Article

Highly Enantioselective Iridium-Catalyzed Coupling Reaction of Vinyl Azides and Racemic Allylic Carbonates

Min Han, Min Yang, Rui Wu, Yang Li, Tao Jia, Yuanji Gao, Hai-Liang Ni, Ping Hu, Bi-Qin Wang, and Peng Cao

J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.0c01766 • Publication Date (Web): 13 Jul 2020

Highly Enantioselective Iridium-Catalyzed Coupling Reaction of Vinyl Azides and Racemic Allylic Carbonates

Min Han,‡ Min Yang,‡ Rui Wu, Yang Li, Tao Jia, Yuanji Gao, Hai-Liang Ni, Ping Hu, Bi-Qin Wang, and Peng Cao*

College of Chemistry and Materials Science, Sichuan Normal University, Chengdu 610068, China

ABSTRACT: The Iridium-catalyzed enantioselective coupling reaction of vinyl azides and allylic electrophiles is presented and provides access to β-chiral carbonyl derivatives. Vinyl azides are used as acetamide enolate or acetonitrile carbanion surrogates, leading to γ,δ-unsaturated β-substituted amides as well as nitriles with excellent enantiomeric excess. These products are readily transformed into chiral *N*-containing building blocks and pharmaceuticals. A mechanism was proposed to rationalize the chemoselectivity of this coupling reaction.

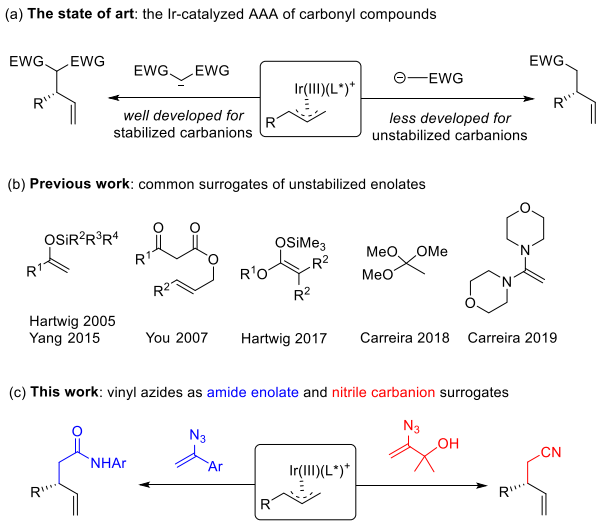
INTRODUCTION

Transition metal-catalyzed asymmetric allylic alkylation (AAA) reaction represents a powerful and appealing tool for construction of nonracemic compounds.[1] The Ir-catalyzed asymmetric allylation of carbonyl compounds is one of the most important methods for generating a stereocenter, particularly, in the β position of carbonyl derivatives. (Scheme 1a) Pioneered by Takeuchi[2a] and Helmchen,[2b] a variety of "soft" or stabilized carbanions (e.g. malonic esters, malononitrile, sulfonylacetic esters and disulfones) have been used in this reaction.[3] However, simple carbonyl compounds with weak α C-H acidity are challenging nucleophiles. The difficulty is attributed to the formed "hard" unstabilized enolates, which are fairly basic and not compatible with the allylic electrophiles or adducts. A desirable solution is to seek appropriate enolates surrogates (Scheme 1b).[4] As the seminal work, Hartwig demonstrated the highly efficient allylation reaction of ketones[4a and 4e], α,β-unsaturated ketones,[4b-d] and aliphatic esters[4f] by using their silyl enol ethers. Meanwhile, the elegant Ir-catalyzed AAA of β-ketocarboxylates,[5] ketene acetal[6a] and ketene aminal[6b] were reported, respectively, by You and Carreira, providing access to a variety of enantioenriched carbonyl compounds.

Amides and nitriles are extremely useful not only in the organic chemistry but also in the bio-chemistry and material science.[7] Nevertheless, few allylation reactions appeared regarding the use of amide enolates or α-carbanion of nitriles as nucleophiles,[8] probably because of side reactions caused by the extremely "hard" property. For example, in the studies on Pd-catalyzed AAA, Hou and coworkers found that the α-carbanion of acetonitrile (pKa $\approx$ 31 in DMSO)[9] couldn't react with allylic electrophiles but attacked another acetonitrile to form enamine (Thorpe reaction).[10] Thus, the highly general and enantioselective alkylation of acetonitrile is still elusive.

Vinyl azides, molecules that contain conjugate alkene and azide moieties, have been known for around a century. Owing to the recent development of more convenient synthetic approaches,[11c] the vinyl azide chemistry has received increasing interests of synthetic chemists.[11] Since the seminal work by Chiba,[12b] Lewis/Brønsted acid-promoted coupling reactions of vinyl azides and C-electrophiles (i.e. aldehydes, imines, propargylic alcohols, *p*-quinone methides) have been developed and become a straightforward approach towards amides and nitriles.[12] We envisioned that the cooperative Lewis acid and chiral transition metal catalysis might facilitate the asymmetric coupling of vinyl azides and C-electrophiles. Herein, the Lewis acid-promoted and Ir-catalysed AAA[13] with vinyl azides was demonstrated, wherein vinyl azides were used as the acetamide enolate as well as acetonitrile carbanion surrogates (Scheme 1c). The method represents the first catalytic enantioselective approach towards synthesis of enantioenriched amides and nitriles with the use of vinyl azides.

Scheme 1. Ir-Catalyzed Enantioselective Allylations of Unstabilized Enolates

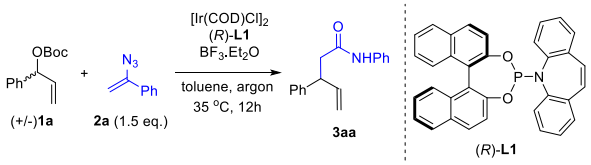


RESULTS AND DISCUSSION

In initial studies, the enantioselective coupling of (1-azidovinyl)benzene (**2a**) and branched allylic alcohols or carbonates was tested with $[Ir(cod)Cl]_2$ (2.5 mol%), (*R*)-**L1** (10 mol%) and $BF_3{\cdot}OEt_2$ (10 mol%) in dichloromethane. The *tert*-butyl (1-phenylallyl) carbonate (**1a**) was found to be the optimal allylic electrophile, producing the desired product **3aa** in 40% yield and 93% ee at 15 °C. (See the supporting information for full optimization details) Through systematic optimization of the Lewis acid, solvent and temperature, a promising result was achieved. (entry 1, Table 1) We then turned our attention to the study of salt effects, in an attempt to accelerate isomerization of intermediary π-allyliridium complexes.[14] Indeed, the use of halide salts as additives improved the catalytic efficiency. Inorganic salts (e.g. LiCl, LiBr, $ZnBr_2$) improved the yield of **3aa**, albeit with erosion of ee value (entries 2-5). Pleasingly, Bu_4NCl or Bu_4NBr as the additive significantly improved the dynamic kinetic asymmetric transformation (DYKAT) of **1a** to afford **3aa** in moderate yields (68% and 65%) with high enantio enrichment (entries 6 and 7). By increasing the loading of $BF_3.Et_2O$ to 50 mol% and lowering the temperature to 10 °C, **3aa** was obtained in good yield (74%) and excellent enantiopurity (entry 9). The dosage of **2a** could be further reduced to 1.2 equiv. without loss of yield or ee (entry 10), indicating that vinyl azides were relatively stable and robust amide enolate surrogates. When changing the chiral ligand or Ir catalyst precursor, the reaction gave worse results. (entries 11-13) Control experiments confirm that no product was observed in the absence of $[Ir(cod)Cl]_2$, the ligand or Lewis acid, (entries 14 and 15) indicating the necessity of each catalyst.

