as well as opened up the possibility for a future one-pot process transformation of **1** to **6**. After thorough optimization of this C−O bond-forming copper-coupling reaction, we found that the best conditions to prepare β-oxyenamides **5** from β-iodoenamides **3** were 2.5 equiv of alcohol, 0.5 equiv of CuI, 0.8 equiv of DMEDA, 4 equiv of Cs_2CO_3, and a 2.0 M concentration of β-iodoenamides **3** in THF. The reaction time was set to 24 h for all copper-coupling reactions. They were carried out in ace pressure tubes and were nitrogen purged before reaction.

We used vinyl iodide **3b** (a lactam) as the substrate to screen copper coupling with a variety of commercially available allylic alcohols **4a**−**f**. The copper coupling between **3b** and unsubstituted allyl alcohol **4a** led to the clean formation of the desired functionalized allyl vinyl ether **7a** with excellent yield (90%) (Table 1, entry 1).

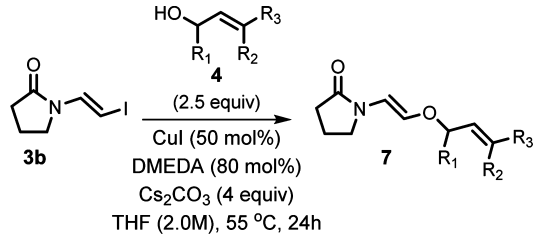
Note that under these reaction conditions, no Claisen rearrangement product was observed, which was easily distinguishable by the lack of its characteristic aldehyde signal in the ^{1}H NMR spectrum. This is not surprising because Buchwald heated similar allyl vinyl ethers at 60 °C (but bearing no nitrogen functionality), produced through copper coupling of allylic alcohols and vinyl monoiodides, and did not observe the Claisen rearrangement product.[20] Incidentally, such rearrangement products were not detected in our copper-coupling reactions with allylic alcohols unless otherwise stated.

When the *trans*-monosubstituted and *cis*-monosubstituted allylic alcohols **4b** and **4c**, respectively, were used, the corresponding functionalized allyl vinyl ethers **7b** and **7c** were obtained with excellent (94%) and fair (60%) yields, respectively (Table 1, entries 2−3). The same tendency was observed when we compared the coupling of geraniol (**4d**, a *trans* isomer) and nerol (**4e**, a *cis* isomer) with **3b**, which led to excellent (92%) and fair (44%) yields, respectively (Table 1, entries 4 and 5).

Not surprisingly, the copper coupling between **3b** and the sterically demanding secondary alcohol **4f** proved to be more difficult and led to only 39% yield of the desired functionalized allyl vinyl ether **7f** (Table 1, entry 6).

After a standard workup, the crude β-allyloxyenamides **7** were purified by flash chromatography, and decomposition was observed during separation. In contrast to the β-iodoenamides **3** (which possess long shelf-lives), β-allyloxyenamides **7** decomposed during storage and precluded the recording of any HR mass spectra. Although the chemical structures of the β-allyloxyenamides were assigned only by recording ^{1}H NMR, ^{13}C NMR, and FTIR spectra, the successful Claisen rearrangement of these compounds into α-nitrogenated aldehydes **10** (Table 3) strongly suggests that these initial structure assignments were correct.

Table 1. Copper Coupling between Vinyl Iodides 3b and Allylic Alcohols 4[a,b]



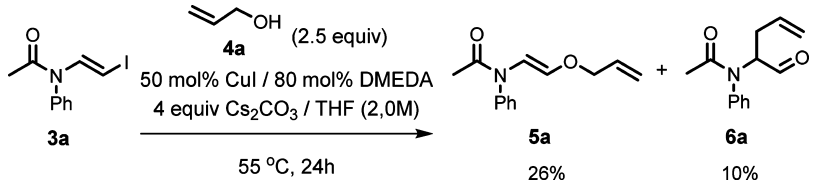
Entry	Allylic alcohol	Functionalized allyl vinyl ethers	Yield
1	4a	7a	90%
2	4b	7b	94%
3	4c	7c	60%
4	4d	7d	92%
5	4e	7e	44%
6	4f	7f	39%

[a]Reaction conditions: 2.5 equiv of allylic alcohol **4**, 50 mol % CuI, 80 mol % DMEDA, 4 equiv of Cs_2CO_3, and THF (2.0M) at 55 °C for 24 h in an ace pressure tube. [b]All couplings were performed on a 100 mg scale, and some were also performed on a 1 g scale with no significant effect on the yield.

After the successful copper-catalyzed coupling reaction between **3b** (a cyclic amide) and various allyllic alcohols, we wanted to assess the reactivity of an acyclic partner. As mentioned previously, compound **3a** was the only acyclic secondary β-iodoenamide we could prepare using our previous methodology[5] and was, therefore, the only acyclic β-

DOI: 10.1021/acs.joc.6b00512
J. Org. Chem. 2016, 81, 5066−5073

Scheme 2. Copper Coupling between Acyclic Vinyl Iodide 3a and Allyl Alcohol 4a

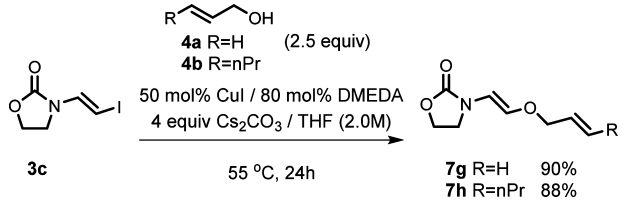


iodoenamide submitted to our coupling conditions with allyl alcohol **4a** (Scheme 2).

This coupling reaction afforded the desired functionalized allyl vinyl ether **5a** with poor yield (26%) along with 10% of the Claisen rearrangement product **6a**. The presence of the Claisen rearrangement product in this particular case suggested that **5a** was under the very same conditions more prone to rearrange than **7a**. The amide moiety of **5a** is acyclic and contains a phenyl group on the nitrogen instead of an alkyl substituent (as in **7a**). This phenyl group seemed to accelerate the Claisen rearrangement which, at first glance, is surprising. Indeed, Carpenter[21] and Barluenga[22] stated in their seminal work on the effects of substituents on the Claisen rearrangement kinetics that an electron-donating group in position 1 (the nitrogen position in our case) facilitates the Claisen rearrangement. Therefore, switching from an alkyl moiety (electron-donating group) to a phenyl moiety (electron-withdrawing group) on the nitrogen should decelerate the rearrangement. This unexpected acceleration might be due to a stabilizing π-stacking interaction between the phenyl group and the allylic moiety, causing the folding of the molecule needed for the rearrangement to be slightly facilitated. The pericyclic transition state of the latter would be lower in energy, triggering a faster rearrangement.

