Iridium-Catalyzed Asymmetric α-Allylic Alkylation of Amides using Vinyl Azide as Amide Enolate Surrogate

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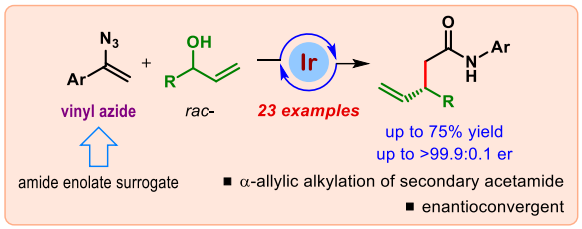
Supporting Information Placeholder



ABSTRACT: Among the unstabilized enolates used as nucleophile in iridium-catalyzed asymmetric allylic alkylation reactions, amide enolates are least explored. Vinyl azides are now employed as amide enolate surrogate for the first time in Ir-catalyzed asymmetric allylic alkylation with branched allylic alcohols as the allylic electrophile. Competing reaction pathways are suppressed through systematic tuning of steric and electronic properties of vinyl azide to effect α-allylic alkylation of secondary acetamides with high atom-economy, exclusive branched selectivity and moderate to excellent enantioselectivity.

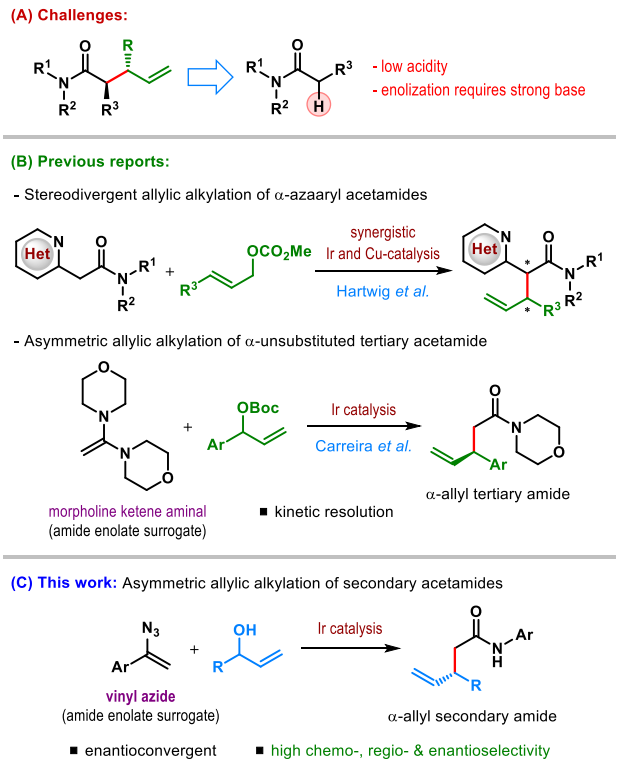
Notwithstanding the phenomenal developments in the field of iridium-catalyzed asymmetric allylic substitution (AAS) reactions in the past two decades,[1] stabilized enolates remain among the most popular and privileged class of carbon nucleophiles.[1,2] In contrast, asymmetric allylic alkylation (AAA) of unstabilized enolates are much less explored. In this context, the paucity of amide enolates in Ir-catalyzed AAA is particularly noteworthy.

Due to the reduced acidity of the α-protons,[3] generation of amide enolates requires strong base and such conditions are often incompatible with some of the AAA conditions (Scheme 1A).[4] Consequently, efforts were mostly confined to easily enolizable oxazolones and thiazolones as precursors for highly substituted amides.[5,6] In 2018, Hartwig *et al.* addressed the low acidity of amides through the use of a synergistic combination of iridium and copper catalysis, to develop a stereodivergent allylic alkylation of α-azaaryl acetamides (Scheme 1B).[7]

However, enantioselective α-allylic alkylation of α-unsubstituted acetamides continued to elude the grasp of available synthetic tools. In 2019, Carreira and co-workers came up with an ingenious solution to this problem by using morpholine ketene aminal as the amide enolate equivalent to develop the first catalytic enantioselective formal allylic alkylation of α-unsubstituted acetamides (Scheme 1B).[8] Using branched allylic carbonates as the allylic electrophile, this reaction proceeds with kinetic resolution and gives rise to α-allyl tertiary amides with excellent enantioselectivity.

In spite of these notable advances, enantioselective α-allylic alkylation of primary and secondary acetamides with the generation of a β-stereogenic center is yet to be accomplished.

