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Enantioselective Rhodium-Catalyzed Allylation of Aliphatic Imines: Synthesis of Chiral C-Aliphatic Homoallylic Amines

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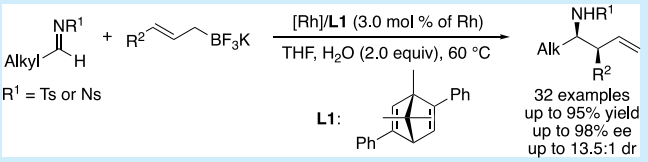
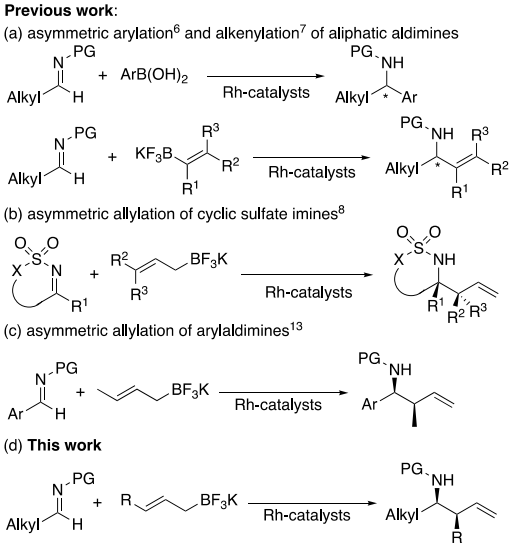
ABSTRACT: Reported herein is a method for the efficient syntheses of optically active 1-alkyl homoallylic amines in yields up to 95%, 13.5:1 dr, and 98% ee under mild, aqueous reaction conditions, via the Rh-catalyzed asymmetric allylation of aliphatic aldimines. This method provides a streamlined synthetic platform for the preparation of indolizidine and piperidine alkaloids, thus demonstrating its usefulness.



Since it was introduced by Tomioka[1a] and Hayashi,[1b] the rhodium-catalyzed asymmetric addition of organoboron reagents[2,3] to aldimines has proven to be a trustworthy route to chiral α-branched amines.[3−8] Aliphatic aldimines, compared to their aryl counterparts, have remained underexploited, primarily hampered by their intrinsically lower stability, their susceptibility to decomposition, self-condensation, and imine−enamine tautomerization. An advantage of these rhodium-catalyzed protocols is the mild reaction conditions,[5] which permit the arylation of challenging aliphatic aldimines employing an (*R*,*R*)-Deguphos,[6a] a chiral diene,[6b] and chiral bis(phosphoramidite) ligands (Scheme 1).[6c] Alkenyl boron reagents have also been found to be compatible prenucleophiles in the diastereoselective[7a,b] and enantioselective[7c] alkenylation of aliphatic aldimines. While these approaches are known to produce enantioenriched 1-aryl and 1-alkenyl alkylamines, similar allylation reactions to afford the corresponding homoallylic amines[8,9] remain unexplored.[10,11] Hence, developing the enantioselective allylation of aliphatic aldimines would be highly desirable to address this deficiency. We report herein on the first asymmetric allylation of aliphatic aldimines in the presence of rhodium/chiral bicyclo[2.2.1]heptadiene catalysts[12,13] to afford optically active C-aliphatic homoallylic amines and its use in the total syntheses of natural indolizidine and piperidine alkaloids.

Scheme 1. Rh-Catalyzed Asymmetric Addition of Organoboron Reagents to Imines



We first examined the asymmetric addition of potassium allyltrifluoroborate (**2a**) with the Ts-protected aldimine **1a** in the presence of 3 mol % of a catalyst generated *in situ* from $[RhCl(C_2H_4)_2]_2$ and the chiral diene ligand **L1** (Table 1). The desired adduct **3aa** was obtained in 18% yield with 88% ee in dioxane at 60 °C when no H_2O was added (entry 1),[13] with the formation of the α,β-unsaturated imine **4a**, derived from the self-condensation of **1a**, and **4a**-degradation accounting for the low product yield. While adding molecular sieves failed to improve the yield (entry 2),[6a] adding H_2O mitigated the formation of **4a**, with **3aa** being produced in up to 96% yield and 93% ee (entries 3 and 4). Among various solvents, THF (entry 6) was found to be optimal (entries 4−8) and was used in further investigations due to its comparatively low toxicity.[14] Using **L2**, an optimal ligand for the alkenylation of aryl aldimines,[4c] **3aa** was produced in only 29% yield with 70% ee (entry 9), but using **L3**, a well-known ligand for the arylation[1j] and allyation[13] of aryl aldimines, **3aa** was produced in 95%