We then applied our coupling reaction to a carbamate. Vinyl iodide **3c** (a cyclic carbamate) was used as a coupling partner with **4a** and **4b** (Scheme 3). The desired functionalized allyl vinyl

Scheme 3. Copper Coupling between Vinyl Iodide 3c and Allyl Alcohols 4a and 4b

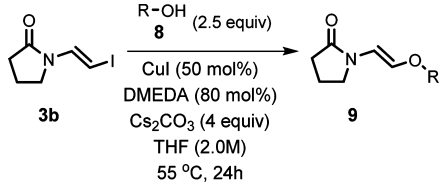


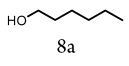
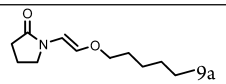
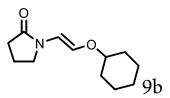
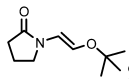
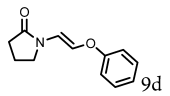
ethers **7g** and **7h** were isolated with excellent yields (90% and 88%, respectively). These yields are almost identical to those obtained for their lactam counterparts **7a** and **7b** (90% and 95%, respectively).

We then performed our C−O bond forming reaction on nonallylic commercially available alcohols (**8a**−**d**) to hopefully extend the scope of our method to various kinds of alcohols. We used **3b** as the nitrogen-containing partner for these copper couplings. To our delight, the copper coupling between **3b** and primary alcohol **8a** afforded the desired functionalized alkyl vinyl ether **9a** in a very good yield (82%) (Table 2, entry 1), though the yield was slightly lower than that of the analogous allylic alcohol **4b** (94%) (Table 1, entry 2).

When secondary alcohol **8b** was used, we obtained only 16% of the desired compound **9b** (Table 2, entry 2), a yield much lower than that of its allylic counterpart **4f** (39%) (Table 1, entry 6). The tertiary nonallylic alcohol **8c** was also tested but afforded

Table 2. Copper Coupling between Vinyl Iodides 3b and Nonallylic Alcohols 8[a,b]



Entry	Alcohol	Functionalized alkyl vinyl ethers	Yield
1	 8a	 9a	82%
2	 8b	 9b	16%
3	 8c	 9c	0%[c]
4	 8d	 9d	5% 8%[d]

[a]Reaction conditions: 2.5 equiv of nonallylic alcohol **8**, 50 mol % CuI, 80 mol % DMEDA, 4 equiv of Cs_2CO_3, and THF (2.0 M) at 55 °C over 24 h in an ace pressure tube. [b]All couplings were performed on a 100 mg scale, and some were also performed on a 1 g scale with no significant effect on the yield. [c]Only traces of *N*-vinylpyrrolidin-2-one were observed. [d]The reaction was carried out at 80 °C.

only traces of the deiodinated product *N*-vinylpyrrolidin-2-one (Table 2, entry 3). Last, we applied our method to phenol (**8d**) but unfortunately obtained a very poor yield, even at a higher temperatures (5% at 55 °C and 8% at 80 °C) (Table 2, entry 4).

As mentioned earlier, we selected our coupling conditions with the goal of moving on to a one-pot process after optimization. We tried the one-pot synthesis of **7b** from the corresponding lactam **1a** by two successive copper-coupling reactions (Scheme 4).

We monitored the consumption of **2** by TLC, added **4b** (2 equiv), and allowed it to react for 18 h (method A). Method B used the same sequence with two simple modifications: (i) addition of a supplementary equivalent of **4b** after 18 h and (ii) a total reaction time of 66 h. The yields obtained were very low with both methods (9% and 15%, respectively) in comparison with the good yield obtained by combination of the two separated steps (71%). Note that those attempts were performed with only 1 equiv of **2** (instead of 2 equiv) to limit secondary reactions. Those preliminary results highlight the need for extensive work to achieve the one-pot synthesis of **7b** from **1a** in high yields. Further investigations on this reaction will be reported in a subsequent communication.

DOI: 10.1021/acs.joc.6b00512
J. Org. Chem. 2016, 81, 5066−5073

Scheme 4. One-Pot Synthesis of β-Allyloxyenamide 7b from Lactam 1a

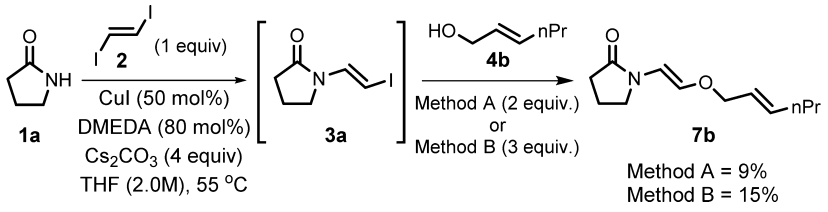
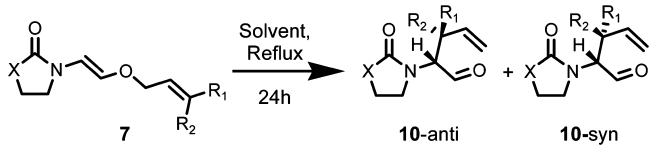


Table 3. Claisen Rearrangement of β-Allyloxyenamide Derivatives 7 in Refluxing Solvents Using Conventional Heating[a,b]



Entry	Substrate	Aldehyde	Solvent	Temperature	Yield (syn + anti)	Ratio anti/syn [c]
1	7a X = CH_2, R_1 = H, R_2 = H	10a	DCM	40 °C	5%	-
2			THF	66 °C	9%	-
3			Benzene	80 °C	58%	-
4			Toluene	110 °C	68%	-
5			*o*-Xylene	144 °C	10%	-
6	7b X = CH_2, R_1 = $CH_2CH_2CH_3$, R_2 = H	10b	Benzene	80 °C	90%	1.8 : 1
7			Toluene	110 °C	90%	1.8 : 1
8			*o*-Xylene	144 °C	67%	1.2 : 1
9			DMF	153 °C	72%	1 : 1
10			H_2O	100 °C	85%	1.5 : 1
11			H_2O/EtOH	78 °C	80%	1 : 1
12	7c X = CH_2, R_1 = H, R_2 = $CH_2CH_2CH_3$	10b	Benzene	80 °C	45%	1 : 1.1
13			Toluene	110 °C	67%	1 : 1.2
14	7i X = O, R_1 = CH_3, R_2 = $(CH_2)_2CH{=}C(CH_3)_2$	10c	Benzene	80 °C	80%	1 : 1.5
15			Toluene	110 °C	82%	1 : 1.5
16			*o*-Xylene	144 °C	60%	1 : 1
17			DMF	153 °C	67%	1 : 1

[a]Reaction conditions: reflux, 24 h. [b]All rearrangements were performed on a 50 mg scale. [c]Based on the 200 MHz ^{1}H NMR spectra of the crude reaction mixture.

