Ir-Catalyzed Chemodivergent Allenylic Alkylation of Vinyl Azides: Highly Enantioselective Synthesis of α-Allenylic Amides and Ketones

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ABSTRACT: Enantioselective allenylic alkylation reactions of unstabilized enolates have never been reported. We now present a unified fragment-coupling strategy for the first enantioselective synthesis of α-allenylic amides and ketones through allenylic alkylation of vinyl azides. In these chemodivergent reactions, cooperatively catalyzed by Ir(I)/(phosphoramidite,olefin) complex and Sc(OTf)3, vinyl azides act as the surrogate for both amide enolates and ketone enolates. The desiccant (molecular sieves) plays a crucial role in controlling the chemodivergency of this enantioconvergent and regioselective reaction: Under otherwise identical reaction conditions, the presence of the desiccant led to α-allenylic amides while its absence resulted in α-allenylic ketones from the same substrate combinations. Utilizing racemic allenylic alcohols as the alkylation agent, the overall process represents a dynamic kinetic asymmetric transformation (DYKAT), where both α-allenylic amides and ketones are formed with the same absolute configuration generally with outstanding enantioselectivity. To the best of our knowledge, this is the first example of the use of vinyl azide as the ketone enolate surrogate in an enantioselective transformation.

1. INTRODUCTION

Building molecular complexity through fragment-coupling reactions has remained a sought-after strategy in organic synthesis.1 In this realm, perhaps few reactions can match the versatility displayed by transition-metal-catalyzed asymmetric allylic substitution (AAS).2 The past five decades have witnessed remarkable developments in this direction, especially under Pd and Ir-catalysis, and resulted in the coupling of innumerable nucleophilic fragments with allylic units.3,4 Therefore, it is perplexing that despite the rich synthetic expediency of the allene functionality,5 the structurally similar allenylic substitution reactions (Scheme 1A) are far less developed. Like AAS reactions, here also the initial studies were focused on Pd-catalysis,6 possibly due to the obvious mechanistic resemblance. A few enantioselective allenylic substitution reactions of selected nucleophiles were subsequently developed, leading to the generation of axial chirality,7 central chirality8 and even both.9 The entry of iridium into the stage of allenylic substitution is a relatively recent phenomenon and followed the discovery of the Ir-catalyzed AAS reactions. In 2004, Takeuchi et al. reported the allenylic alkylation of malonate diesters using an Ir(I)/dppe complex.10 In analogy with the Pd-catalysis, the reaction was proposed to proceed through an η3-butadineyl Ir(III) intermediate. Rather surprisingly, despite notable promise, this report remained in oblivion for more than a decade. In 2018, Carreira and co-workers resurrected this reaction using an Ir(I)/(phosphoramidite,olefin) catalyst and developed the first enantioselective allenylic alkylation reaction under Ir-catalysis.11 A detailed investigation from the Carreira group revealed the mechanistic uniqueness of this Ir-catalyzed allenylic substitution reactions compared to both Pd-catalyzed allenylic substitution6-9 as well as Ir-catalyzed allylic substitution.6 Contrary to the initially postulated η3-butadineyl Ir(III) intermediate,10 these reactions were shown to proceed through an allenylic carbocation intermediate having an η2-coordination of Ir(I) with the terminal double bond of Allenes and do not involve any change in the formal oxidation state of iridium during the reaction (see Scheme 2).11

While further developments are imminent, only a handful of nucleophiles have been employed so far.12 We sensed an opportunity in developing unprecedented fragment-coupling reactions with the goal of introducing allenylic functionality. While considering possible unstabilized nucleophilic fragments, it came to our attention that there is no report on the synthesis of α-allenylic amides, let alone an enantioselective variant (Scheme 1B). This is despite the prevalence of both amides and Allenes in natural products and bioactive compounds.13 An apparent cause of this glaring gap in synthetic toolbox is possibly the attenuated acidity of the amide α-protons,14 which necessitates the use of a strong base for enolization. This shortcoming of amide α-reactivity has previously been supplemented using amide enolate surrogates.15 Vinyl azide is one such surrogate, and the pioneering studies by Chiba and co-workers have demonstrated its synthetic potential.16

We envisioned an enantioselective allenyl alkylation reaction of vinyl azide for the synthesis of α-allenylic amides (Scheme 1C).
Our strategy is based on the cooperative Ir(I) and Lewis acid catalysis (Scheme 2). Allenylic alcohol (A), in the presence of a Lewis acid promoter, has been shown to react with Ir(I) to form an allenylic carbocation B having its terminal double bond coordinated with Ir(I) in an $\eta^2$-fashion.\textsuperscript{12a,c} We realized that B can be trapped by the nucleophilic vinyl azide C to generate iminodiazonium ion D, possibly as a n-equilibrating mixture of (E)- and (Z)-isomers.\textsuperscript{16i} This C–C bond forming step should be irreversible and enantiodetermining. Schmidt rearrangement of (E)-D involving an aryl migration would then result in the nitrilium ion E. Addition of the hydroxide, released from the allenic alcohol, to E followed by tautomerization would then furnish the desired $\alpha$-allenylic amide F.\textsuperscript{17} At the same time, we wondered about turning the chemoselectivity problem (Schmidt rearrangement vs. hydrolysis of D) into our advantage and developing an enantioselective synthesis of $\alpha$-allenylic ketones\textsuperscript{17} from the same set of starting materials by harnessing the reactivities of either (E)-D or E with controlled hydroxide (or water) concentration.

Even though the use of vinyl azide as amide enolate surrogate in enantioselective reactions has recently been reported,\textsuperscript{15a-b,16a} its application as ketone enolate surrogate\textsuperscript{16i} is yet to be disclosed for an enantioselective transformation.
total of six fragment-coupled products are possible (Scheme 3).

The seminal studies by the Carreira group offer sufficient evidence that the regioselectivity in favor of the allene over 1,3-diene could be achieved using the Ir(I)/(phosphoramide,olefin) complex as the catalyst. At the same time, hydroxide concentration can be kept at check with the help of a suitable desiccant to navigate the reaction pathways either towards α-allenyl amides or ketones.

We herein present the successful implementation of this strategy and report a unified enantioselective synthesis of α-allenyl amides and ketones, through an efficient chemodivergent and regioselective allenyl alkylation of vinyl azides (Scheme 1C).

2. RESULTS AND DISCUSSION

Our initial task was to identify the optimum sets of reaction conditions for achieving the desired chemodivergence and regioselectivity besides enantioselectivity. We began our study focusing on the synthesis of α-allenyl amides. It was clear at the outset that in order to achieve this goal, simply controlling the geometry of the initially formed iminodi azonium ion D will not be sufficient (Scheme 2). Its reactivity must also be guided toward Schmidt rearrangement over hydrolysis. Accordingly, 1-(α-methoxyphenyl) vinyl azide 1a (Table 1) was selected with the anticipation of the preferential generation of (E)-D because of the steric bulk of the ary1 group. At the same time, the electron rich nature of the aryl ring should facilitate its migration over hydrolysis of the iminodiazi onium ion.

The allenyl alkylation of 1a with either allenyl alcohol rac-2a or its carbonate rac-2a’ was, therefore, chosen as the model reaction for the synthesis of α-allenyl amide 3aa. No product formation was found to take place when the reaction between 1a and rac-2a’ was carried out in THF at 50 °C in the presence of 6 mol% of a catalyst derived from [Ir(COD)Cl]2 and Carreira’s (P,olefin) ligand (S)L (Table 1, entry 1). In contrast, the reaction with allenyl alcohol rac-2a in combination with 100 mol% of Sc(OTf)3 as the promoter and 4Å molecular sieves (MS) as the desiccant under otherwise identical conditions showed complete conversion of the vinyl azide 1a and led to the formation of 3aa in 44% isolated yield after 72 h with 98.5:1.5 er (entry 2). More importantly, neither any of the 1,3-dienyl products as shown in Scheme 3 nor the competing allenylation products (4 or 5) could be detected. With the increase in the amount of the desiccant, the yield of 3aa was slightly improved (entry 3). However, in both these cases (entries 2-3), a gelatious material was formed, which points to possible polymerization of the allenyl alcohol. Decreasing the amount of Sc(OTf)3 to 20 mol% reduced the extent of polymerization and improved both the yield of 3aa and its er (entry 4). Other Lewis acid promoters were proven to be inferior for this reaction (entries 5-7). The yield of 3aa could be further improved by employing a larger excess of 2a, and the best results were obtained with 2.0 equivalent of 2a. Under these conditions, complete conversion of the vinyl azide 1a took place to furnish 3aa in high yield and with an improved er of 99.5:0.5 (entries 10-11). Further enhancement of enantioselectivity is possible by carrying out the reaction at ambient temperature albeit at the expense of the reaction rate (entry 12).

Table 1. Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>Promoter (mol%)</th>
<th>Yield (%)</th>
<th>Er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a Sc(OTf)3</td>
<td>&lt;5 30 &lt;5 n.d.</td>
<td></td>
</tr>
<tr>
<td>2a Sc(OTf)3</td>
<td>45 &lt;5 &lt;5 98.5:1.5</td>
<td></td>
</tr>
<tr>
<td>3a Sc(OTf)3</td>
<td>53 &lt;5 &lt;5 98.5:1.5</td>
<td></td>
</tr>
<tr>
<td>4a Sc(OTf)3</td>
<td>58 &lt;5 &lt;5 99.5:0.5</td>
<td></td>
</tr>
<tr>
<td>5a La(OTf)3</td>
<td>25 &lt;5 &lt;5 99:1</td>
<td></td>
</tr>
<tr>
<td>6a Zn(OTf)2</td>
<td>22 &lt;5 &lt;5 99:1</td>
<td></td>
</tr>
<tr>
<td>7a Fe(OTf)2</td>
<td>20 &lt;5 &lt;5 99.1</td>
<td></td>
</tr>
<tr>
<td>8a Sc(OTf)3</td>
<td>72 &lt;5 &lt;5 99:1</td>
<td></td>
</tr>
<tr>
<td>9a Sc(OTf)3</td>
<td>60 &lt;5 &lt;5 99.5:0.5</td>
<td></td>
</tr>
<tr>
<td>10a Sc(OTf)3</td>
<td>95 &lt;5 &lt;5 99.5:0.5</td>
<td></td>
</tr>
<tr>
<td>11a Sc(OTf)3</td>
<td>(89) &lt;5 &lt;5 99.5:0.5</td>
<td></td>
</tr>
<tr>
<td>12a Sc(OTf)3</td>
<td>(69) &lt;5 &lt;5 &gt;99.5:0.5</td>
<td></td>
</tr>
<tr>
<td>13a Sc(OTf)3</td>
<td>(72) &lt;5 &lt;5 &gt;99.5:0.5</td>
<td></td>
</tr>
</tbody>
</table>

1. Unless stated otherwise, the reactions were performed using 1.0 equiv of 1, 1.2 equiv of 2 and 100 mg 4Å MS on a 0.1 mmol scale. Yields were determined by 1H NMR spectroscopy with mesitylene as the internal standard. Isolated yields are given in the parentheses.
2. Enantioselective ratio (erb) of the major product as determined by HPLC analysis using a stationary phase chiral column. Reaction with 2a with 50 mg 4Å MS. Reaction with 1.5 equiv of 2a. Reaction with 2.0 equiv of 2a. Reaction on a 0.2 mmol scale. Reaction at 25 °C. Reaction without MS. MS = molecular sieves. n.d. = not determined.

We were delighted to note a complete switch of chemoselectivity when the reaction was performed in the absence of the desiccant (4Å MS): Under otherwise identical reaction conditions, α-allenyl ketone 4ba was isolated essentially as a single enantiomer in 72% yield (Table 1, entry 13). The formation of the α-allenyl ketone with the same sense of enantioinduction as that of α-allenyl amide (vide infra) clearly indicates the involvement of the same C–C bond forming pathway in both these processes and highlights the importance of the desiccant in controlling the endgame (i.e.,
Schmidt rearrangement vs. hydrolysis of iminodiazonium intermediate; see Scheme 2).

The use of a large excess of the racemic allenylic alcohol rac-2a with respect to vinyl azides gives rise to the possibility of a kinetic resolution. However, 2a recovered from incomplete reactions (after 24 h) were found to remain racemic although the products 3aa and 4ba were isolated with the high level of er (Scheme 4). Clearly both the enantiomers of the allenylic alcohol 2a are converted to a single enantiomer of either α-allenylic amide (3aa) or α-allenylic ketone (4ba) in an enantioconvergent process. Therefore, these reactions proceed via a common carbocationic intermediate and hence represent a dynamic kinetic asymmetric transformation (DyKAT).19

Scheme 4. Control Experiments to Eliminate the Possibility of Kinetic Resolution

Having optimized the reaction conditions, we set out to showcase the generality of our desiccant-controlled chemo-divergent allenylic alkylation of vinyl azide for the enantioselective synthesis of α-allenylic amides and ketones. Initially the reaction conditions developed for the synthesis of α-allenylic amides (Table 1, entry 11) were applied to a range of allenylic alcohols (2) bearing electronically diverse aryl groups (Table 2A). When reacted with 1-(o-methoxyphenyl) vinyl azide 1a, α-allenylic amides (3) with excellent level of enantioselectivities were obtained irrespective of the nature and the position of the substituents on the aryl ring. However, the yields of the products appear to be dependent on the electronic nature of the substituents. Moderate yields generally observed for allenylic alcohols having electron-deficient aryl substituent such as 3af supports the involvement of the carbocation intermediate in this reaction. This trend is further corroborated by gradual decrease in the yield while replacing the phenyl group of the allenylic alcohol 2a with monochlorophenyl (2e, 2i) and dichlorophenyl (2k) groups. Ortho-substituent on the aryl ring is detrimental to this allenylic alkylation reaction, presumably due to their inability in stabilizing the carbocation intermediate because of steric crowding. Only 2-methoxyphenyl substituted allenylic alcohol (2j) furnished the product 3aj in modest yield, albeit with excellent enantioselectivity. The similar level of yield and er was observed with heteroaryl substituted allenylic alcohol 2m.

Table 2. Generality of the Enantioselective Synthesis of α-Allenylic Amides

We were pleased to find our optimized reaction conditions to be tolerant to a variety of 1-aryl vinyl azides in addition to the initially assumed 1-(o-methoxyphenyl) vinyl azide 1a (Table 2B). These examples include vinyl azides bearing simple phenyl (1b) and monosubstituted phenyls (1c-g) to 2,4-dimethoxyphenyl (1h) and 2-naphthyl groups (1i). In majority of these reactions, the products were formed with
outstanding enantioselectivity. However, electron deficient 4-trifluoromethylphenyl substituted vinyl azides and sterically congested 1-naphthyl substituted vinyl azides failed to deliver any product under our standard conditions. The examples shown in Table 2C illustrate the modular nature of this fragment coupling strategy, which could be used for synthesizing a library α-allenylic amides.

Table 3. Generality of the Enantioselective Synthesis of α-Allenylic Ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Vinyl Azide</th>
<th>Allenylic Alcohol</th>
<th>Product</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>1b</td>
<td>2a</td>
<td>4a</td>
<td>72%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>1b</td>
<td>1b</td>
<td>2b</td>
<td>4bb</td>
<td>70%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>1c</td>
<td>1b</td>
<td>2c</td>
<td>4bc</td>
<td>71%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>2a</td>
<td>1b</td>
<td>2d</td>
<td>4bd</td>
<td>84%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>2b</td>
<td>1b</td>
<td>2e</td>
<td>4be</td>
<td>80%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>2c</td>
<td>1b</td>
<td>2f</td>
<td>4bf</td>
<td>99.9:0.1</td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>1b</td>
<td>2g</td>
<td>4bg</td>
<td>87%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>3a</td>
<td>1b</td>
<td>2h</td>
<td>4bh</td>
<td>79%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>3b</td>
<td>1b</td>
<td>2i</td>
<td>4bi</td>
<td>76%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>3c</td>
<td>1b</td>
<td>2j</td>
<td>4bj</td>
<td>57%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>3d</td>
<td>1b</td>
<td>2k</td>
<td>4bk</td>
<td>82%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>3e</td>
<td>1b</td>
<td>2l</td>
<td>4bl</td>
<td>67%</td>
<td>&gt;99.9:0.1</td>
</tr>
<tr>
<td>4a</td>
<td>1b</td>
<td>2m</td>
<td>4bm</td>
<td>37%</td>
<td>&gt;99.9:0.1</td>
</tr>
</tbody>
</table>

*Unless noted otherwise, the reaction conditions indicated above were followed. Yields correspond to the isolated yield after chromatographic purification. Enantiomeric ratio (er) as determined by HPLC using a chiral column. †Reaction at 25 °C for 60 h. ‡Reaction at 25 °C for 24 h followed by 50 °C for 48 h. §Reaction with 5 mol% Sc(OTf)₃ at 25 °C for 24 h.

In all these cases, the products were formed as a single regiosomer (allene vs. 1,3-diene). It must also be noted that neither α-allenylic acetophenone (4) nor N-homoallenylic benzamide (5) derivatives could be detected in most of these reactions. Only in the case of phenyl vinyl azide 1b, small amounts of α-allenylic acetophenones were formed.

The structure of 3ad in solid state obtained through X-ray diffraction analysis established its absolute configuration to be (R) (CCDC 2121261, Table 2A). The configurations of the other α-allenylic amides were tentatively assigned to be the same by analogy.

After demonstrating the substrate generality of the route leading to the α allenylic amides, we turned our attention to α allenylic ketones. Under the reaction conditions utilized for the synthesis of α-allenylic amides, minus 4Å molecular sieves (see Table 1, entry 13), the fragment-coupling reaction between vinyl azides (1) and allenylic alcohols (2) took place efficiently to furnish a range of α-allenylic ketones (4) in moderate to good yields with superb enantioselectivity (Table 3). Although 1-phenyl vinyl azide (1b) was initially chosen to examine the scope of allenylic alcohols (Table 3A), we were excited to find that the same substrate combinations used for the synthesis of α-allenylic amides now resulted in α-allenylic ketones with similar yield and equally high enantioselectivity (Table 3B). Once again, no regioisomeric 1,3-diene or the corresponding α-allenylic amide (3) were found to form in any of these reactions. Therefore, this chemodivergency appears to be devoid of steric or electronic bias and controlled primarily by the presence or the absence of the desiccant.

The conversion of the α allenylic ketone 4bl to the corresponding oxime 6 followed by Beckmann rearrangement with p-TsOH-ZnCl₂ led to α-allenylic amide 3bl (Scheme 5). The absolute configuration of 3bl obtained in this reaction is found to be the same as that of 3bl formed under our standard conditions (Table 2) by comparing their specific rotations. These data clearly indicate that the enantiodetermining steps of these chemodivergent allenylic alkylation reactions are identical and precede either the Schmidt rearrangement or the hydrolysis of the iminodiazonium intermediate (see Scheme 2). Therefore, it is likely that the nucleophilic addition of vinyl azide to the allenylic carboxation is the enantiodetermining step in both these reactions.

Scheme 5. Determination of Absolute Configuration of α-Allenylic Ketone 4bl

The scalability of our protocols is exhibited by conducting a few of these allenylic alkylation reactions on a 1.0 mmol
scale (Scheme 6A). In all these cases, the products were obtained in equally high yields with similar level of enantioselectivities as seen for smaller scale reactions (Tables 2-3).

**Scheme 6.** (A) One mmol Scale Synthesis of α-Allenyl Amides and Ketones. (B) Synthetic Elaboration of α-Allenyl Amide and (C) Ketones

![Scheme 6](image_url)

The presence of the synthetically versatile allene and carbonyls in the products makes them amenable to a wide variety of functional group elaborations. A few such synthetic diversifications are demonstrated in Scheme 6. For example, heating with Lawesson’s reagent in toluene turned the α-allenylic amide 3aa into the corresponding thioamide 7 (Scheme 6B). Catalytic hydrogenation of 3aa led to the complete reduction of the allene functionality and furnished N-aryl-3-phenylhexanamide 8 in quantitative yield. Although the Pd-catalyzed aminoarylation of allene 22 directly on 3aa remained unsuccessful, the reaction proceeded efficiently on the terminal double bond of allene of the corresponding N-Boc-protected α-allenyl amide 9. The resulting aminoarylation product 10 was obtained in good yield but as a 4:1 mixture of diastereomers.

Selective reduction of the functionalities in α-allenyl ketones is possible under controlled hydrogenation conditions. While the selective hydrogenation of the allene functionality in 4ba can be achieved in EtOAc within 1.5 h, prolonged exposure to hydrogen under Pd/C in MeOH met with global reduction of 4ba (Scheme 6C). In both these cases, the products 11 and 12 were formed in quantitative yield. Even though the ketone 11 can be viewed as the conjugate addition product of an enone, direct enantioselective synthesis of the chiral hydrocarbon 12 may not be straightforward.

Skipped polyenes is an important functionality whose enantioselective synthesis is rather challenging. We envisioned an easy access to such skipped polyenes starting from α allenyl ketones. As exemplified with 4bl, reduction of ketone to the corresponding alcohol followed by dehydration under acidic conditions delivered the skipped eneallene 13 in decent yield over two steps.

### 3. CONCLUSION

In conclusion, we have discovered the first enantioselective syntheses of α-allenylic amides and ketones. In these chemodivergent allenyl alkylation reactions, cooperatively catalyzed by an Ir(I)/(phosphoramidite,olefin) complex and Sc(OTf)

Supporting Information

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.
Experimental details and characterization data
NMR spectra and HPLC chromatograms

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Notes
The authors declare no competing financial interest.

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- Chemodivergent
- Regioselective
- Dynamic kinetic asymmetric transformation

α-allyl ketones
up to 84% yield
up to >99.9:0.1 er

α-allyl amides
up to 89% yield
up to >99.9:0.1 er

without 4Å MS

vinyl azide
(amide & ketone enolate surrogate)

racemic

with 4Å MS