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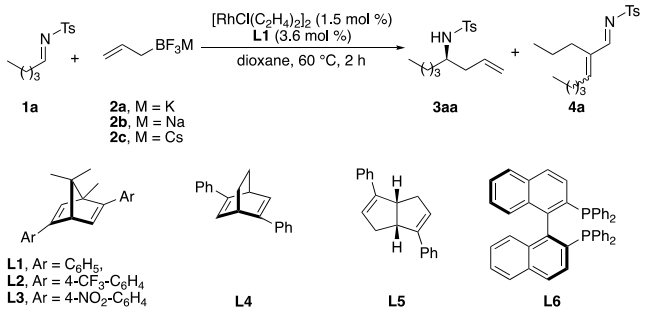
Table 1. Optimization for Asymmetric Allylation of 1a[a]



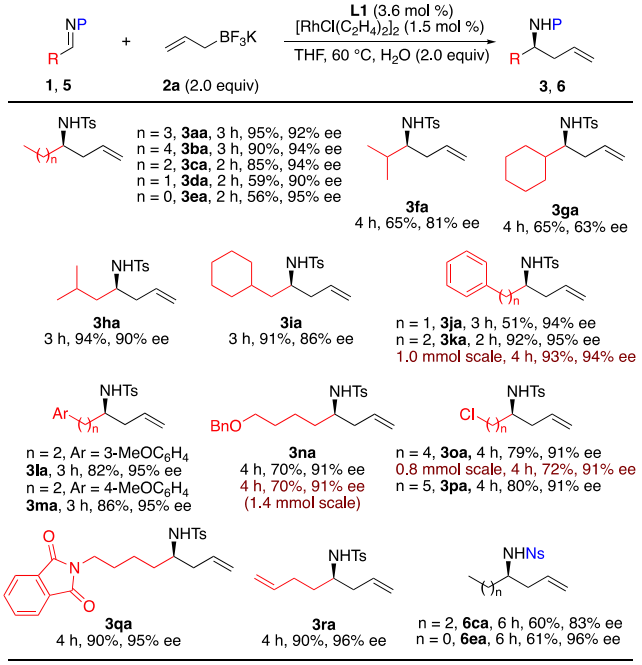
entry	variation from above conditions	yield (%)	ee (%)
1[b]	none	18	88
2	MS 4 Å (100 wt %) was added	36	89
3	H_2O (1.0 equiv) was added	86	92
4	H_2O (2.0 equiv) was added	96	93
5	Toluene instead of dioxane, 6.5 h	85	92
6	THF instead of dioxane, 3 h	95	92
7	DME instead of dioxane, 3 h	92	92
8	CH_3CN instead of dioxane, 1.5 h	83	90
9	**L2** instead of **L1** in THF, 6 h	29	70
10	**L3** instead of **L1** in THF, 3 h	95	92
11	**L4** instead of **L1** in THF, 15 h	27	−92
12	**L5** instead of **L1** in THF, 15 h	N.R.[c]	N.D.[d]
13	**L6** instead of **L1** in THF, 15 h	N.R.[c]	N.D.[d]
14	**2b** instead of **2a**, 17 h	23	84
15	**2c** instead of **2a**, 3 h	55	88

[a]Conditions: compound **1a** (0.2 mmol), **2a** (0.4 mmol), [RhCl-$(C_2H_4)_2]_2$ (1.5 mol %), **L** (3.6 mol %) in dioxane (1 mL). Isolated yields of **3aa** are reported. The ee values of **3aa** were determined by chiral HPLC analysis. [b]5% of **4a** was isolated. [c]No reaction. [d]Not determined.

yield and 92% ee (entry 10). The use of the bicyclo[2.2.2]-octadiene ligand **L4** gave **3aa** with −92% ee, but in only 27% yield (entry 11). In contrast, no reaction occurred in the cases of the bicyclo[3.3.0]octadiene ligand **L5** (entry 12) and (*S*)-BINAP (**L6**) (entry 13), indicating the critical nature of the catalytic activity and enantioselectivity of diene ligands in this transformation. Furthermore, using **2b** and **2c**,[15] sodium and cesium analogs of **2a** afforded **3aa** in only 23% yield with 84% ee and 55% yield with 88% ee, respectively (entries 14 and 15). Based on these optimal conditions, the scope of the reaction in THF with respect to aldimines was further examined (Scheme 2).