Scheme 1. Ir-Catalyzed Asymmetric α-Allylic Alkylation (AAA) of Amides

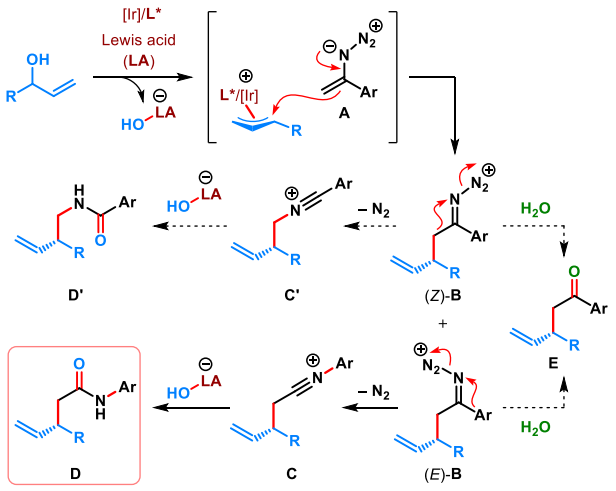


Vinyl azides, owing to their structural resemblance with enamine (*vide infra*), have recently emerged as an amide enolate surrogate since the pioneering work of Chiba and co-workers.[9] While vinyl azides have been used for formal α-functionalization of amides,[10] their applications in enantioselective reaction are scarce. Only recently Terada *et al.* developed the first enantioselective reaction of vinyl azides for addition to *N*-acyl aldimines under chiral Brønsted acid catalysis.[11]

With our interest in Ir-catalyzed AAS reactions,[12] we envisaged that the reaction of vinyl azide with an *in situ* generated electrophilic π-allyl-Ir complex could lead to an overall α-allylic alkylation of α-unsubstituted secondary acetamides (Scheme 1C).

However, this catalytic strategy is associated with a number of challenges (Scheme 2). Nucleophilic addition of vinyl azide (**A**) to the more substituted terminal of an electrophilic π-allyl-Ir complex is expected to generate the branched iminodiazonium ion **B**, which can form as a mixture of (*E*)- and (*Z*)-isomers. Schmidt-type rearrangement of (*E*)-**B** through the 1,2-aryl migration followed by hydration of the resulting nitrilium ion **C** would then furnish the α-functionalized acetamide **D**. We surmised that using branched allylic alcohol as the allylic electrophile in combination with a Lewis or Brønsted acid promoter would make this process highly atom-economic by providing the hydroxide necessary for the conversion of nitrilium ion **C** to the product amide **D**. A competitive pathway involving (*Z*)-**B** would favor 1,2-alkyl migration to form an isomeric nitrilium ion **C'** and eventually to *N*-homoallylbenzamide derivative **D'**. Controlling the geometry of **B** is crucial to ensure the desired aryl migration. Another competitive pathway comprises of the hydrolysis of iminodiazonium ion **B** to the α-allyl ketone **E**. The suppression of the latter two pathways would be the key to the success of this strategy. In addition, decomposition of vinyl azide to the corresponding methyl ketone through protonation and hydrolysis is yet another hurdle to be surmounted.

Scheme 2. Asymmetric Allylic Alkylation (AAA) of Vinyl Azides: Catalytic Hypothesis and Challenges

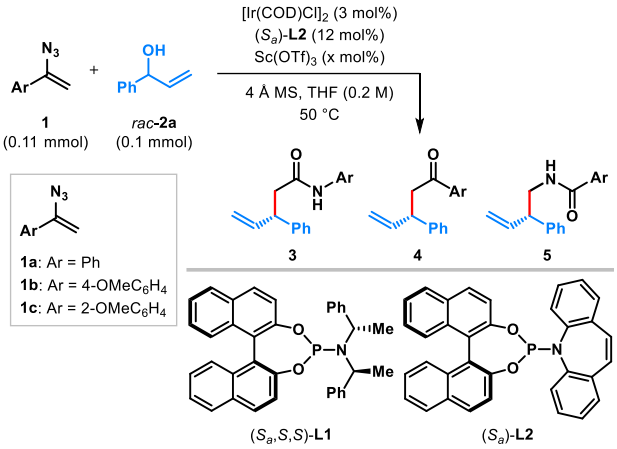


We herein report the results of our investigation, which successfully culminated in the first catalytic enantioselective allylic alkylation of vinyl azides *en route* to α-allylic secondary amides.[13]

At the outset of this study, we tested the reactivity of 1-phenyl vinyl azide **1a** towards the π-allyl-Ir complex generated *in situ* from various combinations of allylic electrophiles and Ir-catalysts derived from either Feringa's phosphoramidite ligand[14] (S_a,*S*,*S*)-**L1** or Carreira's (phosphoramidite,olefin)-ligand[1b] (S_a)-**L2** (Table 1).[15] The catalyst generated from $[Ir(COD)Cl]_2$ and (S_a,*S*,*S*)-**L1**[16] was found to be completely inactive when used in combination with linear allylic carbonates. Similarly, no reaction took place when branched allylic carbonate was used under the influence of the catalyst generated from $[Ir(COD)Cl]_2$ and (S_a)-**L2**.[17]

In contrast, the conversion of vinyl azide **1a** was observed when the reaction was carried out using branched allylic alcohol **2a** in the presence of only 3 mol % $[Ir(COD)Cl]_2$, 12 mol % (S_a)-**L2** and 10 mol % of $Sc(OTf)_3$ as the promoter in THF at 50 °C. Unfortunately, the isolated product was found to be α-allyl acetophenone **4** and no trace of the desired α-allyl amide **3aa** was detected (Table 1, entry 1).

Table 1. Optimization of Reaction Parameters



entry	x	1	*t* (h)	yield (%)[b]			er of 3[c]
				3	4	5	
1[a]	10	**1a**	48	<5	30	<5	n.d.
2	10	**1a**	48	21	9	<5	99.5:0.5
3[d]	20	**1a**	60	29	8	<5	99:1
4[e,f]	20	**1a**	72	28	<5	<5	98.5:1.5
5[e,f]	100	**1a**	72	52	11	<5	99:1
6[f]	100	**1b**	72	42	<5	40	99:1
7[f]	100	**1c**	72	65	<5	<5	89:11
8[f,g,h]	100	**1c**	72	63	<5	<5	99:1

[a]Reaction without molecular sieves. [b]Yields correspond to the isolated yield after chromatographic purification. [c]Enantiomeric ratio (er) as determined by HPLC analysis on a chiral stationary phase. [d]Using 1.5 equiv of **1a**. [e]Reaction in 1,4-dioxane. [f]Using 2.0 equiv of **2a**. [g]Reaction at 25 °C. [h]Reaction on a 0.2 mmol scale. MS = molecular sieves. n.d. = not determined.

As anticipated (see Scheme 2), removal of moisture by adding 4 Å MS suppressed the formation of ketone and resulted in substantial amount of the desired amide **3aa** exclusively as the branched isomer with outstanding enantioselectivity (entry 2). Efforts in ameliorating the yield of **3aa** by using other Lewis or Brønsted acidic promoters proved futile and $Sc(OTf)_3$ remained the optimum.[15] Use of

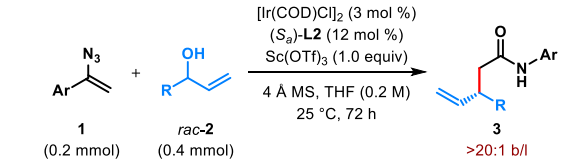
a larger excess of vinyl azide in combination with 20 mol % $Sc(OTf)_3$ slightly improved the yield of **3aa** (entry 3). Screening of solvents[15] revealed 1,4-dioxane as the optimum (entry 4). The reaction with 2.0 equiv of allylic alcohol **2a** and 100 mol % of $Sc(OTf)_3$ in 1,4-dioxane led to 52% isolated yield of **3aa** with 99:1 er (entry 5). Nevertheless, the modest yield of **3aa** and the formation of a measurable amount of ketone **4** remained a cause of concern.

We reasoned that the use of a more electron-rich aryl substituent on the vinyl azide might favor the Schmidt rearrangement pathway over the undesired hydrolysis of the iminodiazonium intermediate (**B** in Scheme 2). Although the ketone formation was completely suppressed when the reaction was carried out with 1-(*p*-methoxyphenyl) vinyl azide **1b** in THF at 50 °C, the undesired alkyl migration was found to compete with aryl migration. The resulting products **3ba** and **5** were isolated almost as a 1:1 mixture with excellent er of both **3ba** and **5** (entry 6). As discussed above, the formation of (*E*)-iminodiazonium intermediate was deemed to be the key for a productive aryl migration. With the anticipation of increasing the steric bulk on the aryl ring to favor (*E*)-**B** over (*Z*)-**B** (see Scheme 2), while maintaining its electron-rich nature, we sought to apply 1-(*o*-methoxyphenyl) vinyl azide **1c** as the amide enolate surrogate. We were pleased to note that the use of **1c** eliminated both these undesired pathways and resulted in α-allyl amide **3ca** as the sole product, albeit with only 89:11 er (entry 7). Carrying out the reaction at 25 °C restored the enantioselectivity to 99:1 er and **3ca** was isolated in 63% yield (entry 8). It must be noted that even though 2.0 equiv of racemic allylic alcohol (**2a**) was used in this reaction with respect to vinyl azide, no kinetic resolution was observed and the recovered **2a** remained racemic.

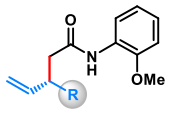
With the optimum reaction conditions (Table 1, entry 8) at hand, we tested the compatibility of this protocol with other branched allylic alcohols. As shown in Table 2A, allylic alcohols having electronically diverse aryl substituents were found to react smoothly with 1-(*o*-methoxyphenyl) vinyl azide **1c** and furnished the corresponding α-allyl *N*-arylacetamide derivatives in moderate to good yield with exquisite regio- (b vs l) as well as chemoselectivity. While the products derived from allylic alcohols containing electron-rich aryl substituents were formed with moderate to good enantioselectivity (entries 2-4), allylic alcohols bearing electron-deficient aryl substituents at various positions fared extremely well and in most cases, the products were isolated with outstanding level of enantioselectivity. Only in the case of *m*-bromophenyl substituted allylic alcohol **2m**, the product (**3cm**) was obtained with modest er (entry 13). Allylic alcohols bearing heteroaryl substituents such as dioxolane and thienyl (**2t-u**) also afforded the products with good to excellent enantioselectivity, albeit with somewhat less yield (entries 20-21). Please note that neither α-allyl acetophenone nor *N*-homoallylbenzamide derivatives (**E** and **D'**, respectively in Scheme 2) were detected in any of these reaction. Unfortunately, no reaction was observed in the case of alkyl or alkenyl substituted allylic alcohols[15] and marks a limitation of this protocol.

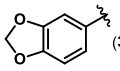
The scope of vinyl azide was also found to be very limited. Reaction with a number of 1-aryl vinyl azides apart from **1a-c** were tested and no desired product was obtained in any of these cases.[15] However, 1-phenyl vinyl azide **1a** could be used with other branched allylic alcohols as shown for *p*-bromophenyl derivative **2h**: Although the product **3ah** was isolated with only 54% yield, it was formed with 98:2 er (Table 2B). Enantioselectivity was further improved through a single recrystallization, which afforded diffraction quality crystals. Single-crystal X-ray diffraction analysis of **3ah** revealed its absolute configuration to be (*S*) (CCDC 2020776, Table 2B). The configurations of the other products were tentatively assigned as the same by analogy.

Table 2. Scope Asymmetric Allylic Alkylation of Vinyl Azides[a]

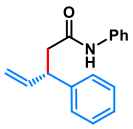


(A)

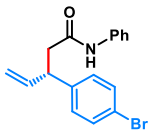


entry	R (3)	yield (%)	er
1	Ph (**3ca**)	63	99:1
2	4-MeC_6H_4 (**3cb**)	61	97:3
3	4-(*i*-Pr)C_6H_4 (**3cc**)	63	95:5
4	4-$OMeC_6H_4$ (**3cd**)	51	86:14
5	4-$CF_3C_6H_4$ (**3ce**)	70	99.7:0.3
6	4-FC_6H_4 (**3cf**)	60	99.5:0.5
7	4-ClC_6H_4 (**3cg**)	71	99.5:0.5
8	4-BrC_6H_4 (**3ch**)	58	99.5:0.5
9	4-CNC_6H_4 (**3ci**)	75	99.7:0.3
10	4-$(CO_2Me)C_6H_4$ (**3cj**)	60	99.8:0.2
11	3-FC_6H_4 (**3ck**)	65	98.5:1.5
12	3-ClC_6H_4 (**3cl**)	71	99.5:0.5
13	3-BrC_6H_4 (**3cm**)	70	85:15
14	3-MeC_6H_4 (**3cn**)	55	98.5:1.5
15	2,4-$Cl_2C_6H_3$ (**3co**)	64	99.8:0.2
16	3,4-$Cl_2C_6H_3$ (**3cp**)	75	99.8:0.2
17	2,5-$F_2C_6H_3$ (**3cq**)	70	>99.9:0.1
18	C_6F_5 (**3cr**)	75	99.9:0.1
19	2-Naphth (**3cs**)	60	98:2
20[b]	 (**3ct**)	40	97:3
21[c]	2-Thienyl (**3cu**)	45	99:1

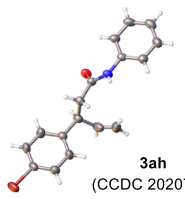
(B)



3aa[d]
52% yield, 99:1 er



3ah[d]
54% yield, 98:2 er
(99:1 er)[e]



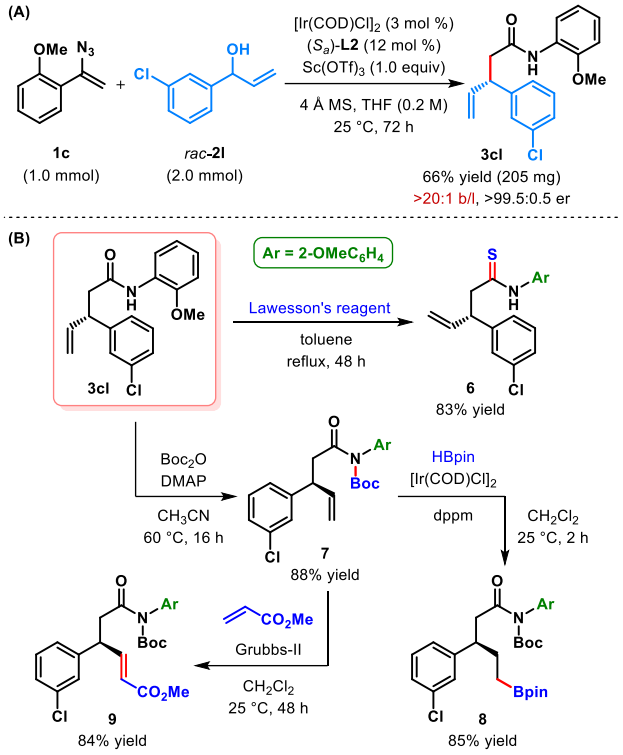
3ah
(CCDC 2020776)

[a]Unless noted otherwise, the reaction conditions indicated above were followed. Yields refer to the isolated product after chromatographic purification. Enantiomeric ratios (er) were determined by HPLC analysis on a chiral stationary phase. [b]Reaction with 50 mol % $Sc(OTf)_3$. [c]Reaction with 25 mol % $Sc(OTf)_3$. [d]Reaction at 50 °C. [e]The value in parenthesis indicate er of **3ah** after a single recrystallization.

To verify the scalability of this protocol, the allylic alkylation reaction between vinyl azide **1c** and allylic alcohol **2l** was carried out on a 1.0 mmol scale under our standard reaction conditions (Scheme 3). The corresponding α-allyl *N*-arylacetamide **3cl** was isolated in 66% yield with >99.5:0.5 er. The synthetic potential of the product was demonstrated through the conversion of the newly built

functionalities. Amide of **3cl** was converted to the corresponding thioamide **6** by refluxing with Lawesson's reagent in toluene. Protection of the secondary amide in **3cl** with Boc enabled further functionalizations. For example, hydroboration of the terminal double bond of **7** with pinacolborane could be accomplished under Ir-catalysis[18] and furnished the alkyl boronate **8** in 85% yield. Olefin cross-metathesis of **7** with methyl acrylate in the presence of Grubbs' 2nd generation catalyst afforded the α,β-unsaturated ester **9** in high yield.

Scheme 3. (A) Scale-up Synthesis and (B) Synthetic Elaboration of α-Allyl *N*-Arylacetamide 3cl



In summary, we have developed the first catalytic enantioselective allylic alkylation of vinyl azides as amide enolate surrogate.[13] With N_2 as the only byproduct, this highly atom-economic transformation, catalyzed by Ir(I)/(phosphoramidite,olefin) complex, utilizes easy-to-prepare branched allylic alcohols as the allylic electrophile along with $Sc(OTf)_3$ as the Lewis acid promoter. Through systematic modulation of steric and electronic properties of vinyl azide, competing reaction pathways are circumvented and ultimately results in α-allyl acetamides with exclusive branched selectivity and moderate to excellent enantioselectivity. Use of easily accessible allylic electrophiles and the reaction at ambient temperature are some of the practical advantages of our protocol. It also complements the use of morpholine ketene aminal as the amide enolate surrogate: α-Allyl secondary amides are the products in this reaction, whereas the latter gives rise to α-allyl tertiary amides.

ASSOCIATED CONTENT

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

Accession Codes

CCDC 2020776 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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