Claisen Rearrangement of Functionalized Allyl Vinyl Ethers 5. The Claisen rearrangement is a [3,3]-sigmatropic rearrangement in which an allyl vinyl ether is converted to a nonconjugated unsaturated carbonyl compound. This rearrangement generally proceeds via a chair-like transition state that allows the synthesis of chiral carbonyl compounds with stereoselectivity. It has been used in numerous studies and has been the subject of many reviews in the past decade.[23] However, study of the Claisen rearrangement of nitrogenated allyl vinyl ether has been given very little attention. About 25 years ago, Barluenga[22] demonstrated the influence of substituents on the Claisen rearrangement of some allyl oxyenamines. A decade later, Kazmaier[24] developed a method to prepare α-amino acids from *N*-protected amino acid allylic esters. This last method gives good yields and excellent selectivity while allowing the formation of a quaternary center. However, the methodology requires use of a strong base (i.e., LDA). A thorough search of the literature revealed only one example of Claisen rearrangement of an allyl oxyenamide, published by Farran in 2008.[25] We concluded that there is a need for a systematic study of the Claisen rearrangement of β-allyloxyenamides to produce γ,δ-unsaturated α-aminoaldehydes **6**.

Our first results are listed in Table 3. We solubilized β-allyloxyenamide derivatives **7** in different solvents under stirring while refluxing for 24 h. When **7a** was refluxed in dichloromethane or THF, the desired aldehyde **10a** was isolated in very low yields (5% and 9%, respectively) (Table 3, entries 1 and 2). When refluxed in higher temperatures (benzene or toluene, entries 3 and 4), compound **7a** rearranged to **10a** in fair yields in both cases (58% and 68%, respectively), but the yield collapsed (10%) when *o*-xylene was used as the solvent (Table 3, entry 5). **7b** (bearing a *trans* C=C bond) in refluxing benzene or toluene underwent rearrangement that led to aldehyde **10b** in excellent yield (90%) but with low dr (1.8/1 *anti*/*syn*) in both cases (Table

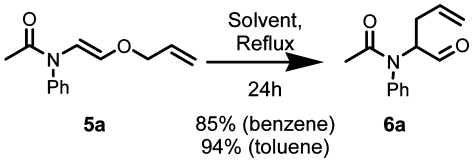
DOI: 10.1021/acs.joc.6b00512
J. Org. Chem. 2016, 81, 5066−5073

3, entries 6 and 7). The structure assignment of the diastereoisomers of **10b** is based on the well-established chair transition state model for the Claisen rearrangement and has been confirmed by both ^{1}H and ^{13}C NMR analysis and the X-ray crystal structure of the carboxylic acid derivative of *anti*-**10b** (see theExperimental Section). When *o*-xylene was used as the solvent, compound **7b** produced the desired aldehyde in a lower yield (67%) and with a lower dr (1.2/1 *anti*/*syn*) (Table 3, entry 8). In refluxing DMF, **10b** was obtained in good yield (72%) but without any selectivity (dr = 1/1 *anti*/*syn*) (Table 3, entry 9). When carried out in refluxing water, the reaction led to **10b** in very good yield (85%) and with a low dr (1.5/1 *anti*/*syn*) (Table 3, entry 10), while aqueous ethanol afforded the desired aldehyde with similar yield (80%) but without selectivity (dr = 1/1 *anti*/*syn*) (Table 3, entry 11). **7c**, in which the C═C geometry is of the *Z*-configuration, underwent rearrangement in refluxing benzene or toluene to afford **10b** in poor and fair yields, respectively (45% and 67%) with very low dr in favor of the opposite relative configuration (1/1.1 and 1/1.2 *anti*/*syn*, respectively) (Table 3, entries 12 and 13). When carbamate **7i** was refluxed in benzene or toluene, compound **10c** was obtained in good yields (80 and 82%, respectively) but with low dr (both 1/1.5 *anti*/*syn*) (Table 3, entries 14 and 15). In refluxing *o*-xylene or DMF, we obtained lower yields (60% and 67%, respectively) with no selectivity (Table 3, entries 16 and 17).

In all, the dr did not exceed 1.8/1. Note that these low selectivities cannot be attributed to epimerization in refluxing solvents. Indeed, when we submitted a 6/1 *anti*/*syn* mixture of **10b** to refluxing toluene for 24 h, no change of the dr was observed. We did the same experiment with *o*-xylene and DMF, and both led to very little epimerization (5.6/1 and 4.9/1 *anti*/*syn*, respectively).

We then performed the reaction with an acyclic counterpart of *β*-allyloxyenamide derivative **7**, **5a**. When **5a** was heated in refluxing benzene or toluene, **6a** was obtained in very good to excellent yields (85% and 94%, respectively) (Scheme 5).

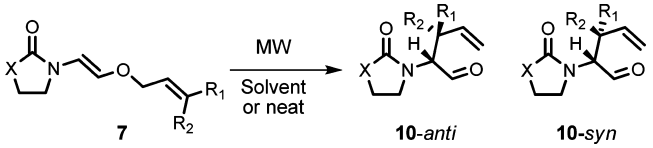
Scheme 5. Claisen Rearrangement of *β*-Allyloxyenamide Derivative 5a in Refluxing Solvents Using Conventional Heating



The Claisen rearrangement using conventional heating offered very good yields for the transformation of *β*-allyloxyenamide derivatives but seemed inappropriate to access high dr. To overcome this problem, we decided to substitute conventional heating with microwave heating, which is known to efficiently accelerate Claisen rearrangement.[23c,26]

We initially catalyzed the Claisen rearrangement of *β*-allyloxyenamides with an easily available domestic microwave oven. To our delight, neat **7a** and **7i** rapidly underwent the Claisen rearrangement when heated by microwaves to afford the desired aldehydes **10a** and **10d** in excellent yields (96% and 92%, respectively) (Table 4, entries 1 and 2). Neat **7b** and **7h** generated the desired **10b** and **10c** in excellent yields (94% and 90%, respectively) and with good dr (4/1 and 1/6.1 *anti*/*syn*, respectively) under the same conditions (Table 4, entries 3 and 4).

Table 4. Claisen Rearrangement of *β*-Allyloxyenamide Derivatives 7 Using Domestic and Laboratory Microwave Heating[a]



Entry	7	Aldehyde	Yield (Ratio *anti*/*syn*)[b] Reaction time (min) Domestic MW[c] Neat	DMF	H_2O	EG[e]	Lab MW[d] Neat
1	**7a**	 **10a**	96% (-) 1	-	-	-	>99% (-) 5
2	**7g**	 **10d**	92% (-) 1	-	-	-	>99% (-) 5
3	**7b**	 **10b**	94% (4:1) 5	90% (1.5:1) 2	82% (6.1:1) 2	89% (9:1) 2	>99% (6.1:1) 10
4	**7i**	 **10c**	90% (1:6.1) 7	88% (1:1.9) 4	94% (1:6.1) 4	91% (1:9) 3	>99% (1:6.1) 15

[a]All rearrangements were performed on a 50 mg scale, and some were also performed on a 300 mg scale with slightly lower yields. [b]Based on the 200 MHz ^{1}H NMR spectra of the crude reaction mixture. [c]30 s pulses of heat at maximum intensity (700 W). [d]Continuous heating at maximum intensity (400 W). [e]EG = ethylene glycol.

We then carried out microwave-assisted Claisen rearrangement of **7b** and **7i** in different solvents to evaluate the influence of the solvents on yield and selectivity. When DMF was used, **10b** and **10c** were obtained in excellent yields (90% and 88%, respectively) but with low dr (1.5/1 and 1/1.9 *anti*/*syn*, respectively) (Table 4, entries 3 and 4). While water gave the desired **10b** and **10c** in very good yields (82% and 94%, respectively) and with good dr (6.1/1 and 1/6.1 *anti*/*syn*, respectively), ethylene glycol led to even better yields (89% and 91%, respectively) and higher dr (9/1 and 1/9 *anti*/*syn*, respectively) (Table 4, entries 3 and 4).

Heartened by these results, we performed some Claisen rearrangement reactions using a laboratory microwave oven available at another institution (see the Acknowledgments). We carried out those tests with neat *β*-allyloxyenamide derivatives to keep the method simple and convenient. The transformations were quantitative in all four cases and led to good dr (6.1/1 and 1/6.1 *anti*/*syn* for **10b** and **10c**, respectively) (Table 4, entries 1−4).

The yields obtained for the Claisen rearrangement of *β*-allyloxyenamide derivatives when using microwave heating were higher than when using conventional heating. Overall, when **7b** and **7i** underwent Claisen rearrangements under microwave irradiation, the presence of solvent decreased reaction time, and the nature of the solvent seemed to greatly affect the selectivity.

Note that we also tried to catalyze our Claisen rearrangement using a number of Lewis acids,[27,28] including Me_3Al, iBu_3Al,

DOI: 10.1021/acs.joc.6b00512
J. Org. Chem. 2016, 81, 5066−5073

$FeCl_2$, $Cu(OTf)_2$, Pd(II)-1,10-phenanthroline, $EtAlCl_2$, and $Hg(OAc)_2$. The yields never exceeded 20% and the dr were consistently lower than 2/1.

CONCLUSION

The copper-catalyzed coupling reaction between β-iodoenamide derivatives and allylic alcohols generated the corresponding β-allyloxyenamides. We were able to synthesize and isolate various β-allyloxyenamide derivatives in excellent yields under mild conditions despite their apparent instability. This method constitutes one of the few examples allowing the preparation of β-alkoxyenamides, which are known to be useful synthetic intermediates and precursors.[29] To the best of our knowledge, only one group before us prepared β-alkoxyenamides under coupling conditions similar to ours.[30] We are the first to synthesize and isolate various β-allyloxyenamide derivatives.

Conventional heating of β-allyloxyenamide derivatives proved that they can undergo Claisen rearrangement in excellent yields but low selectivity to generate the corresponding α-nitrogenated aldehydes. The replacement of conventional thermal heating by microwave heating (domestic) significantly reduced reaction times while increasing selectivity and yields. The selectivities were highest when water or ethylene glycol were used as the solvent. When neat β-allyloxyenamide derivatives underwent Claisen rearrangement in a laboratory microwave oven, the yields of α-nitrogenated aldehydes were quantitative in all cases, and the selectivities were very good.

Our previous work on the synthesis of β-iodoenamide derivatives through copper-catalyzed coupling reactions[5] combined with the present results form a unique three-step sequence that allows the synthesis of α-nitrogenated aldehydes starting from readily available (*E*)-1,2-diiodoethene, simple amide derivatives, and allylic alcohols.

EXPERIMENTAL SECTION

General Information. All reactions were nitrogen purged and run in resealable pressure tubes (13 mm × 17.8 cm). All solvents were distilled prior to use. *N*,*N*′-dimethylethylenediamine (DMEDA) and alcohols were used without further purification. Thin-layer chromatography (TLC) was carried out using 250 μm commercial silica gel plates containing an F-254 indicator. Visualization was accomplished with UV light followed by the plates being dipped in phosphor-molybdic acid (PMA) solution and then heated. Purification of the reactions was carried out by flash chromatography using silica gel 230−400 mesh (40−63 μm) treated with triethylamine (1% v/v solution in hexane) prior to use.

^{1}H NMR spectra were recorded on a Varian 200 MHz NMR spectrometer using $CDCl_3$ (δ 7.26 ppm) as the reference. ^{13}C NMR spectra were recorded on a Varian 200 MHz NMR spectrometer using $CDCl_3$ (δ 77.16 ppm) as the reference. NMR data are reported as follows: chemical shifts (reported in parts per million), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, qt = quintet, sx = sextet, m = multiplet), number of protons, and coupling constants (reported in Hertz). Reactions carried out in a domestic microwave reactor were performed using model RMW700 of the company RCA (700 W), and the reactions carried out in a laboratory microwave reactor were performed using a Biotage initiator 2.0 (400 W) with an external sensor to measure the temperature.

General Procedure for the Synthesis of β-(Allyl or Alkyl)-oxyenamide Derivatives. To a mixture of a β-iodoenamide derivative (1.0 equiv), cesium carbonate (4.0 equiv), copper iodide (0.50 equiv), *N*,*N*′-dimethylethylenediamine (0.80 equiv), and THF (2.0 M) in an ace pressure tube was added the respective alkyl or allyl alcohol (2.5 equiv). The vessel was capped, degassed with anhydrous nitrogen, and heated in an oil bath at 55 °C for 24 h. The reaction mixture was then cooled to room temperature, diluted with DCM, and filtered with a Buchner funnel. The filtrate was dried over magnesium sulfate and concentrated in vacuo. The crude products were purified by silica gel flash column chromatography (gradient eluent, EtOAc in hexane) to afford the desired β-(allyl or alkyl)oxyenamide derivative. **5a** and **7a−h** decomposed upon storage which precluded the recording of any HR mass spectra.

*(E)-N-(2-(Allyloxy)vinyl)-N-phenylacetamide (**5a**).* Colorless oil (26%, 20.2 mg); IR (neat, ν) 3086−2857, 1662 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.83 (s, 3H), 4.14 (d, *J* = 6 Hz, 2H), 5.23 (m, 2H), 5.72 (d, *J* = 12 Hz, 1H), 5.86 (m, 2H), 7.18 (m, 2H), 7.44 (m, 3H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 22.7, 70.9, 113.6, 117.6, 128.4, 128.8, 130.0, 133.1, 139.3, 140.5, 167.9.

*(E)-N-(2-(Allyloxy)vinyl)pyrrolidin-2-one (**7a**).* Colorless oil (90%, 53.7 mg); IR (neat, ν) 3072−2984, 1753 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.09 (q, *J* = 8 Hz 2H), 2.35 (t, *J* = 8 Hz, 2H), 3.35 (t, *J* = 8 Hz, 2H), 4.21 (d, *J* = 8 Hz, 2H), 5.20 (m, 1H), 5.30 (m, 1H), 5.90 (m, 1H), 6.33 (d, *J* = 12 Hz, 1H), 6.66 (d, *J* = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.5, 30.7, 45.6, 70.9, 108.3, 117.8, 133.1, 136.2, 172.3.

*N-((E)-2-((E)-Hex-2-enyloxy)vinyl)pyrrolidin-2-one (**7b**).* Colorless oil (94%, 70.2 mg); IR (neat, ν) 2959−2871, 1686 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.74 (t, *J* = 7 Hz, 3H), 1.20 (m, 4H), 1.88 (m, 4H), 2.65 (t, *J* = 7 Hz, 2H), 3.93 (d, *J* = 5 Hz, 2H), 5.49 (m, 2H), 6.13 (d, *J* = 12 Hz, 1H), 6.90 (d, *J* = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.6, 17.3, 22.3, 30.3, 34.4, 44.9, 70.7, 108.5, 125.7, 134.7, 135.8, 171.4.

*N-((E)-2-((Z)-Hex-2-enyloxy)vinyl)pyrrolidin-2-one (**7c**).* Colorless oil (60%, 44.8 mg); IR (neat, ν) 3096−2870, 1682 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7 Hz, 3H), 1.35 (sx, *J* = 7 Hz, 2H), 2.04 (m, 4H), 2.40 (t, *J* = 4 Hz, 2H), 3.37 (t, *J* = 7 Hz, 2H), 4.21 (d, *J* = 5 Hz, 2H), 5.53 (m, 2H), 6.28 (d, *J* = 12 Hz, 1H), 6.61 (d, *J* = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.6, 17.5, 22.5, 29.6, 30.7, 45.6, 65.8, 107.8, 124.4, 134.4, 136.4, 172.4.

*N-((E)-2-((E)-3,7-Dimethylocta-2,6-dienyloxy)vinyl)pyrrolidin-2-one (**7d**).* Colorless oil (92%, 86.5 mg); IR (neat, ν) 2965−2876, 1692 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.63 (s, 6H), 2.09 (m, 6H), 2.42 (t, *J* = 7 Hz, 2H), 3.37 (t, *J* = 7 Hz, 2H), 4.18 (d, *J* = 7 Hz, 2H), 5.03 (m, 1H), 5.32 (t, *J* = 7 Hz, 1H), 6.30 (d, *J* = 12 Hz, 1H), 6.60 (d, *J* = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 16.7, 17.7, 17.8, 25.8, 26.4, 30.9, 39.6, 45.8, 66.8, 107.8, 119.3, 123.9, 131.8, 136.7, 141.6, 172.5.

*N-((E)-2-((Z)-3,7-Dimethylocta-2,6-dienyloxy)vinyl)pyrrolidin-2-one (**7e**).* Colorless oil (44%, 41.4 mg); IR (neat, ν) 3092, 2966−2871, 1683 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.63 (s, 3H), 1.72 (s, 3H), 2.02 (m, 6H), 2.40 (t, *J* = 7 Hz, 2H), 3.37 (t, *J* = 7 Hz, 2H), 4.14 (d, *J* = 7 Hz, 2H), 5.03 (m, 1H), 5.33 (t, *J* = 7 Hz, 1H), 6.28 (d, *J* = 12 Hz, 1H), 6.60 (d, *J* = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.8, 17.9, 23.7, 25.9, 26.8, 30.9, 32.5, 45.9, 66.6, 107.9, 120.2, 123.8, 132.3, 136.7, 142.1, 172.5.

*(E)-N-(2-(Cyclohex-2-enyloxy)vinyl)pyrrolidin-2-one (**7f**).* Colorless oil (39%, 28.9 mg); IR (neat, ν) 3070−2835, 1678 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.78 (m, 4H), 2.08 (m, 4H), 2.43 (t, *J* = 9 Hz, 2H), 3.41 (t, *J* = 8 Hz, 2H), 4.20 (m, 1H), 5.75 (m, 1H), 5.92 (m, 1H), 6.21 (d, *J* = 12 Hz, 1H), 6.73 (d, *J* = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.6, 18.8, 25.0, 28.2, 30.7, 45.8, 74.1, 110.0, 126.1, 132.3, 135.0, 172.3.

*(E)-N-(2-(Allyloxy)vinyl)oxazolidin-2-one (**7g**).* Colorless oil (90%, 54.4 mg); IR (neat, ν) 3061−2984, 1753 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.54 (t, *J* = 8 Hz, 2H), 4.10 (d, *J* = 6 Hz, 2H), 4.32 (t, *J* = 8 Hz, 2H), 5.20 (m, 1H), 5.30 (m, 1H), 5.80 (m, 1H), 6.00 (d, *J* = 12 Hz, 1H), 6.33 (d, *J* = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 43.4, 62.3, 71.5, 108.9, 118.1, 133.2, 135.5, 155.8.

*N-((E)-2-((E)-Hex-2-enyloxy)vinyl)oxazolidin-2-one (**7h**).* Colorless oil (88%, 66.4 mg); IR (neat, ν) 2959−2871, 1686 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.90 (t, *J* = 8 Hz, 3H), 1.41 (t, *J* = 8 Hz, 2H), 2.18 (q, *J* = 8 Hz, 2H), 3.60 (t, *J* = 8 Hz, 2H), 4.18 (d, *J* = 8 Hz, 2H), 4.42 (t, *J* = 8 Hz, 2H), 5.60 (m, 1H), 5.79 (m, 1H), 6.20 (d, *J* = 12 Hz, 1H), 6.41 (d, *J* = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 14.1, 22.3, 34.9, 43.8, 62.5, 71.9, 108.8, 124.6, 135.8, 136.5, 155.9.

*(E)-N-(2-(Hexyloxy)vinyl)pyrrolidin-2-one (**9a**).* Colorless oil (82%, 61.9 mg); IR (neat, ν) 2925, 1683 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.77 (t, *J* = 7 Hz, 3H), 1.23 (m, 6H), 1.55 (m, 2H), 1.99 (m, 2H), 2.33 (t, *J* = 7 Hz, 2H), 3.31 (t, *J* = 7 Hz, 2H), 3.55 (t, *J* = 7 Hz, 2H), 6.20 (d, *J* = 12

DOI: 10.1021/acs.joc.6b00512
J. Org. Chem. 2016, 81, 5066−5073

Hz, 1H), 6.50 (d, J = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 14.1, 17.7, 22.7, 25.7, 29.3, 30.9, 31.6, 45.9, 70.2, 107.5, 137.1, 172.5; HRMS (ESI/TOF-Q) found m/z 212.1651 $[M + H]^+$; calcd for $C_{12}H_{21}NO_2$ + H 212.1652.

*(E)-N-(2-(Cyclohexyloxy)vinyl)pyrrolidin-2-one (**9b**).* White solid (16%, 12.0 mg); mp 69−71 °C; IR (neat, ν) 3088−2855, 1656 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.38 (m, 6H), 1.74 (m, 2H), 1.86 (m, 2H), 2.08 (m, 2H), 2.44 (t, J = 8 Hz, 2H), 3.41 (t, J = 7 Hz, 2H), 3.64 (m, 1H), 6.18 (d, J = 12 Hz, 1H), 6.72 (d, J = 12 Hz, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.6, 26.5, 25.5, 30.8, 31.8, 45.8, 78.8, 109.7, 135.1, 172.3; HRMS (ESI/TOF-Q) found m/z 210.1495 $[M + H]^+$, calcd for $C_{12}H_{19}NO_2$ + H 210.1499.

*(E)-N-(2-(Phenoxy)vinyl)pyrrolidin-2-one (**9d**).* White solid (5%, 3.6 mg); mp 79−81 °C; IR (neat, ν) 3090−2894, 1666 cm^{-1}; ^{1}H NMR (200 MHz, CDCl3) δ 2.16 (q, J = 7 Hz, 2H), 2.50 (t, J = 7 Hz, 2H), 3.52 (t, J = 7 Hz, 2H), 6.46 (d, J = 11 Hz, 1H), 7.02 (m, 3H), 7.12 (d, J = 11 Hz, 1H), 7.32 (m, 2H); ^{13}C NMR (200 MHz, $CDCl_3$) δ197.4, 142.9, 138.4, 136.7, 136.3, 136.1, 133.9, 133.3, 133.0, 130.5, 129.8, 129.8, 129.7, 129.1, 128.4, 127.9, 127.8, 126.9, 126.7, 124.5, 122.9, 76.9, 76.6, 76.3, 21.1; HRMS (ESI/TOF-Q) found m/z 204.1025 $[M + H]^+$; calcd for $C_{12}H_{13}NO_2$ + H 204.1035.

General Procedure for the Synthesis of α-Nitrogenated Aldehydes with Conventional Heating. A round-bottom flask was charged with β-allyloxyenamide derivative (1.0 equiv) and solvent (10 mM) and topped with a condenser. The reaction mixture was stirred while refluxing for 24 h. The reaction mixture was cooled to room temperature and then concentrated in vacuo. A pure mixture of *syn* and *anti* α-amino aldehydes was obtained without purification.

General Procedure for the Synthesis of α-Nitrogenated Aldehydes with Domestic Microwave Heating. A 20 mL vial was charged with β-allyloxyenamide derivative (1.0 equiv) and solvent (100 mM). The reaction mixture was heated by successive 30 s runs until completion. The reaction mixture was cooled to room temperature and then concentrated in vacuo. A pure mix of *syn* and *anti* α-aminoaldehydes was obtained without purification.

General Procedure for the Synthesis of α-Nitrogenated Aldehydes with Laboratory Microwave Heating. A laboratory microwave oven was charged with β-allyloxyenamide derivative (50 mg), and the temperature was set to 200 °C for 10 min. A pure mix of *syn* and *anti* α-aminoaldehydes was obtained without purification.

*N-(Oxopent-4-en-2-yl)-N-phenylacetamide (**6a**).* Colorless oil (94%, 47.0 mg); IR (neat, ν) 3066−2825, 1737, 1652 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.50 (m, 1H), 2.71 (m, 1H), 4.48 (dd, J = 6 and 9 Hz, 1H), 5.14 (m, 2H), 5.80 (m, 1H), 7.27 (m, 2H), 7.39 (m, 3H), 9.74 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 22.6, 31.7, 67.0, 118.1, 128.6, 128.8, 129.8, 134.2, 141.6, 171.0, 198.0; HRMS (ESI/TOF-Q) found m/z 136.0767 $[M + H - C_5H_6O]^+$, calcd for $C_{13}H_{15}NO_2$ + H − C_5H_6O 136.0763 (loss of the oxopent-4-en-2-yl moiety).

*2-(2-Oxopyrrolidinyl)-pent-4-enal (**10a**).* Colorless oil (99%, 49.2 mg); IR (neat, ν) 2957−2825, 1741, 1649 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.98 (m, 2H), 2.38 (m, 2H), 2.50 (t, J = 7 Hz, 1H), 2.65 (m, 1H), 3.30 (m, 2H), 4.60 (dd, J = 7 and 4 Hz, 1H), 5.10 (m, 2H), 5.70 (m, 1H), 9.58 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 18.6, 30.8, 31.0, 44.3, 60.1, 119.4, 133.8, 176.9, 198.1; HRMS (ESI/TOF-Q) found m/z 168.1025 $[M + H]^+$, calcd for $C_9H_{13}NO_2$ + H 168.1024.

*2-(2-Oxopyrrolidinyl)-3-vinylhexanal (**10b**).* Colorless oil (99%, 49.3 mg); IR (neat, ν) 2955−2820, 1736, 1658 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.84 (t, J = 6 Hz, 3H), 1.35 (m, 4H), 2.01 (m, 2H), 2.40 (m, 2H), 3.30 (m, 1H), 3.44 (m, H), 4.52 (d, J = 8 Hz, 1H), 5.13 (m, 2H), 5.72 (m, 1H), 9.67 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 14.1, 18.4, 19.3, 30.7, 34.0, 43.1, 45.0 63.2, 119.3, 137.9, 176.4, 199.2; HRMS (ESI/TOF-Q) found m/z 210.1495 $[M + H]^+$, calcd for $C_{12}H_{19}NO_2$ + H 210.1485.

*3,7-Dimethyl-2-(2-oxooxazolidin-3-yl)-3-vinyloct-6-enal (**10c**).* Colorless oil (99%, 49.6 mg); IR (neat, ν) 2963−2831, 1739, 1683 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) 1.30 (s, 3H), 1.57 (m, 8H), 1.97 (m, 2H), 3.70 (m, 2H), 4.27 (m, 2H), 4.45 (s, 1H), 5.04 (t, J = 7 Hz, 1H), 5.20 (m, 2H), 5.80 (m, 1H), 9.78 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 17.5, 19.3, 20.9, 22.3, 25.5, 38.7, 43.2, 62.5, 68.5, 115.2, 123.4, 132.1, 141.7, 160.0, 198.1; HRMS (ESI/TOF-Q) found m/z 266.1757 $[M + H]^+$, calcd for $C_{15}H_{23}NO_3$ + H 266.1740.

*2-(2-Oxooxazolidin-3-yl)-pent-4-enal (**10d**).* Colorless oil (99%, 49.7 mg); IR (neat, ν) 2958−2830, 1735, 1672 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.38 (m, 1H), 2.74 (m, 1H), 3.52 (m, 2H), 4.40 (m, 3H), 5.17 (m, 2H), 5.80 (m, 1H), 9.61 (s, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 30.2, 41.9, 61.2, 62.3, 118.9, 132.8, 158.4, 198.1; HRMS (ESI/TOF-Q) found m/z 170.0818 $[M + H]^+$, calcd for $C_8H_{11}NO_3$ + H 170.0816.

Procedure for the Oxidation of α-Nitrogenated Aldehyde 10b.[25] A 20 mL vial was charged with α-nitrogenated aldehyde **10b** (41 mg, 0.194 mmol, 1.0 equiv), sodium chlorite (36 mg, 0.393 mmol, 2.0 equiv), 2-methyl-2-butene (0.4 mL of a 2.0 M solution in THF, 0.800 mmol, 4.0 equiv), and methanol (1.5 mL, 0.13 M). The reaction mixture was stirred at room temperature for 21 h. The reaction was quenched with 75 mL of a saturated $NaHCO_3$ solution and 30 mL of Et_2O. The aqueous layer was extracted 3 times with 30 mL of Et_2O to remove impurities and was then acidified with 12 M HCl until the pH reached 2. The aqueous layer was saturated with NaCl and then extracted 5 times with 30 mL of AcOEt. The combined organic layers were dried over $MgSO_4$, filtered by gravity, and concentrated under vacuo to afford a colorless oil. The crude product was crystallized in a hexane-ether mix to afford 20 mg (0.089 mmol) of a pure mix of *syn* and *anti* α-amino acids **11** as a white solid.

*2-(2-Oxopyrrolidinyl)-3-vinylhexanoic Acid (**11**).* White solid (45%, 19.7 mg); mp 121−122 °C; IR (neat, ν) 3419, 2951−2866, 1727, 1622 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.31 (m, 4H), 2.09 (m, 2H), 2.47 (t, J = 8 Hz, 2H), 2.69 (m, 1H), 3.47 (m, 1H), 3.64 (m, 1H), 4.47 (d, J = 10 Hz, 1H), 5.14 (m, 2H), 5.59 (m, 1H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 13.9, 18.5, 19.8, 31.1, 32.9, 43.3, 46.8, 77.2, 107.2, 118.6, 136.9, 173.4; HRMS (ESI/TOF-Q) found m/z 226.1444 $[M + H]^+$, calcd for $C_{12}H_{19}NO_3$ + H 226.1451.

Procedure to Isolate a Single Diastereoisomer of α-Amino Acid 11. In a 20 mL vial, 20 mg (0.089 mmol) of the mix of *syn* and *anti* α-amino acids **11** was diluted in the minimum amount of AcOEt. Drops of AcOEt were added. The opened vial was placed in a jar containing hexane. The jar was then capped and placed in the fridge (4 °C) for 2 days until apparition of white crystals occurred. The solvent was removed from the vial. The crystals were washed with cold (kept on ice) hexane 5 times and then dried under vacuo to afford the pure *anti* α-amino acids **11** as a single diastereoisomer.

X-ray Crystallographic Analysis of 11. A colorless rhomb-like specimen of $C_{12}H_{19}NO_3$ (dimensions 0.177 × 0.256 × 0.298 mm) was used for the X-ray crystallographic analysis. X-ray diffraction data were collected at 150 K on a Bruker APEX DUO instrument at Cu Kα (λ = 1.54178 Å, IμS microfocus source) radiation. A total of 5856 frames were collected. The frames were integrated with the Bruker SAINT software package using a narrow-frame algorithm. The integration of the data using a monoclinic unit cell yielded a total of 15 511 reflections to a maximum θ angle of 68.93° (0.83 Å resolution), of which 2153 were independent (average redundancy 7.204, completeness = 95.4%, R_{int} = 4.66%, R_{sig} = 2.60%) and 1896 (88.06%) were greater than 2$\sigma(F^2)$. The final cell constants of $\underline{a}$ = 5.7156(3) Å, $\underline{b}$ = 11.8755(7) Å, $\underline{c}$ = 18.0555(10) Å, β = 92.991(3)°, and volume = 1223.86(12) Å^3 are based upon refinement of the XYZ-centroids of 8431 reflections above 20 $\sigma(I)$ with 8.911° < 2θ < 136.5°. Data were corrected for absorption effects using the multiscan method (SADABS). The ratio of minimum to maximum apparent transmission was 0.891. The calculated minimum and maximum transmission coefficients (based on crystal size) were 0.6712 and 0.7531. The structure was solved and refined with the Bruker SHELXTL Software Package using the space group $P2_1/n$ with Z = 4 for the formula unit, $C_{12}H_{19}NO_3$. The final anisotropic full-matrix least-squares refinement on F^2 with 147 variables converged at R1 = 4.71%, for the observed data and wR2 = 12.32% for all data. The goodness-of-fit was 1.091. The largest peak in the final difference electron density synthesis was 0.287 e$^-$/Å^3, and the largest hole was −0.223 e$^-$/Å^3 with an RMS deviation of 0.046 e$^-$/Å^3. On the basis of the final model, the calculated density was 1.223 g/cm^3, and F(000) was 488 e$^-$. The crystallographic data for **11** have been deposited at the Cambridge Crystallographic Data Centre with the deposition no. 1023544.

DOI: 10.1021/acs.joc.6b00512
J. Org. Chem. 2016, 81, 5066−5073

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00512.

Crystallographic data (CIF)

^{1}H and ^{13}C NMR spectra of all new compounds and X-ray diffraction structures for **11** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: benoit.daoust@uqtr.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Science and Engineering Research Council of Canada (NSERC) for financial support of this work (Grant 238520-04). We also thank Professor René Roy (Université du Québec à Montréal) for allowing us to use the laboratory microwave oven and Professor Xavier Ottenwaelder (Concordia University) for the X-ray determination.

■ REFERENCES

(1) (a) Sewald, N.; Jakubke, H. *Peptides: Chemistry and Biology*; Wiley-VCH: Weinheim, 2002. (b) Grant, G. A. *Synthetic Peptides*; Oxford University Press: Oxford, 2002. (c) Magliery, T. J. *Med. Chem. Rev.–Online* **2005**, *2*, 303.

(2) (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162. (c) Liang, X.; Andersch, J.; Bols, M. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136−2157.

(3) (a) Davies, S. G.; Epstein, S. W.; Garner, A. C.; Ichihara, O.; Smith, A. D. *Tetrahedron: Asymmetry* **2002**, *13*, 1555−1565. (b) Adessi, C.; Soto, C. *Curr. Med. Chem.* **2002**, *9*, 963−978.

(4) Karjalainen, O. K.; Koskinen, A. M. P. *Org. Biomol. Chem.* **2012**, *10*, 4311−4326.

(5) Sanapo, G. F.; Daoust, B. *Tetrahedron Lett.* **2008**, *49*, 4196−4199.

(6) (a) Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202−12206. (b) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368−2369. (c) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560−14561. (d) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318−5365. (e) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *J. Org. Chem.* **2011**, *76*, 5295−5308. (f) Bariwal, J.; Van der Eycken, E. *Chem. Soc. Rev.* **2013**, *42*, 9283−9303. (g) China Raju, B; Veera Prasad, K.; Saidachary, G.; Sridhar, B. *Org. Lett.* **2014**, *16*, 420−423.

(7) (a) Ullmann, F. *Liebigs Ann.* **1904**, *332*, 38−81. (b) Ullmann, F.; Sponagel, P. *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 2211−2212.

(8) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691−1692.

(9) (a) Mann, G.; Hartwig, J. F. *Tetrahedron Lett.* **1997**, *38*, 8005. (b) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224.

(10) (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396. (b) Aranyos, A.; Old, D. W.; Kiyomori, A.; Wolfe, J. P.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 4369−4378. (c) Torraca, K. E.; Huang, X.; Parrish, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 10770−10771.

(11) Sperotto, E.; van Klink, G. P. M.; van Koten, G.; de Vries, J. G. *Dalton Trans.* **2010**, *39*, 10338−10351.

(12) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054−3131.

(13) Selected examples: (a) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315−4317. (b) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623−1626. (c) He, H.; Wu, Y.-J. *Tetrahedron Lett.* **2003**, *44*, 3445. (d) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799−3802. (e) Zhang, H.; Cai, Q.; Ma, D. *J. Org. Chem.* **2005**, *70*, 5164−5173. (f) Chattopadhyay, S. K.; Bandyopadhyay, A.; Pal, B. K. *Tetrahedron Lett.* **2007**, *48*, 3655−3659. (g) Chan, D. M. T.; Monaco, K. L.; Wang, R. P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933−2936. (h) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941−2944.

(14) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809−1812.

(15) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667−3669.

(16) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr *J. Am. Chem. Soc.* **2003**, *125*, 7889−7901.

(17) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927−4931.

(18) Acyclic secondary amides are known to be unreactive toward copper coupling with vinyl halides. See *Organotransition Metal Chemistry: From Bonding to Catalysis*; Hartwig, J., Ed.; University Science Books, University of California: Berkeley, 2010; pp 923−925.

(19) Jiang, B.; Tian, H.; Huang, Z.-G.; Xu, M. *Org. Lett.* **2008**, *10*, 2737−2740.

(20) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978−4979.

(21) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983−6984.

(22) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Org. Chem.* **1987**, *52*, 5190−5194.

(23) Selected examples: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939−3002. (b) Hiersemann, M. *The Claisen Rearrangement: Methods and Applications*; John Wiley & Sons: Hoboken, NJ, 2007; p 591. (c) Majumdar, K. C.; Alam, S.; Chattopadhyay, B. *Tetrahedron* **2008**, *64*, 597.

(24) (a) Krebs, A.; Kazmaier, U. *Tetrahedron Lett.* **1996**, *37*, 7945−7946. (b) Kazmaier, U. *J. Org. Chem.* **1996**, *61*, 3694−3699.

(25) Farran, D.; Parrot, I.; Toupet, L.; Martinez, J.; Dewynter, G. *Org. Biomol. Chem.* **2008**, *6*, 3989−3996.

(26) (a) Davis, C. J.; Hurst, T. E.; Jacob, A. M.; Moody, C. J. *J. Org. Chem.* **2005**, *70*, 4414−4422. (b) Lingam, V. S. P.; Dahale, D. H.; Mukkanti, K.; Gopalan, B.; Thomas, A. *Tetrahedron Lett.* **2012**, *53*, 5695−5698. (c) Nushiro, K.; Kikuchi, S.; Yamada, T. *Chem. Commun.* **2013**, *49*, 8371−8373. (d) Mansha, M.; Ullah, N. *Synth. Commun.* **2015**, *45*, 599−604.

(27) (a) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 3985. (b) Boeckman, R. K., Jr; Neeb, M. J.; Gaul, M. D. *Tetrahedron Lett.* **1995**, *36*, 803−806.

(28) Pd(II) complexes as Lewis acids: (a) Sugiura, M.; Nakai, T. *Chem. Lett.* **1995**, 697−698. (b) Kerrigan, N. J.; Bungard, C. J.; Nelson, S. G. *Tetrahedron* **2008**, *64*, 6863.

(29) (a) Rey-Rodriguez, R.; Retailleau, P.; Bonnet, P.; Gillaizeau, I. *Chem. - Eur. J.* **2015**, *21*, 3572−3575. (b) Bogacki, R.; Gill, D. M.; Kerr, W. J.; Lamont, S.; Parkinson, J. A.; Paterson, L. C. *Chem. Commun.* **2013**, *49*, 8931−8933. (c) Gigant, N.; Dequirez, G.; Retailleau, P.; Gillaizeau, I.; Dauban, P. *Chem. - Eur. J.* **2012**, *18*, 90−94.

(30) Okamoto, K.; Sakagami, M.; Feng, F.; Togame, H.; Takemoto, H.; Ichikawa, S.; Matsuda, A. *Org. Lett.* **2011**, *13*, 5240−5243.

DOI: 10.1021/acs.joc.6b00512
J. Org. Chem. 2016, 81, 5066−5073