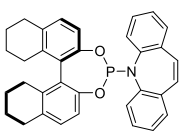
With optimal conditions in hand, various (hetero)aryl substituted allylic alcohol carbonates were tested with **2a** to give the corresponding products with good to high yields and nearly all in absolute stereochemical control. (Table 2) The stereo- and electronic nature of the aryl groups on the allylic substrates had little effect on the yields and enantioselectivities. Aryl units bearing alkyl (Me and ^{i}Pr), phenyl, CF_3 and halo (Cl and Br) substituents were successfully incorporated into *β*-aryl *γ*,*δ*-unsaturated amides (**3ab**-**aj**). The (*R*)-configuration of **3aj** was confirmed by the X-ray diffraction of single crystal. The allylic carbonates with 3,4- or 2,6-dichloro substituted aryl groups were also reactive to produce **3ak** and **3al** in moderate yields (69% and 63%) with excellent ees (>99% and 97%). Fused ring- (*α*- or *β*-naphthyl) and hetero-aryl (3-thienyl or 3-indolyl) substituted allylic carbonates were readily transformed into enantiopure amides (**3am**-**ap**). And the asymmetric transformation of alkyl-substituted allylic electrophiles was demonstrated by synthesis of **3aq** in 37% yield with 99% ee. However, 2-phenylbut-3-en-2-ol or 2-methyl-1-phenylprop-2-en-1-ol derived carbonates had no reactivity, probably due to the steric hindrance. In order to get insights into the electronic effects of vinyl azides on the allylic substitution as well as Schmidt rearrangement process, the scope of vinyl azides was evaluated. The catalysis was tolerant of alkyl, aryl, alkoxyl, halo, carbonyl, nitro, ester, CF_3 and cyano groups (for **3ba**-**3ma**) installed on the *p*- or *m*-position of *α*-aryl unit of vinyl azides, but not tolerant of *o*-substituents on aryl groups. On the other hand, *α*-alkyl or alkenyl-substituted vinyl azides were also tested, but had no reactivity.

Table 1. Development of the Vinyl Azide-Allyl Coupling Reaction.[a]

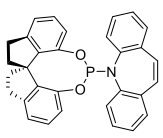


entry	changes of reaction conditions	yield (%)[b]	ee (%)[c]
1	none	63	90
2	LiCl (10 mol%) as the additive	74	88
3	LiBr (10 mol%) as the additive	73	84
4	$ZnCl_2$ (10 mol%) as the additive	63	56
5	$ZnBr_2$ (10 mol%) as the additive	77	50
6	Bu_4NCl (10 mol%) as the additive	68	98
7	Bu_4NBr (10 mol%) as the additive	65	99
8	Bu_4NI (10 mol%) as the additive	34	99
9[d]	Bu_4NBr (10 mol%) as the additive	74	99
10[d,e]	**Bu_4NBr (10 mol%) as the additive**	**76**	**99**
11[d,e]	(*R*)-**L2** as the ligand	59	99
12[d,e]	(*R*)-**L3** as the ligand	trace	/
13[d,e]	**C1** as the Ir catalyst	trace	/
14[d,e]	without $BF_3.Et_2O$	0	/
15[d,e]	without Ir or (*R*)-**L1**	0	/

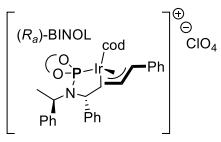
[a] The reaction was performed with **1a** (0.2 mmol), **2a** (0.3 mmol), $[Ir(COD)Cl]_2$ (2.5 mol%), (*R*)-**L1** (10 mol%), $BF_3.Et_2O$ (30 mol%) in toluene (2.0 mL). [b] The isolated yield of **3aa**. [c] Determined by chiral HPLC. [d] The reaction was performed at 10 °C with 50 mol% of $BF_3.Et_2O$. [e] 1.2 equiv. of **2a** and 4.0 mL of toluene were used.