Aldimines prepared from ethanal, propanal, butanal, and hexanal afforded **3ba**−**3ea** in 56−90% yields and 90−95% ee. Although α-branched aldimines were unfavorable reaction partners, providing the adducts **3fa** and **3ga** both in 65% yield with 81% ee and 63% ee, respectively, β-branched congeners were compatibly producing adducts **3ha** and **3ia** in 94% and 91% yields with 90% and 86% ee. This high asymmetric induction is not limited to simple linear aliphatic aldimines containing no functionalities; substrates adorned with various functional groups on the aliphatic chain ranging from an aromatic ring, a benzyloxy group, a chloride, a phthalimido group, and an olefin also smoothly underwent allylation, providing **3ja**−**3ra** in 51−92% yields with 91−96% ee. No erosion of catalytic activity or enantioselectivity was observed when the reaction was carried out on a larger scale (for products **3ka**, **3na**, and **3oa**). Substrates bearing an Ns (4-

Scheme 2. Substrate Scope (I)[a]



[a]Conditions: **1** (P = Ts) and **5** (P = Ns, 4-NO_2-$C_6H_4SO_2$) (0.2 mmol), **2a** (0.4 mmol), [RhCl$(C_2H_4)_2]_2$ (1.5 mol %), **L1** (3.6 mol %), H_2O (2.0 equiv) in THF (1 mL) at 60 °C.

nitrophenylsulfonyl) group were tolerated, providing **6ca** and **6ea** in 60% and 61% yields with 83% and 96% ee, respectively.

In subsequent experiments, the addition reaction of potassium (*E*)-crotyl trifluoroborate ((*E*)-**2d**) with **1a** was examined (Scheme 3). The adducts were isolated in a combined yield of 91% with a 4.5/1 (*syn*-**7ad**/*anti*-**8ad**) diastereomeric ratio, and the major isomer *syn*-**7ad** was obtained in 95% ee. Conducting this reaction at 40 °C slightly enhanced the dr to 5.2/1, though in a lower yield (51%), without losing high enantioselectivity (94% ee). The crotylation of various aliphatic aldimines furnished the corresponding adducts in 44−87% yields with dr ranging from 5.0/1 to 13.5/1 and with 85−98% ee. The absolute configuration of the adduct *syn*-**7qd** was unambiguously determined by an X-ray crystallographic analysis to be (3*R*, 4*R*). Similarly, high enantioselectivity was observed in the allylation of (*E*)-**2e**, giving the *syn*-**7ke** in 97% ee. When (*Z*)-**2d** and (±)-**2f** were used in the crotylation reaction of **1a** at 60 °C, *syn*-**7ad** was produced as the major isomer (*syn*-**7ad**/*anti*-**8ad** 1.5/1 and 2.8/1; 92% and 94% ee, respectively). The reaction conducted at 40 °C using (*Z*)-**2d** afforded the *anti*-**8ad** (**7ad**/**8ad** 1/2.2) in 19% yield with 92% ee, whereas major *syn*-**7ad** was obtained (**7ad**/**8ad** 3.2/1) in 37% yield with 96% ee utilizing (±)-**2f**. Moreover, potassium allyl trifluoroborate **2g** underwent allylation with **1a** to give **7ag** in 52% yield and 94% ee.[16]

Syntheses of naturally occurring alkaloids were performed to demonstrate the synthetic applications of this protocol (Schemes 4−7). When the Ts-protected homoallylic amine **3na** was treated with $(Boc)_2O$ and Mg, it was smoothly transformed into the corresponding Boc-protected product **9**, which, on one-pot catalytic hydrogenation and hydrogenolysis, gave the amino alcohol **10** in high yield. The ensuing sequential steps involving mesylation and base mediated *N*-

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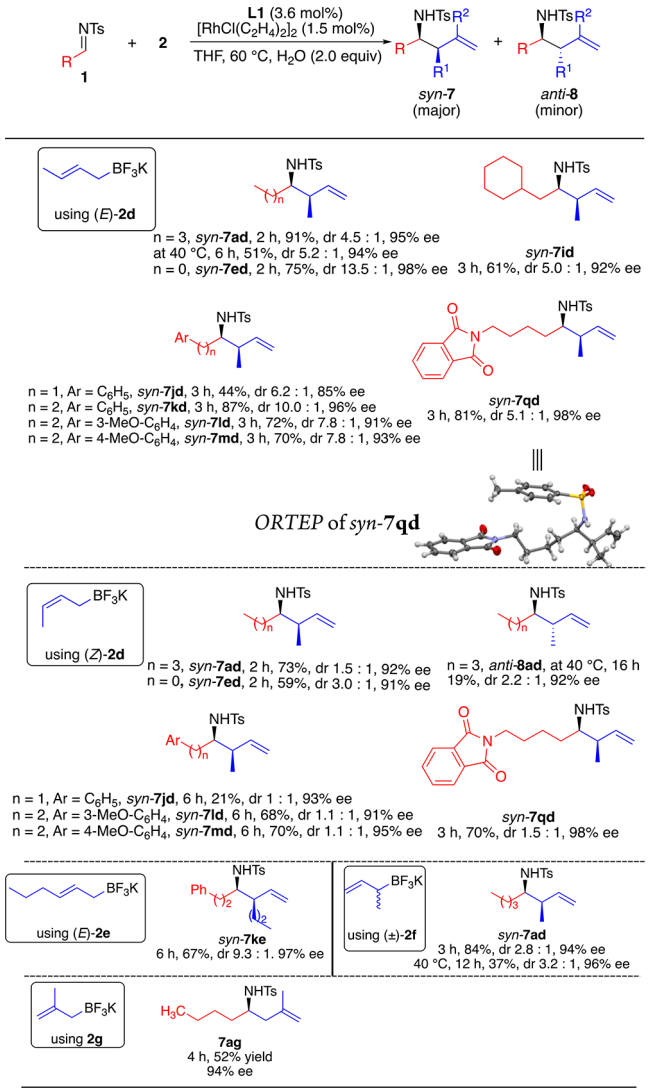
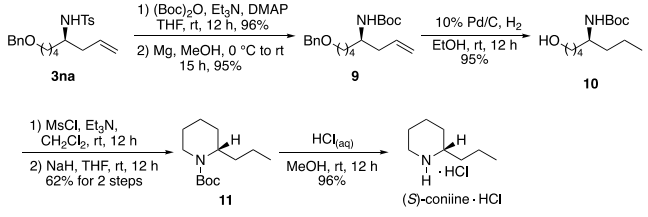
Scheme 3. Substrate Scope (II)[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $[RhCl(C_2H_4)_2]_2$ (1.5 mol %), **L1** (3.6 mol %), H_2O (7.2 μL) in THF (1 mL) at 60 °C. The ratio of **7** and **8** was determined by ^1H NMR analysis. The combined isolated yield of **7** and **8** is reported. The ee of the major diastereomer was determined by HPLC analysis.

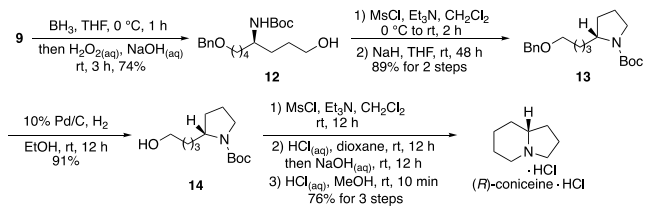
Scheme 4. Asymmetric Synthesis (*S*)-Coniine·HCl



cyclization provided the piperidine **11** in 62% yield from **10**. Removal of the Boc group under acidic conditions afforded the hydrochloride salt of (*S*)-coniine in 96% yield (Scheme 4).[17]

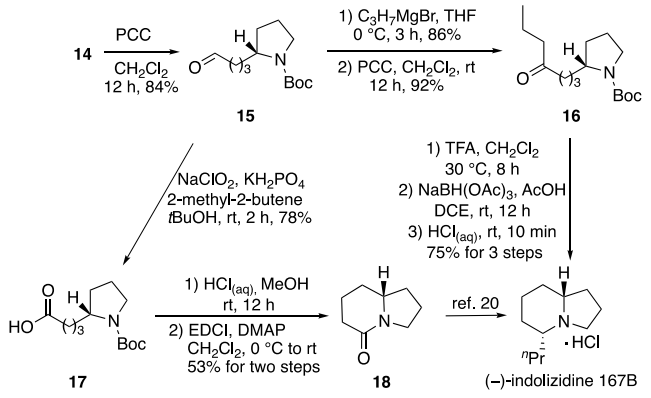
In the preparation of (*R*)-coniceine, the hydroboration and oxidation of **9** furnished the alcohol **12** in 74% yield, and the subsequent cyclization by the stepwise treatment with methanesulfonyl chloride and NaH afforded **13** in 89% yield in two steps. Finally, the sequential transformations of **14**, which was produced in 91% yield from the catalytic hydrogenolysis of **13**, involving mesylate formation, Boc deprotection, cyclization, and acidification with methanolic HCl, supplied (*R*)-coniceine·HCl in 76% yield (Scheme 5).[18]

Scheme 5. Asymmetric Synthesis (*R*)-Coniceine·HCl



The oxidation of **14** using PCC gave the corresponding aldehyde **15**, which was utilized in the straightforward synthesis of (−)-indolizidine 167B (Scheme 6). Treating **15**

Scheme 6. Asymmetric Synthesis and Formal Synthesis of (−)-Indolizidine 167B



with propyl magnesium bromide provided the corresponding alcohol in 86% yield, and a subsequent PCC oxidation furnished **16** in 92% yield. The final operations, involving the removal of the Boc protecting group, cyclizing reductive amination, and acidification, gave the hydrochloride salt of (−)-indolizidine 167B in 75% yield.[19] The synthetic significance of **15** was also demonstrated in the facile preparation of **18** for the formal syntheses of indolizidine alkaloids (−)-167B[20] and (−)-209D.[21] The Pinnick oxidation of **15** produced the corresponding acid **17** in 78% yield, and subsequent sequential reactions involving Boc deprotection and amide formation gave **18** in 53% yield.

In a two-step operation, **3oa** was readily converted into the Boc-protected amine **19**, which, after base-mediated cyclization, gave **20** in 76% yield. The Tsuji−Wacker oxidation of **20** gave the corresponding ketone in 81% yield, and the Boc protecting group was then removed by treatment with TFA to afford (−)-pelletierine in 93% yield (Scheme 7).[22]

In summary, a quest for the straightforward synthesis of optically active C-aliphatic homoallylic amines led us to develop the first successful Rh(I)-catalyzed allylation of aliphatic aldimines, employing a catalyst *in situ* generated from the chiral diene ligand **L1**. The asymmetric addition of various potassium allyltrifluoroborates with assorted aliphatic aldimines furnished the corresponding enantioenriched homoallylic amines in up to 13.5:1 dr, 95% yield, and 98% ee. Notably, the major diastereomers with (3*R*,4*R*)-configuration

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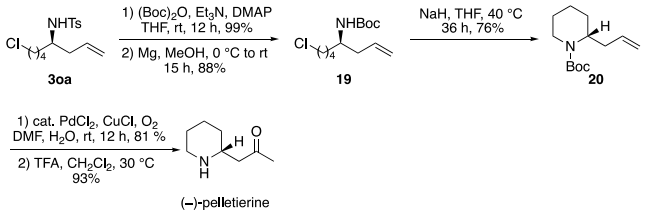
Scheme 7. Asymmetric Synthesis of (−)-Pelletierine



were obtained when using (*Z*)-**2d** and (±)-**2c** at 60 °C. The syntheses of (*S*)-coniine·HCl, (*R*)-coniceine·HCl, (−)-indolizidine 167B, and (−)-pelletierine clearly demonstrate the applicability of this approach.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02069.

Experimental procedures, complete characterization data, HPLC chromatograms, and NMR spectra (PDF)

Accession Codes

CCDC 1995023 contains 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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■ REFERENCES

(1) For selected examples of rhodium-catalyzed enantioselective 1,2-arylation of aryl imines, see: (a) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128. (b) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 13584. (c) Weix, D. J.; Shi, