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Communication

Enantioselective and Diastereodivergent Allylation of Propargylic C−H Bonds

Jin Zhu, Yidong Wang, Aaron D. Charlack, and Yi-Ming Wang*

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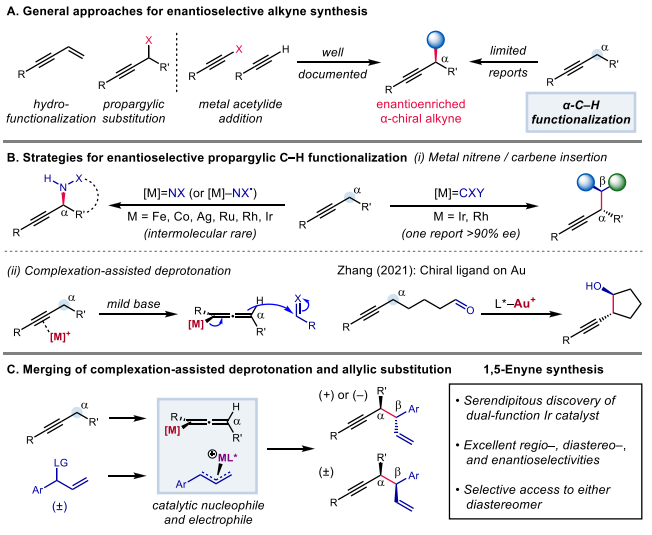
ABSTRACT: An iridium-catalyzed stereoselective coupling of allylic ethers and alkynes to generate 3,4-substituted 1,5-enynes is reported. Under optimized conditions, the coupling products are formed with excellent regio-, diastereo-, and enantioselectivities, and the protocol is functional group tolerant. Moreover, we report conditions that allow the reaction to proceed with complete reversal of diastereoselectivity. Mechanistic studies are consistent with an unprecedented dual role for the iridium catalyst, enabling the propargylic deprotonation of the alkyne through π-coordination, as well as the generation of a π-allyl species from the allylic ether starting material.

The enantioselective functionalization of C(sp^3)−H bonds constitutes a conceptually simple and direct approach for the synthesis of valuable stereodefined products from simple starting materials.[1] Given the widespread availability of alkyne derivatives,[2] the enantioselective construction of a C−C or C−X (X = N, O, etc.) bond at the propargylic position is an especially attractive strategy for accessing versatile chiral building blocks en route to stereochemically and functionally complex targets.[3,4] However, in contrast to a variety of well-developed protocols that employ prefunctionalized alkyne derivatives for asymmetric propargylation[5−7] or metal acetylide precursors for enantioselective nucleophilic addition to synthesize α-chiral alkynes,[8,9] the use of simple alkynes for enantioselective propargylic C−H functionalization remains an underdeveloped approach (Scheme 1A).[10−12]

Scheme 1. Asymmetric Propargylic Functionalization for 1,5-Enyne Synthesis



Metal nitrene or carbene insertion constitutes one general strategy for enantioselective propargylic C−H functionalization (Scheme 1B, top). A number of transition metals and ligand systems have been reported to facilitate enantioselective nitrene (or nitrene radical) transfer.[10a−h,11a−c] Likewise, several examples of enantioselective carbene insertion into a propargylic C−H bond have been disclosed.[10i,11d] In addition, enantioselective propargylic C−H functionalization reactions proceeding via radical−organometallic crossover mechanisms are also known, constituting another promising strategy.[12] Given their potential applicability toward establishing stereochemistry at both the α- and β-positions of the alkyne,[5f,8i,11d] the development of new stereoselective propargylic C−H functionalization strategies has continued to attract interest.

Our research group and others have previously demonstrated an alternative approach to catalytic propargylic C−H functionalization wherein deprotonation of an α-C−H bond of a metal-bound alkyne enables the subsequent electrophilic trapping of the resultant allenylmetal nucleophile to deliver the product of propargylic functionalization (Scheme 1B, bottom).[13,14] Zhang and co-workers have further demonstrated that such a process could be rendered enantioselective in the intramolecular sense using a chiral Au catalyst.[14a]

In this context, we wondered whether we could develop an intermolecular coupling strategy by intercepting the allenylmetal species with a stereodefined organometallic electrophile.[15] Although originally envisaged as a cooperative catalysis strategy,[16] we disclose herein our serendipitous finding that a single dual-function catalyst enables the simultaneous activation and subsequent coupling of two starting materials,[17]

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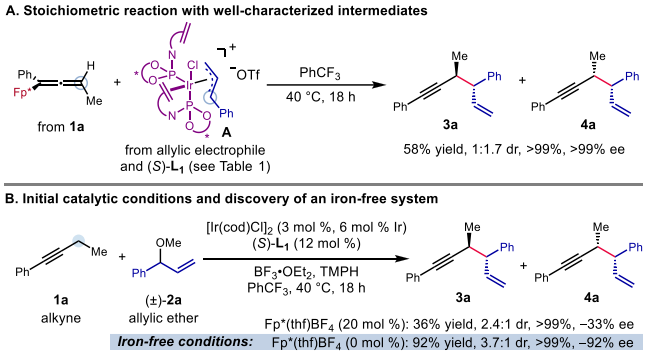
an alkyne and an allylic ether, to generate synthetically versatile 1,5-enyne products with high levels of regio- and stereoselectivity (Scheme 1C).[18]

We initially hypothesized that, by combining our previously reported Fe-based catalysts for propargylic C−H deprotonation[13] with an Ir-based system for enantioselective allylic substitution,[19,20] we could develop a cooperative strategy for the enantioselective synthesis of 1,5-enynes by intercepting a chiral, nonracemic electrophilic π-allyliridium intermediate with a nucleophilic σ-allenyliron intermediate. To validate the proposed reactivity, we examined the stoichiometric reaction of an Fp*-based σ-allenyliron species (Fp* = $(\eta^5$-$C_5Me_5)Fe(CO)_2$)[13a] toward a previously characterized π-allyliridium complex ($\mathbf{A}^+TfO^-$) bearing a phosphoramidite−alkene ligand system developed by Carreira and co-workers.[20a] Indeed, the desired product was obtained in moderate yield and excellent enantioselectivity, albeit with little control over the diastereoselectivity (1:1.7 dr) (Scheme 2A).

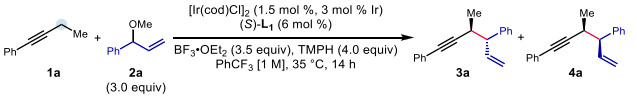
Scheme 2. Preliminary Results for Propargylic C−H Allylation



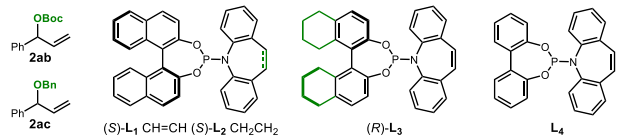
Next, we attempted to implement a catalytic system by using 1-phenyl-1-butyne and allylic ether **2a** as starting materials while employing substoichiometric amounts of Fe (20 mol %) and Ir (3 mol % $[Ir(cod)Cl]_2$, 6 mol % based on Ir) complexes. In addition, in analogy to our previously reported Fe-catalyzed α-C−H functionalization reactions, $BF_3{\cdot}OEt_2$ and 2,2,6,6-tetramethylpiperidine (TMPH) were included in the reaction mixture to promote ionization of the allylic ether and to deprotonate the metal−alkyne complex, respectively.[13] These conditions afforded the same coupling product, though with lower yield and significant differences in the stereoisomeric composition (Scheme 2B). During the course of optimization, we performed a series of control experiments and found, to our surprise, that the reaction proceeded in excellent yield *without the need for the iron complex*.[21] These results suggested the possibility that, in addition to facilitating the generation of the π-allyl electrophile, the Ir complex could serve the additional role of activating the alkyne to allow for the removal of a propargylic proton under mildly basic conditions. To the best of our knowledge, this second role has not previously been demonstrated for Ir−phosphoramidite complexes.[20k]

After extensive optimization of the identity and stoichiometry of allylic electrophile, base, ligand, and Lewis acid, conditions that delivered the *anti*-diastereomer **3a** in high yield and superb stereoselectivity (91% isolated yield, >20:1 dr, >99% ee) were identified (Table 1, entry 1). Of note, the use of additional allylic methyl ether (3.0 equiv) was found to improve diastereoselectivity (entry 1 vs 2). Moreover, the

Table 1. Optimization of the Ir-Catalyzed Alkyne-Allyl Coupling Reaction[a]



entry	variation	% yield (% ee)	3a:4a[b]
1	none	92[c] (>99)	>20:1
2	**2a** (2.0 equiv)	88 (>99)	5.1:1
3	**2ab** instead of **2a**	NP[d]	--
4	**2ac** instead of **2a**	69 (>99)	>20:1
5	Et_3N, DBU, or KO*t*Bu as base	NP	--
6	BPh_3 or $B(C_6F_5)_3$ as Lewis acid	NP	--
7[e]	[Ir]:(*S*)-**L**$_1$ = 1:1, with 3 mol % Ir	NP	--
8[e]	(*S*)-**L**$_2$ or (*R*)-**L**$_3$ as ligand	NP	--
9[e]	**L**$_4$ as ligand	<10	<1:20
10[f]	(±)-**L**$_1$ as ligand	99	<1:20
11[f]	[Ir]:(*S*)-**L**$_1$ = 1:2, with 1 mol % Ir	19 (>99)	>20:1
12	at rt (23 °C)	70 (>99)	>20:1
13	no [Ir], (*S*)-**L**$_1$, TMPH, or $BF_3{\cdot}OEt_2$	NP	--



[a]On 0.1 mmol scale. Yields (**3a**+**4a**) were determined by ^1H NMR spectroscopy of the crude reaction mixture, using 2,4-dinitrotoluene as the internal standard. Enantiomeric excesses were determined by chiral HPLC. [b]Diastereomeric ratios (**3a**:**4a**) were determined by ^1H NMR spectroscopy of the crude mixture. [c]In 91% isolated yield. [d]NP: no desired product observed. [e]CH_2Cl_2 (1 M) as solvent. [f]2.0 equiv **2a** were added.

ligand-to-metal ratio was found to be critical (entry 1 vs 7).[8i,20b,j] Surprisingly, when achiral ligand **L**$_4$ was employed, a complete reversal of the diastereoselectivity was observed, with *syn*-diastereomer **4a** formed in >20:1 dr though in low yield (entry 9). By using racemic ligand (±)-**L**$_1$, **4a** could be obtained in excellent yield and diastereoselectivity (entry 10). Control experiments showed that the reaction fails in the absence of $[Ir(cod)Cl]_2$, (*S*)-**L**$_1$, TMPH, or $BF_3{\cdot}OEt_2$, indicating the necessity of each component (entry 13).

With optimized conditions in hand, we investigated the generality of the *anti*-selective propargyl−allyl coupling protocol with respect to the alkyne coupling partner (Table 2). A collection of aryl ethyl acetylenes bearing electron-donating (**3b**, **3c**, **3g**, **3h**) or electron-withdrawing substituents (**3d**, **3e**) were transformed into the corresponding 1,5-enynes in moderate to high yields and excellent diastereo- and enantioselectivities. Furthermore, a number of heterocycles were accommodated, including a thiophene (**3i**), a furan (**3j**), and a benzofuran (**3k**). An alkyne bearing a phthalimido group (**3l**) also reacted efficiently with high stereoselectivity. Moreover, higher aryl alkyl acetylenes, including those possessing pendent ether or sulfonate ester groups (**3m**−**3o**), were also competent substrates. The synthesis of **3n** bearing a *p*-toluenesulfonate ester was carried out on 5 mmol scale to deliver 1.58 g of the product (73% isolated yield, >99:1 dr,

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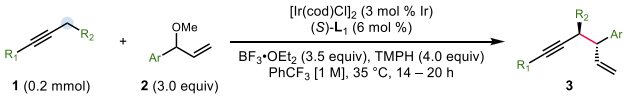
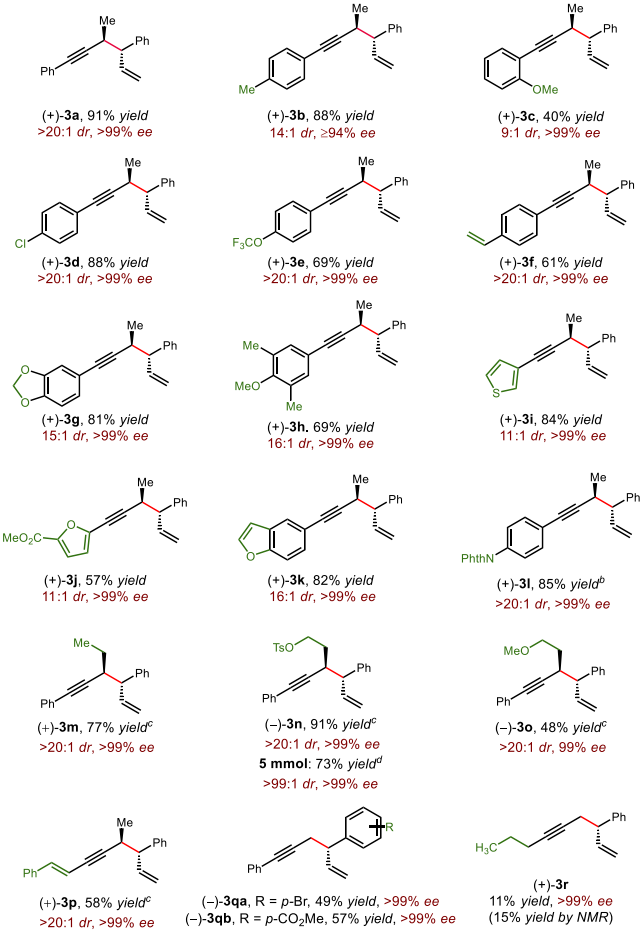
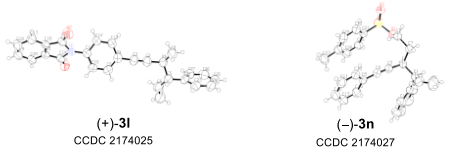
Table 2. Substrate Scope for the Alkyne Coupling Partner[a]

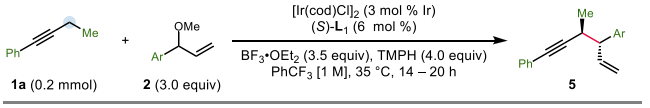


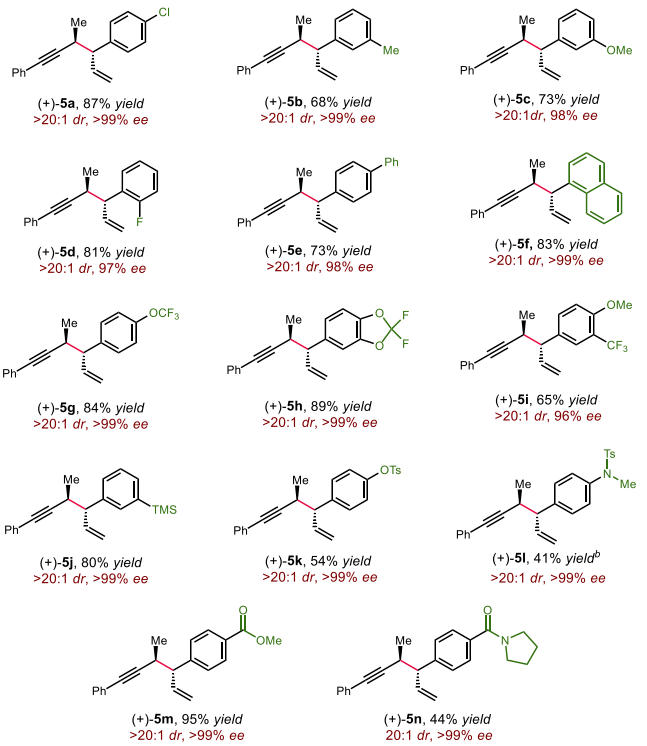




[a]Isolated yields. Enantiomeric excesses were determined by chiral HPLC. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude material. [b]CH_2Cl_2 (0.2 mL) as solvent. [c]$[Ir(cod)Cl]_2$ (6 mol % Ir), (*S*)-**L$_1$** (12 mol %) were used. [d]$[Ir(cod)Cl]_2$ (4 mol % Ir), (*S*)-**L$_1$** (8 mol %), 36 h; purified by recrystallization.

Table 3. Substrate Scope for the Allylic Ether Coupling Partner[a]





[a]Isolated yields. Enantiomeric excesses were determined by chiral HPLC. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude material. [b]CH_2Cl_2 (0.2 mL) as solvent.

>99% ee) after recrystallization of the crude material. A conjugated enyne (**3p**) likewise delivered a successful outcome. The primary propargylic C−H bonds of aryl methyl acetylenes could also be functionalized (**3qa**−**3qb**),[11a,22] giving the final product with good enantioselectivity, albeit in only moderate yields. Finally, we tested the reactivity of a dialkyl acetylene, 2-hexyne (**3r**). Only one regioisomer was isolated in excellent enantiomeric excess, though the low yield demonstrates a limitation of our current protocol.

Subsequently, the scope with respect to the allylic ether coupling partner was examined (Table 3). A range of racemic allylic ethers could be coupled to give the desired 1,5-enyne products in moderate to high yields as a single diastereomer. Aryl groups with various substitution patterns (**5a**−**5i**) were compatible substrates, as were substrates bearing a trimethylsilyl substituent (**5j**), a sulfonate ester (**5k**), a sulfonamide (**5l**), a carboxylic ester (**5m**), and a tertiary amide (**5n**).

We then examined a subset of the alkyne/allylic ether combinations from Tables 2 and 3 to probe the generality of the reaction conditions employing (±)-**L$_1$** that selectively affords the *syn*-diastereomer of the 1,5-enyne (Table 4). In all cases examined, nearly complete reversal of the reaction diastereoselectivity was observed. Moreover, the yields of coupling products (±)-**4** and (±)-**6** were generally comparable or higher than those observed for the formation of the corresponding diastereomeric products **3** and **5**. Notably, the synthesis of (±)-**4a** could be performed on 1 mmol scale with near-quantitative yield, even at a reduced catalyst loading of 2 mol % Ir.

The synthetic value of this method was further demonstrated through the preparation of diverse carbo- and heterocyclic scaffolds with high molecular complexity (Scheme 3). The Au-catalyzed cycloisomerization of 1,5-enynes efficiently afforded bicyclo[3.1.0]hexene **7n** in 91% yield with >99% ee and 12:1 dr.[18a] Moreover, tricyclic indole derivative **8n** was synthesized via a palladium-catalyzed cascade process in 52% yield without the loss of enantioselectivity.[23] Finally, a chemo- and regioselective hydroboration−oxidation sequence, followed by *O*-tosylation and cyclization with

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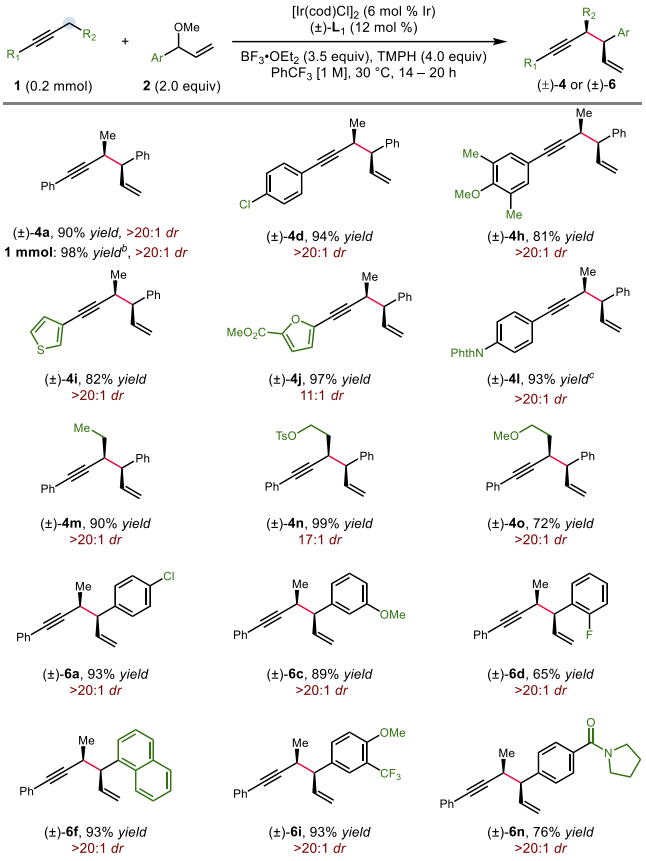
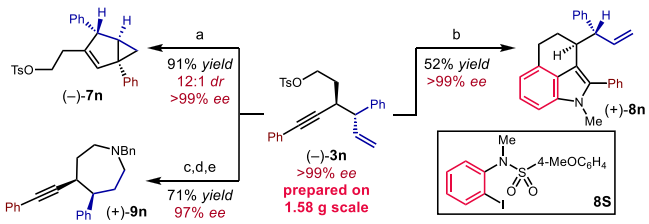
Table 4. Diastereoselective Synthesis of the *syn*-Isomer[a]



[a]Isolated yields. Diastereomeric ratios were determined by ^{1}H NMR spectroscopy of the crude material. [b]$[Ir(cod)Cl]_2$ (2 mol % Ir), (±)-**L**$_1$ (4 mol %) were used, 24 h. [c]CH_2Cl_2 (0.2 mL) as solvent.

Scheme 3. Diversification of Product 3n[a]

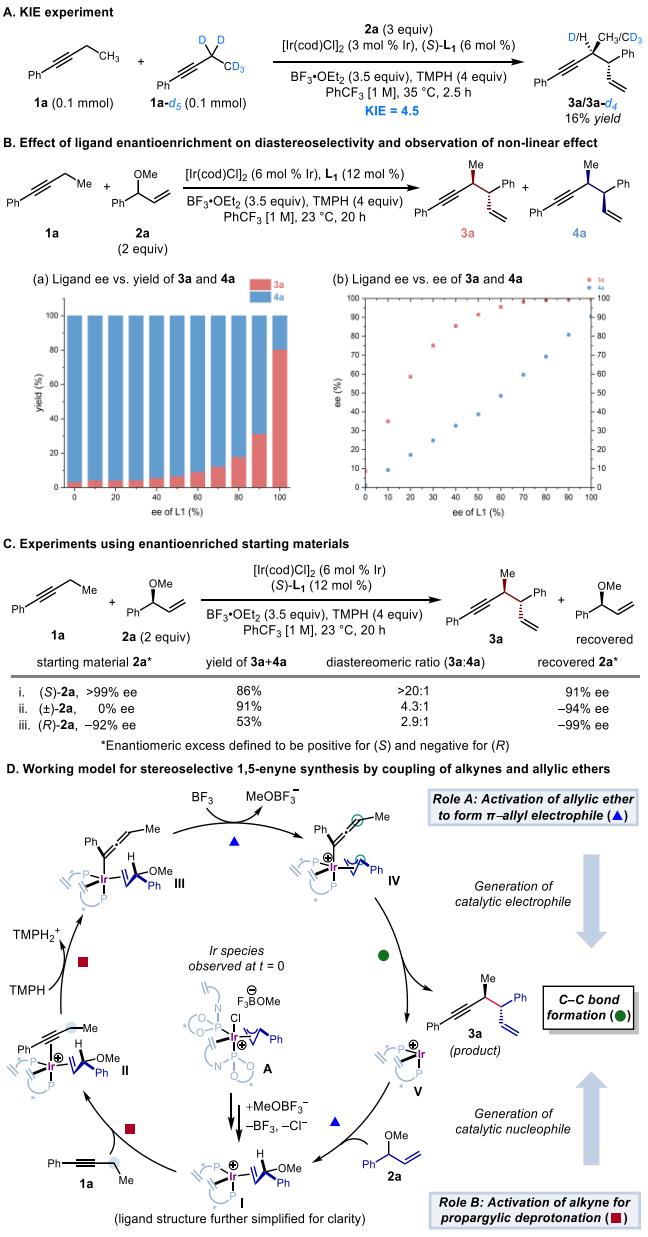


[a]Conditions: (a) Ph_3PAuCl (cat.), $AgSbF_6$ (cat.), CH_2Cl_2, rt, 0.5 h; (b) Sulfonamide **8S**, $Pd(OAc)_2$ (cat.), Ph_3P (cat.), Cs_2CO_3, CsI, norbornene, DMF, 130 °C, 12 h; (c) 9-BBN, THF, 2 h; $NaBO_3{\cdot}H_2O$, H_2O, rt, 3 h; (d) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 4 h; (e) $BnNH_2$, K_2CO_3, MeCN, reflux, 22 h.

$BnNH_2$ as a lynchpin, afforded 4,5-disubstituted azepane **9n** in good yield and excellent enantioselectivity.

We performed a series of additional experiments to gain some insight into the mechanistic details of the catalytic system (Scheme 4). First, a plot of conversion of **1a** over time revealed that the reaction was subject to an induction period. While this complicated efforts to measure rate constants, we next subjected ethyl-deuterated **1a**-d_5 to the same conditions and observed a smaller maximum velocity and slower overall rate, indicating a significant kinetic isotope effect (KIE). Under conditions of intermolecular competition, a KIE of k_H/k_D = 4.5 was measured (Scheme 4A). Combined, these data suggest rate-limiting proton abstraction at the propargylic position.[24]

Scheme 4. Selected Mechanistic Studies and Proposed Catalytic Cycle



To probe the nature of the stereocontrol of this transformation, we investigated the relationship between the enantiomeric excess of the ligand and the diastereo- and enantiomeric composition of the product (Scheme 4B). The observation of nonlinear effects[25] (particularly for formation of product **3a**) suggests the presence of two ligands on the metal center in the enantiodetermining transition states. Moreover, the (*S*,*S*)-(**L**$_1$)$_2$[Ir] homochiral complex is primarily responsible for formation of **3a**, while formation of **3a** from the (*R*,*S*)-(**L**$_1$)$_2$[Ir] heterochiral complex is slow. The effect of the enantiomeric composition of **2a** was then examined (Scheme 4C). When racemic **2a** was used, a kinetic resolution was observed, with the less reactive (*R*)-**2a** accumulating in the reaction mixture. In addition, a large difference in the diastereomeric ratio of the product was observed when (*S*)- and (*R*)-**2a** were used as starting materials.[26] This suggests that departure of the methoxy group of the iridium-coordinated

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allylic ether takes place after coordination (and perhaps deprotonation) of the alkyne coupling partner.[20d]

On the basis of these results, a plausible though still speculative mechanism is proposed in Scheme 4D. Carreira's complex (in the form of $\mathbf{A}^+[BF_3OMe]^-$) was observed to be the sole Ir−phosphoramidite species by $^{31}P\{^1H\}$ NMR analysis of the reaction mixture at the beginning of the reaction and continued to be the major phosphorus-containing species in the reaction mixture up to 14 h later.[20a] Moreover, $\mathbf{A}^+TfO^-$ was found to be a competent catalyst for the reaction (89% NMR yield, >20:1 dr, >99% ee). Thus, we postulate that 18-electron complex $\mathbf{A}^+$ acts as an initial reservoir for on-cycle catalytically active species. In particular, we propose that formation of allylic ether complex **I** with loss of Cl^- allows for binding of the alkyne,[27] with the key deprotonation step taking place from cationic intermediate **II**.[28] Subsequent abstraction of methoxide from the bound allylic ether and ligand coupling with reduction at Ir then furnishes **3a**.[6a,29] Finally, coordination of the allylic ether to **V** regenerates **I** to close the catalytic cycle.

In summary, we have described the Ir-catalyzed enantioselective and diastereodivergent propargylic C(sp^3)−H allylation of alkynes, including a mechanistically novel role for the catalyst. Further studies of the detailed mechanism and explorations of additional applications of this strategy are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.2c07297.

Experimental procedures, spectroscopic data for the substrates and products, and crystallographic data for **3l** (CCDC 2174025) and **3n** (CCDC 2174027). (PDF)

Accession Codes

CCDC 2174025 and 2174027 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.

■ AUTHOR INFORMATION

Corresponding Author

Yi-Ming Wang − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States;* orcid.org/0000-0001-6414-0908; Email: ym.wang@pitt.edu

Authors

Jin Zhu − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Yidong Wang − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States; School of Chemistry & Chemical Engineering, Yangzhou University, Yangzhou, Jiangsu 225002, China;* orcid.org/0000-0001-9560-3186

Aaron D. Charlack − *Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.2c07297

Notes

The authors declare no competing financial interest.

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(24) No desired product was detected when 1-phenyl-1,2-butadiene was used as the starting material, excluding the involvement of the isomeric allene in this process. For previous reports of iridium-mediated alkyne-to-allene isomerization, see: (a) Phadke, N.; Findlater, M. Isomerization of Internal Alkynes to Iridium(III) Allene Complexes via C−H Bond Activation: Expanded Substrate Scope, and Progress towards a Catalytic Methodology. *Molecules* **2015**, *20*, 20195−20205. (b) Phadke, N.; Findlater, M. Formation of Iridium-(III) Allene Complexes via Isomerization of Internal Alkynes. *Organometallics* **2014**, *33*, 16−18.

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(26) In a previous study on an Ir-catalyzed allylation, a much smaller difference in diastereoselectivity was observed when antipodal enantioenriched allylic electrophiles were employed: Davis, C. R.; Luvaga, I. K.; Ready, J. M. Enantioselective Allylation of Alkenyl Boronates Promotes a 1,2-Metalate Rearrangement with 1,3-Diastereocontrol. *J. Am. Chem. Soc.* **2021**, *143*, 4921−4927.

(27) Addition of $[BnMe_3N]^+Cl^-$ (10 mol %) to the reaction mixture was found to completely inhibit formation of the desired product. On the other hand, conducting the reaction using an Ir catalyst solution prepared using $AgBF_4$ to remove Cl^- resulted in a reaction profile with almost no induction period (see the Supporting Information for details).

(28) A reviewer suggested that complexation of the alkyne to unreacted $[Ir(cod)Cl]_2$ could activate it toward deprotonation. However, use of excess ligand ([Ir]:(*S*)-$\mathbf{L}_1$ = 1:4) for the coupling of **1a** and **2a** did not significantly change the result (83% NMR yield, >20:1 dr, >99% ee), making this hypothesis less likely. We cannot currently rule out a mechanism involving two phosphoramidite-ligated Ir centers.

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