(*R*)-**L2**

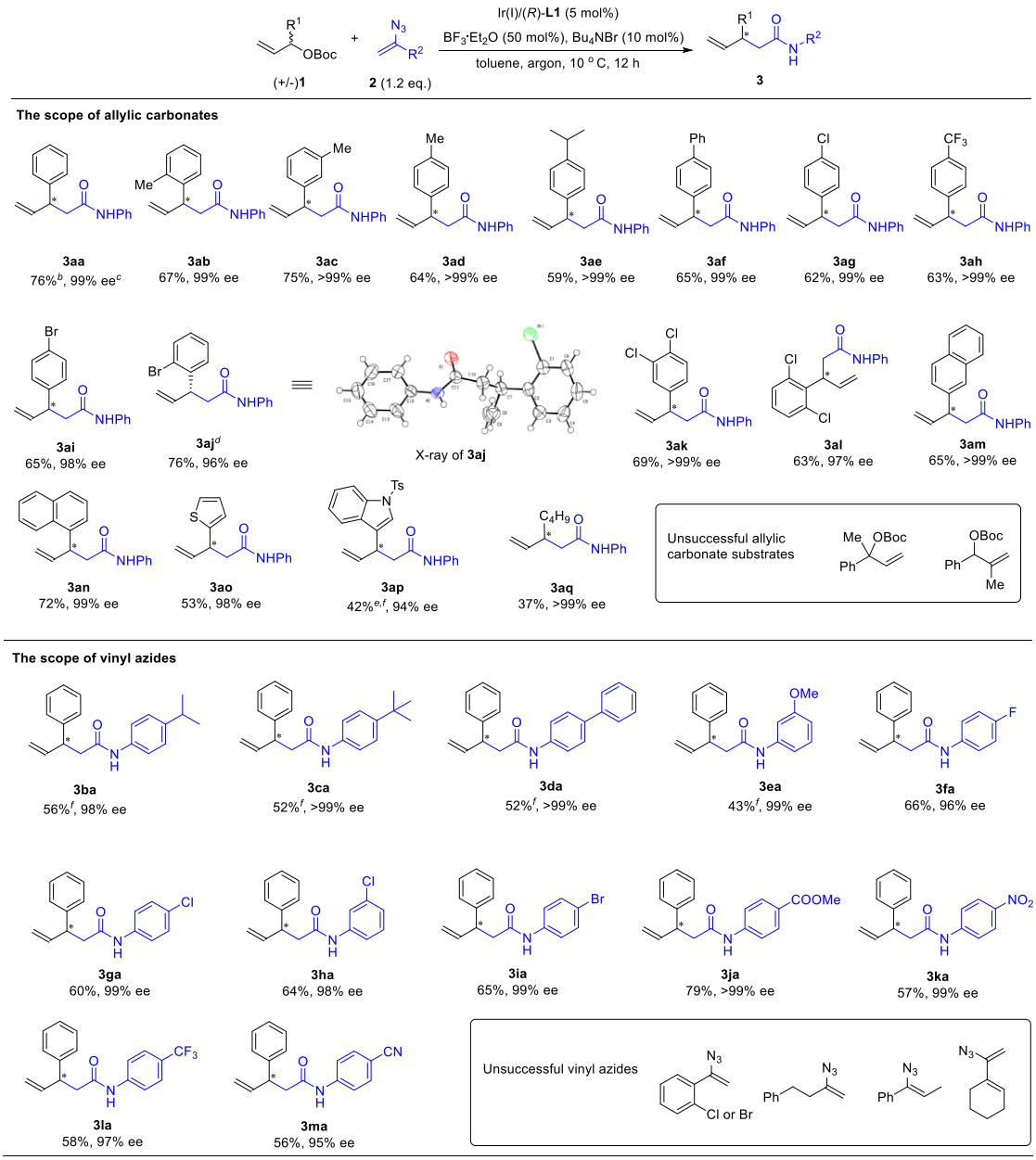


(*R*)-**L3**



C1

Table 2. Synthesis of Enantioenriched β-Substituted γ,δ-Unsaturated Amides[a]

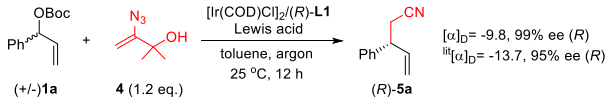


[a] The reaction was performed with **1** (0.20 mmol), **2** (0.24 mmol), $[Ir(COD)Cl]_2$ (2.5 mol%), (*R*)-**L1** (10 mol%), $BF_3.Et_2O$ (50 mol%) and Bu_4NBr (10 mol%) in toluene (4.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC. [d] The absolute configuration of **3aj** was confirmed by the X-ray diffraction (CCDC 1950457). [e] The reaction was performed at 35 °C. [f] The dosage of vinyl azide **2** was 0.30 mmol.

Next, the method was applied to synthesize chiral nitriles with α-hydroxypropan-2-yl substituted vinyl azide (**4**)[15] as acetonitrile carbanion surrogate. Initially, the coupling of **1a** and **4** failed with the standard conditions of Table 2. None of product was formed, while both substrates were decomposed. (entry 1, Table 3) The effect of Lewis acid was then evaluated and zinc salts were found to promote the reaction. (entries 3, 6 and 9) The strong Lewis acids would decompose the vinyl azide to erode the yield (entries 2 and 4), while the weak Lewis acids couldn't facilitate the catalytic process (entries 5 and 8). Finally, the reaction, promoted both by $ZnBr_2$ (15 mol%) and Ir/(*R*)-**L1** (5 mol%), gave the enantiopure (*R*)-3-phenylpent-4-enenitrile (**5a**) in excellent yield (entry 10), the absolute configuration determined by the comparison of its specific rotation with that in the literature.[16] Under the optimized reaction conditions ($ZnCl_2$ or $ZnBr_2$ as the Lewis acid), an array of racemic aryl-substituted allylic carbonates were efficiently transformed into enantiopure β-(hetero)aryl pent-4-enenitriles. As depicted in Table 4, a wide range of functional groups, including alkyl, alkynyl, aryl, halo, carbonyl, carbonate, on the aryl units of allylic carbonates were tolerated and provided the enantioenriched homoallylic nitriles (**5b**-**5p**) in moderate to high yields with excellent ees. Meanwhile, fused ring- (α- or β-naphthyl) and hetero-aryl (3-thienyl or 3-indolyl) substituted allylic carbonates were readily transformed into

nearly enantiopure nitriles. (**5q**-**5t**) Although the alkoxyl(MeO or BnO)-aryl derived allylic carbonate was unstable and unable to provide the desired product, the corresponding allylic alcohol was appropriate to participate in the catalytic asymmetric coupling (the transformation of **13** into **14** in the Scheme 2). To the best of our knowledge, this is the first catalytic method for asymmetric synthesis of β-substituted pent-4-enenitriles, which are difficult to prepare through other methods, for example unavailable by enantioselective allylation of acetonitrile or asymmetric conjugated addition of α,β-unsaturated nitriles.[17]

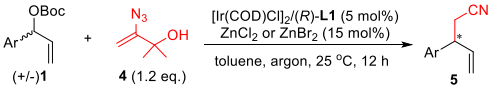
Table 3. The Enantioselective Coupling Reaction of α-Hydroxypropan-2-yl Substituted Vinyl Azide (4)[a]

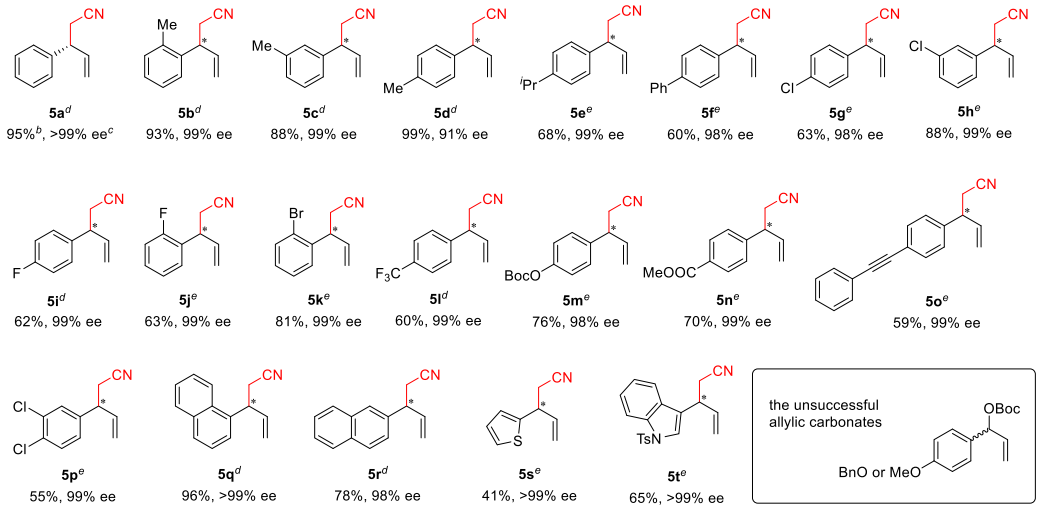


Entry	Lewis acid	yield (%)[b]	ee (%)[c]	Entry	Lewis acid	yield (%)[b]	ee (%)[c]
1	$BF_3.Et_2O$	trace	nd	6	$ZnCl_2$	86	99
2	$Sc(OTf)_3$	trace	nd	7	$InCl_3$	69	99
3	$Zn(OTf)_2$	45	99	8	$MgCl_2$	n.r.	--
4	$In(OTf)_3$	38	99	9	$ZnBr_2$	93	98
5	$Mg(OTf)_2$	8	--	10[d]	$ZnBr_2$	95	99

[a] The reaction was performed with **1** (0.20 mmol), **4** (0.24 mmol), $[Ir(COD)Cl]_2$ (2.5 mol%), (*R*)-**L1** (10 mol%) and the Lewis acid (10 mol%) in toluene (2 mL). [b] The isolated yield. [c] Determined by chiral HPLC. [d] 15 mol% of $ZnBr_2$ was used.

Table 4. Synthesis of Enantioenriched β-Substituted γ,δ-Unsaturated Nitriles [a]



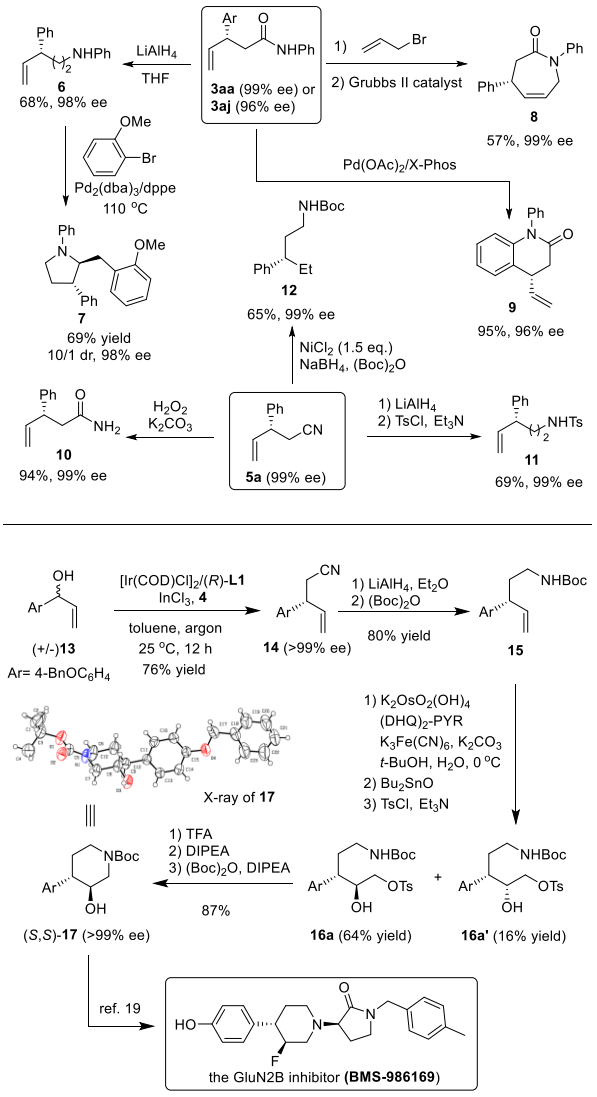


[a] The reaction was performed with **1** (0.20 mmol), **4** (0.24 mmol), $[Ir(COD)Cl]_2$ (2.5 mol%), (*R*)-**L1** (10 mol%) and the Lewis acid (15 mol%) in toluene (2 mL). [b] The isolated yield. [c] Determined by chiral HPLC. [d] $ZnCl_2$ as the Lewis acid. [e] $ZnBr_2$ as the Lewis acid.

To demonstrate the utility of this catalytic approach, synthetic transformations of products were carried out. (Scheme 2) The reduction of enantiopure **3aa** by $LiAlH_4$ enabled access to *N*-phenyl pent-4-enylamine (**6**) (68% yield, 98% ee), which underwent an intramolecular alkene-carboamination to obtain 2,3-bissubstituted pyrrolidine (**7**) in moderate yield with excellent stereoselectivity. The sequential *N*-allylation and ring-closing metathesis was successful to transform **3aa** into a seven membered lactam **8** in 57% yield and 99% ee. In addition, a Pd-catalyzed intramolecular cyclization of **3aj** via the C-N bond formation was demonstrated to obtain 3,4-dihydroquinolinone (**9**) in 95% yield with no detriment to the enantiomeric excess. Enantioenriched homoallylic nitrile products were readily transformed into important N-containing building blocks. For example, the enantiopure **5a** underwent the hydrolysis, in the presence of hydrogen peroxide and base,[8] to afford free amide **10** in high yield and conservation of enantiomeric excess. The selective reduction of **5a** by $LiAlH_4$ gave **11** without loss of ee value. Meanwhile, the Ni-mediated

reduction system enable hydrogenation of both cyano and alkenyl moieties to afford **12** in moderate yield with excellent ee.

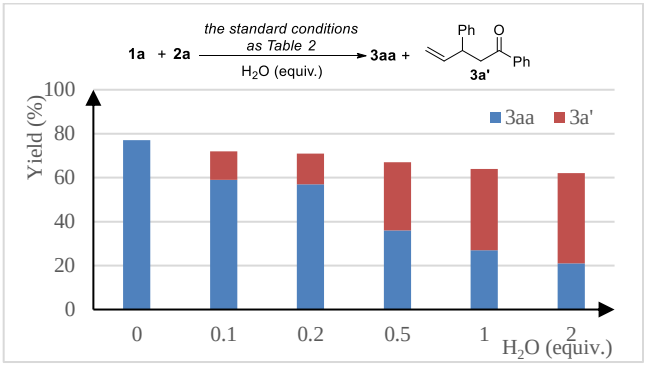
Scheme 2. Synthetic Transformations of Products



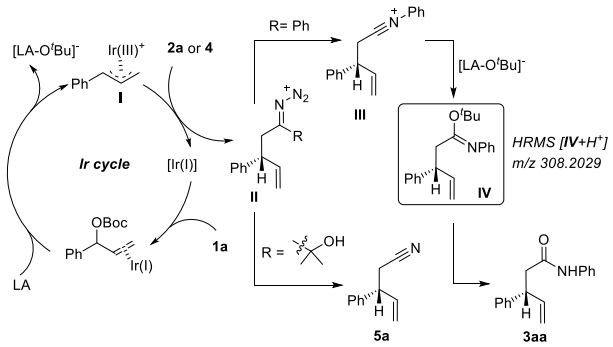
Moreover, the asymmetric method was successfully applied to prepare a potent GluN2B inhibitor (**BMS-986169**), which is used to treat major depressive disorder.[18] The previous synthetic method for this chiral molecule relies on chiral HPLC resolution of the racemic piperidine intermediate.[19] Herein, the first asymmetric and formal synthetic protocol was realized. The synthetic route began with the (*R*)-**L1**/Ir-catalyzed allylic coupling with 1-(4-(benzyloxy)phenyl)prop-2-en-1-ol (**13**) as the allylic electrophile, due to the incompetence of corresponding allylic carbonate. Fortunately, the catalytic reaction proceeded smoothly with $InCl_3$ as the Lewis acid and afforded the enantiopure homoallylic nitrile (**14**) in 76% yield. And the *N*-Boc homoallylic amine (**15**) was obtained through a $LiAlH_4$ reduction and *N*-Boc protection sequence in 80% yield. Followed by the asymmetric Sharpless dihydroxylation[20] and then the selective sulfonylation of primary hydroxyl group,[21] both **16a** and **16a'** were given with moderate ratio (4/1). The mixture could be separated by column chromatography to afford the desired isomer (**16a**) in 64% yield. Finally, a sequential three-step transformation of **16a** successfully gave the enantiopure **17** in high yield.[22] The absolute configuration of (*S,S*)-**17** was confirmed by the X-ray diffraction (CCDC 2012123) and found consistent with that of the target.[19]

Mechanistic Considerations. The mechanism was proposed to explain chemo- and stereoselectivity of the catalytic coupling reaction. (Scheme 3) In the presence of Lewis acid (i.e. $BF_3{\cdot}OEt_2$ or Zn(II) salt), the chiral Ir(I) complex activates allylic carbonate (**1a**) through oxidative addition to form an Ir(III) intermediate (**I**) and [LA-O^{t}Bu]$^-$. An enantioselective C-C bond coupling of **I** and vinyl azide follows to generate enantioenriched iminodiazonium ion (**II**). When bearing a 2-hydroxypropan-2-yl group at the α position (i.e., from **4**), the intermediate **II** undergoes a fragmentation process to give **5a**. When R is a phenyl group, the 1,2-phenyl migration (Schmidt rearrangement) leads to the highly reactive nitrilium ion (**III**), the latter immediately trapped by [LA-O^{t}Bu]$^-$ to form *tert*-butyl imidate (**IV**)[23] or directly hydrolyzed to the amide product. High resolution mass spectrum (HRMS) study on the reaction system indicated a major species matching the imidate intermediate **IV** with a proton. (For the detail, see SI) And the control experiment demonstrated that trace of water would lead to the ketone product (**3a'**) formation (Chart 1), probably via direct hydrolysis of the iminodiazonium intermediate **II**. These results indicate that, in the coupling reaction of α-aromatic-substituted vinyl azides and allyl *tert*-butyl carbonates, the desired amide products are obtained through the Schmidt rearrangement/alcoholysis pathway.

Chart 1. Water Effect on the Coupling Reaction



Scheme 3. A Proposed Mechanism



CONCLUSIONS

In summary, vinyl azides were explored in the transition metal-catalyzed coupling reaction, for the first time, as the equivalent of acetamide enolate and acetonitrile carbanion. The amide/nitrile moiety and the chiral center were generated simultaneously in a single step. The utility of products was demonstrated through transformations into several pharmaceutical cores, including chiral pyrrolidine and piperidine (the key intermediate of **BMS-986169**). Preliminary evidence suggests that the nitrilium ion (**IV**) is trapped by an alkoxyl group (i.e. -O^{t}Bu) en route to the desired amide products. The method complements significantly the catalytic asymmetric alkylation reactions with vinyl azides.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization data are available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* cao_peng@outlook.com

Author Contributions

‡These authors contributed equally.

ACKNOWLEDGMENT

We thank the NSFC (grant No. 21572218, 21901176 and 21901177) for financial support. The authors also thank Prof. Zhang-Jie Shi (University of Fudan) and Dr Gregory Perry (University of Manchester) for helpful comments.

REFERENCES

(1) Selected reviews: (a) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwies, M.; Weihofen, R. Iridium-catalysed asymmetricallylic substitutions. *Chem. Commun.* **2007**, 675-691. (b) Liu, W.-B.; Xia, J.-B.; You, S.-L. Iridium-catalyzed asymmetric allylic substitutions: U. Kazmaier in transition metal catalyzed enantioselective allylic substitution in organic synthesis. Topics in organometallic chemistry, 38, Springer, Berlin, Heidelberg, **2011**. (c) Zhuo, C.-X.; Zheng, C.; You, S.-L. Transition-metal-catalyzed asymmetric allylic dearomatization reactions. *Acc. Chem. Res.* **2014**, *47*, 2558-2573. (d) Qu, J.; Helmchen, G. Applications of iridium-catalyzed asymmetric allylic substitution reactions in target-oriented synthesis. *Acc. Chem. Res.* **2017,** *50*, 2539-2555. (e) Wan, L.; Tian, L.; Liu, J.; Niu, D. Iridium-catalyzed asymmetric umpolung allylation of *N*-fluorenyl imines to prepare 1,4-disubstituted homoallylic Aamines. *Synlett* **2017,** *28*, 2051-2056. (f) Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. Intermolecular stereoselective iridium-catalyzed allylic alkylation: An evolutionary account. *Synlett* **2018,** *29*, 2481-2492. (g) Rössler, S. L.; Petrone, D. A.; Carreira, E. M. Iridium-catalyzed asymmetric synthesis of functionally rich molecules enabled by (phosphoramidite,olefin) ligands. *Acc. Chem. Res.* **2019,** *52*, 2657-2672. (h) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-catalyzed asymmetric allylic substitution reactions. *Chem. Rev.* **2019,** *119*, 1855-1969.

(2) (a) Takeuchi, R.; Kashio, M. Highly selective allylic alkylation with a carbon nucleophile at the more substituted allylic terminus catalyzed by an iridium complex: An efficient method for constructing quaternary carbon centers. *Angew. Chem. Int. Ed.* **1997,** *36*, 263-265. (b) Janssen, J. P.; Helmchen, G. First enantioselective alkylations of monosubstituted allylic acetates catalyzed by chiral iridium complexes. *Tetrahedron Lett.* **1997**, *38*, 8025-8026.

(3) For selective examples of malonic acid derivatives as pronucleophiles, see: (a) Kinoshita, N.; Marx, K. H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. Enantioselective allylic substitution of cinnamyl esters catalyzed by iridium–chiral aryl phosphite complex: Conspicuous change in the mechanistic spectrum by a countercation and solvent. *J. Org. Chem.* **2004,** *69*, 7960-7964. (b) Alexakis, A.; Polet, D. Very Efficient Phosphoramidite ligand for asymmetric iridium-catalyzed allylic alkylation. *Org. Lett.* **2004,** *6*, 3529-3532. (c) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. Phosphoramidite ligands in iridium-catalyzed allylic substitution. *Chem.-Eur. J.* **2006,** *12*, 3596-3609. (d) Lipowsky, G.; Miller, N.; Helmchen, G. Regio-and enantioselective iridium-catalyzed allylic alkylation with in situ activated P, C-chelate complexes. *Angew. Chem. Int. Ed.* **2004,** *43*, 4595-4597. (e) Schelwies, M.; Dübon, P.; Helmchen, G. Enantioselective modular synthesis of 2, 4-disubstituted cyclopentenones by iridium-catalyzed allylic alkylation. *Angew. Chem. Int. Ed.* **2006,** *45*, 2466-2469. (f) Giacomina, F.; Riat, D.; Alexakis, A. ω-Ethylenic allylic substrates as alternatives to cyclic substrates in copper-and iridium-catalyzed asymmetric allylic alkylation. *Org. Lett.* **2010,** *12*, 1156-1159. (g) Xia, J.; Zhuo, C.; You, S. Synthesis of cyclopropane-containing building blocks via Ir-catalyzed enantioselective allylic substitution reaction. *Chin. J. Chem.* **2010,** *28*, 1525-1528. (h) Peng, F.; Hall, D. G. Preparation of α-substituted allylboronates by chemoselective iridium-catalyzed asymmetric allylic alkylation of 1-propenylboronates. *Tetrahedron Lett.* **2007,** *48*, 3305-3309. (i) Butcher, T. W.; Hartwig, J. F. Enantioselective synthesis of tertiary allylic fluorides by iridium-catalyzed allylic fluoroalkylation. *Angew. Chem., Int. Ed.* **2018,** *130*, 13125-13129. For selective examples of malononitrile and masked acyl cyanide as pronucleophiles, see: (j) Foerster, S.; Tverskoy, O.; Helmchen, G. Malononitrile as acylanion equivalent. *Synlett* **2008,** *2008*, 2803-2806. (k) Shockley, S. E.; Hethcox, J. C.; Stoltz, B. M. Enantioselective synthesis of acyclic α-quaternary carboxylic acid derivatives through iridium-catalyzed allylic alkylation. *Angew. Chem. Int. Ed.* **2017,** *56*, 11545-11548. (l) Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. Enantioselective synthesis of vicinal all-carbon quaternary centers via iridium-catalyzed allylic alkylation. *Angew. Chem. Int. Ed.* **2018,** *57*, 8664-8667. For sulfonylacetic esters and disulfones as pronucleophiles, see: (m) Gärtner, M.; Satyanarayana, G.; Förster, S.; Helmchen, G. Syntheses of the hexahydroindene cores of indanomycin and stawamycin by combinations of iridium-catalyzed asymmetric allylic alkylations and intramolecular diels–alder reactions. *Chem.-Eur. J.* **2013,** *19*, 400-405. (n) Liu, W.-B.; Zheng, S.-C.; He, H.; Zhao, X.-M.; Dai, L.-X.; You, S.-L. Iridium-catalyzed regio- and enantioselective allylic alkylation of fluorobis (phenylsulfonyl) methane. *Chem. Commun.* **2009**, 6604-6606. (o) Chen, J.; Zhao, X.; Dan, W. Diasteroselective and enantioselective Ir-catalyzed allylic substitutions of 1-substituted 1-fluoro-1-(arenesulfonyl) methylene derivatives. *J. Org. Chem.* **2017,** *82*, 10693-10698. For selective examples of prochiral stabilized enolates as pronucleophiles, see: (p) Chen, W.; Hartwig, J. F. Control of diastereoselectivity for iridium-catalyzed allylation of a prochiral nucleophile with a phosphate counterion. *J. Am. Chem. Soc.* **2013,** *135*, 2068-2071. (q) Chen, W.; Hartwig, J. F. Cation control of diastereoselectivity in iridium-catalyzed allylic substitutions. Formation of enantioenriched tertiary alcohols and thioethers by allylation of 5H-oxazol-4-ones and 5H-thiazol-4-ones. *J. Am. Chem. Soc*. **2014**, *136,* 377-382. (r) Liu, W.-B.; Reeves, C. M.; Virgil, S. C.; Stoltz, B. M. Construction of vicinal tertiary and all-carbon quaternary stereocenters via Ir-catalyzed regio-, diastereo-, and enantioselective allylic alkylation and applications in sequential Pd catalysis. *J. Am. Chem. Soc.* **2013,** *135*, 10626-10629. (s) Liu, W.-B.; Reeves, C. M.; Stoltz, B. M. Enantio-, diastereo-, and regioselective iridium-catalyzed asymmetric allylic alkylation of acyclic β-ketoesters. *J. Am. Chem. Soc*. **2013**, *135*, 17298-17301. (t) Liu, W.-B.; Okamoto, N.; Alexy, E. J.; Hong, A. Y.; Tran, K.; Stoltz, B. M. Enantioselective γ-alkylation of α, β-unsaturated malonates and ketoesters by a sequential Ir-catalyzed asymmetric allylic alkylation/cope

rearrangement. *J. Am. Chem. Soc*. **2016**, *138*, 5234-5237. (u) Hethcox, J. C.; Shockley, S. E.; Stoltz, B. M. Iridium-catalyzed stereoselective allylic alkylation reactions with crotyl chloride. *Angew. Chem. Int. Ed.* **2016,** *55*, 16092-16095. (v) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. Enantio-and diastereodivergent dual catalysis: α-Allylation of branched aldehydes. *Science* **2013,** *340*, 1065-1068. (w) Jiang, X.; Boehm, P.; Hartwig, J. F. Stereodivergent allylation of azaaryl acetamides and acetates by synergistic iridium and copper catalysis. *J. Am. Chem. Soc.* **2018**, *140*, 1239-1242. For selective examples of imine fluorene and esters as pronucleophiles, see: (x) Liu, J.; Cao, C.-G.; Sun, H.-B.; Zhang, X.; Niu, D. Catalytic asymmetric umpolung allylation of imines. *J. Am. Chem. Soc.* **2016**, *138*, 13103-13106. (y) Wei, L.; Zhu, Q.; Xu, S.-M.; Chang, X.; Wang, C.-J. Stereodivergent synthesis of α, α-disubstituted α-amino acids via synergistic Cu/Ir catalysis. *J. Am. Chem. Soc*. **2018**, *140,* 1508-1513. (z) Huo, X.; Zhang, J.; Fu, J.; He, R.; Zhang, W. Ir/Cu dual catalysis: enantio-and diastereodivergent access to α, α-disubstituted α-amino acids bearing vicinal stereocenters. *J. Am. Chem. Soc*. **2018,** *140*, 2080-2084.

(4) Selected examples: (a) Graening, T.; Hartwig, J. F. Iridium-catalyzed regio-and enantioselective allylation of ketone enolates. *J. Am. Chem. Soc.* **2005**, *127*, 17192-17193. (b) Chen, M.; Hartwig, J. F. Iridium-catalyzed enantioselective allylic substitution of unstabilized enolates derived from α, β-unsaturated ketones. *Angew. Chem. Int. Ed.* **2014**, *53*, 8691-8695. (c) Chen, M.; Hartwig, J. F. Iridium-catalyzed enantioselective allylic substitution of enol silanes from vinylogous esters and amides. *J. Am. Chem. Soc.* **2015**, *137*, 13972-13979. (d) Liang, X.; Wei, K.; Yang, Y.-R. Iridium-catalyzed enantioselective allylation of silyl enol ethers derived from ketones and α, β-unsaturated ketones. *Chem. Commun.* **2015**, *51*, 17471-17474. (e) Jiang, X.; Hartwig, J. F. Iridium-catalyzed enantioselective allylic substitution of aliphatic esters with silyl ketene acetals as the ester enolates. *Angew. Chem. Int. Ed.* **2017**, *56*, 8887-8891.

(5) (a) He, H.; Zheng, X.-J.; Li, Y.; Dai, L.-X.; You, S.-L. Ir-catalyzed regio-and enantioselective decarboxylative allylic alkylations. *Org. Lett.* **2007,** *9*, 4339-4341. (b) Liu, X.-J.; Jin, S.; Zhang, W.-Y.; Liu, Q.-Q.; Zheng, C.; You, S.-L. Sequence-dependent stereodivergent allylic alkylation/fluorination of acyclic ketones. *Angew. Chem. Int. Ed.* **2020**, *59*, 2039-2043.

(6) (a) Sempere, Y.; Carreira, E. M. Trimethyl orthoacetate and ethylene glycol mono-vinyl ether as enolate surrogates in enantioselective iridium-catalyzed allylation. *Angew. Chem.* **2018,** *130*, 7780-7784. (b) Sempere, Y.; Alfke, J. L.; Rössler, S. L.; Carreira, E. M. Morpholine ketene aminal as amide enolate surrogate in iridium-catalyzed asymmetric allylic alkylation. *Angew. Chem.* **2019,** *131*, 9637-9641.

(7) (a) Rappoport, Z. The chemistry of the cyano group, Wiley, London, 1970. (b) "Supplement C: The Chemistry of Triple-Bonded Functional Groups, Part 2": A. J. Fatiadi in The Chemistry of Functional Groups (Eds.: Z. Pappoport, S. Patai), Wiley, London, **1983**, p. 1057. (c) Fleming, F. Nitrile-containing natural products. *Nat. Pro. Rep.* **1999,** *16*, 597-606. (d) Greenberg, A.; Breneman, C. M.; Liebman, J. F. The amide linkage: structural significance in chemistry, bio-chemistry, and materials science. Wiley-Interscience, New York, **2000**. (e) Fleming, F. F.; Wang, Q. Unsaturated nitriles: conjugate additions of carbon nucleophiles to a recalcitrant class of acceptors. *Chem. Rev.* **2003,** *103*, 2035-2078. (f) Fleming, F. F.; Yao, L.; Ravikumar, P.; Funk, L.; Shook, B. C. Nitrile-containing pharmaceuticals: efficacious roles of the nitrile pharmacophore. *J. Med. Chem.* **2010,** *53*, 7902-7917. (g) López, R.; Palomo, C. Cyanoalkylation: alkylnitriles in ctalytic C-C bond-forming reactions. *Angew. Chem. Int. Ed.* **2015,** *54*, 13170-13184. (h) Pitzer, J.; Steiner, K. Amides in nature and biocatalysis. *J. Biotechnol.* **2016**, *235*, 32.

(8) (a) Zhang, K; Peng, Q.; Hou, X. L.; Wu, Y. D. Highly enantioselective palladium-catalyzed alkylation of acyclic amides. *Angew. Chem. Int. Ed.* **2008**, *47*, 1741-1744. (b) Trost. B. M.; Michaelis, D. J.; Charpentier, J.; Xu, J. Palladium-catalyzed allylic alkylation of carboxylic acid derivatives: *N*-acyloxazolinones as ester enolate equivalents. *Angew. Chem. Int. Ed.* **2012**, *51*, 204-208. (c)Turnbull, B. W.; Evans, P. A. Enantioselective rhodium-catalyzed allylic substitution with a nitrile anion: construction of acyclic quaternary carbon stereogenic centers. *J. Am. Chem. Soc.* **2015,** *137*, 6156-6159.

(9) Bordwell, F. G. Equilibrium acidities in dimethyl sulfoxide solution. *Acc. Chem. Res.* **1988,** *21*, 456-463.

(10) Bai, D. C.; Liu, X. Y.; Li, H.;Ding, C. H.; Hou, X. L. Tandem thorpe reaction/palladium catalyzed asymmetric allylic alkylation: Access to chiral β-enaminonitriles with excellent enantioselectivity. *Chem.–Asian J.* **2017,** *12*, 212-215.

(11) Selected reviews: (a) Jung, N.; Bräse, S. Vinyl and alkynyl azides: well-known intermediates in the focus of modern synthetic methods. *Angew. Chem. Int. Ed.* **2012,** *51*, 12169-12171. (b) Hu, B.; DiMagno, S. G. Reactivities of vinyl azides and their recent applications in nitrogen heterocycle synthesis. *Org. Biomol. Chem.* **2015,** *13*, 3844-3855. (c) Fu, J.; Zanoni, G.; Anderson, E. A.; Bi, X. α-Substituted vinyl azides: an emerging functionalized alkene. *Chem. Soc. Rev.* **2017,** *46*, 7208-7228. (d) Hayashi, H.; Kaga, A.; Chiba, S. Application of vinyl azides in chemical synthesis: A recent update. *J. Org. Chem.* **2017**, *82*, 11981-11989.

(12) (a) Hassner, A.; Ferdinandi, E. S.; Isbister, R. J. Stereochemistry. XLVII. Hydrolysis of vinyl azides. Comparison with the Schmidt reaction. *J. Am. Chem. Soc.* **1970,** *92*, 1672-1675. (b) Zhang, F. L.; Wang, Y. F.; Lonca, G. H.; Zhu, X.; Chiba, S. Amide synthesis by nucleophilic attack of vinyl azides. *Angew. Chem. Int. Ed.* **2014,** *53*, 4390-4394. (c) Zhang, F.-L.; Zhu, X.; Chiba, S. Tf_2NH-catalyzed amide synthesis from vinyl azides and alcohols. *Org. Lett.* **2015,** *17*, 3138-3141. (d) Zhang, Z.; Kumar, R. K.; Li, G.; Wu, D.; Bi, X. Synthesis of 4-ynamides and cyclization by the vilsmeier reagent to dihydrofuran-2 (3-H)-ones. *Org. Lett.* **2015,** *17*, 6190-6193. (e) Lin, C.; Shen, Y.; Huang, B.; Liu, Y.; Cui, S. Synthesis of amides and nitriles from vinyl azides and p-quinone methides. *J. Org. Chem*. **2017,** *82*, 3950-3956. (f) Rasool, F.; Ahmed, A.; Hussain, N.; Yousuf, S. K.; Mukherjee, D. One-pot regioselective and stereoselective synthesis of C-glycosyl amides from glycals using vinyl azides as glycosyl acceptors. *Org. Lett.* **2018,** *20*, 4036-4039.

(13) Selected examples: (a) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. Iridium-catalyzed enantioselective allyl–alkene coupling. *J. Am. Chem. Soc.* **2014,** *136*, 3006-3009. (b) Liu, X. J.; Zheng, C.; Yang, Y. H.; Jin, S.; You, S. L. Iridium-catalyzed asymmetric allylic aromatization reaction. *Angew. Chem. Int. Ed.* **2019,** *58*, 10493-10499.

(14) (a) Bartels, B.; Yebra, C. G. a.; Rominger, F.; Helmchen, G. Iridium-catalysed allylic substitution: stereochemical aspects and isolation of Ir^{III} complexes related to the catalytic cycle. *Eur. J. Inorg. Chem* **2002,** *2002*, 2569-2586. (b) Bartels, B.; García-Yebra, C.; Helmchen, G. Asymmetric Ir^{I}-catalysed allylic alkylation of monosubstituted allylic acetates with phosphorus amidites as ligands. *Eur. J. Org. Chem.* **2003,** *2003*, 1097-1103.

(15) A concise synthetic method towards 2-azidoallyl alcohols was reported by Bi and co-workers: Liu, Z.; Liu, J.; Zhang, L.; Liao, P.; Song, J.; Bi, X. Silver (I)-catalyzed hydroazidation of ethynyl carbinols: synthesis of 2-azidoallyl alcohols. *Angew. Chem. Int. Ed.* **2014,** *53*, 5305-5309.

(16) Matsunami, A.; Takizawa, K.; Sugano, S.; Yano, Y.; Sato, H.; Takeuchi, R. Synthesis of chiral homoallylic nitriles by iridium-catalyzed allylation of cyanoacetates. *J. Org. Chem.* **2018**, *83*, 12239-12246.

(17) Chong, Q.; Yue, Z.; Zhang, S.; Ji, C.; Cheng, F.; Zhang, H.; Hong, X.; Meng, F. *N*-Heterocyclic carbene–Cu-catalyzed enantioselective conjugate additions with alkenylboronic esters as nucleophiles. *ACS Catalysis* **2017**, *7*, 5693-5698.

(18) (a) King, D.; Thompson, L. A., III; Shi, J.; Thangathirupathy, S.; Warrier, J. S.; Islam, I.; Macor, J. E. (Bristol-Myers Squibb Company, Princeton, NJ, USA). Selective NR2B antagonists. U.S. Pat. Appl. Pub. US 20150191452 A1, 2015. (b) Thompson, L. A., III; Macor, J. E. (Bristol-Myers Squibb Company, Princeton, NJ, USA). (*R*)-3-((3*S*,4*S*)-3-Fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one and its prodrugs for the treatment of psychiatric disorders. U.S. Pat. Appl. Pub. US 20150191496 A1,

2015. (c) Bristow, L. J.; Gulia, J.; Weed, M. R.; Srikumar, B. N.; Li, Y.-W.; Graef, J. D.; Naidu, S.; Sanmathi, C.; Aher, T.; Bastia; Paschapur, M.; Kalidindi, N.; Kumar, K. V.; Molski, T.; Pieschl, R.; Fernandes, A.; Brown, J.; Sivarao, D. V.; Newberry, K.; Bookbinder, M.; Polino, J.; Keavy, D.; Newton, A.; Shields, E.; Simmermacher, J.; Kempson, J.; Li, J.; Zhang, H.; Mathur, A.; Kallem, R. R.; Sinha, M.; Ramarao, M.; Vikramadithyan, R. K.; Thangathirupathy, S.; Warrier, J.; Islam, I.; Bronson, J. J.; Olson, R. E.; Macor, J. E.; Albright, C. F.; Sinz, M.; King, D.; Thompson, L. A.; Marcin, L. R. Preclinical characterization of (*R*)-3-((3S,4S)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (BMS-986169), a novel, intravenous, glutamate *N*-methyl-D-aspartate 2B receptor negative allosteric modulator with potential in major depressive disorder. *J. Pharmacol. Exp. Ther.* **2017**, *363*, 377–393. (d) Marcin, L. R.; Warrier, J.; Thangathirupathy, S.; Shi, J.; Karageorge, G. N.; Pearce, B. C.; Ng, A.; Park, H.; Kempson, J.; Li, J.; Zhang, H.; Mathur, A.; Reddy, A. B.; Nagaraju, G.; Tonukunuru, G.; Gupta, G. V. R. K. M.; Kamble, M.; Mannoori, R.; Cheruku, S.; Jogi, S.; Gulia, J.; Bastia, T.; Sanmathi, C.; Aher, J.; Kallem, R.; Srikumar, B. N.; Vijaya, K. K.; Naidu, P. S.; Paschapur, M.; Kalidindi, N.; Vikramadithyan, R.; Ramarao, M.; Denton, R.; Molski, T.; Shields, E.; Subramanian, M.; Zhuo, X.; Nophsker, M.; Simmermacher, J.; Sinz, M.; Albright, C.; Bristow, L. J.; Islam, I.; Bronson, J. J.; Olson, R. E.; King, D.; Thompson, L. A.; Macor, J. E. BMS-986163, a negative allosteric modulator of GluN2B with potential utility in major depressive disorder. *ACS Med. Chem. Lett.* **2018**, *9*, 472–477.

(19) Kempson, J.; Zhang, H.; Wong, M. K. Y.; Li, J.; Li, P.; Wu, D.-R.; Rampulla, R.; Galella, M. A.; Dabros, M.; Traeger, S. C.; Muthalagu, V. Gupta, A.; Arunachalam, P. N.; Mathur, A. Evolution of a scale-up synthesis to a potent GluN2B inhibitor and its prodrug. *Org. Process Res. Dev.* **2018**, *22*, 846–855.

(20) (a) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. Improved enantioselectivity in asymmetric dihydroxylations of terminal olefins using pyrimidine ligands. *J. Org. Chem.* **1993**, *58*, 3785-3786. (b) Wang, Z.-M.; Sharpless, K. B. Asymmetric dihydroxylation of tertiary allylic alcohols. *Tetrahedron Lett.* **1993**, *34*, 8225-8228.

(21) (a) Shanzer, A. Metalloid derivatives for synthesis: monoderivatization of symmetric diols. *Tetrahedron Lett.* **1980**, *21*, 221-222. (b) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. Dibutyltin oxide catalyzed selective sulfonylation of α-chelatable primary alcohols. *Org. Lett.* **1999**, *1*, 447-450.

(22) Gao, X.; Zhang, Y. J.; Krische, M. J. Iridium-catalyzed *anti*-diastereo- and enantioselective carbonyl (α-trifluoromethyl)allylation from the alcohol or aldehyde oxidation level. *Angew. Chem. Int. Ed.* **2011**, *50*, 4173-4175.

(23) The highly reactive nitrilium ion has been trapped by the methanol to form methyl imidate, reported by Chiba in the ref. 13b.

SYNOPSIS TOC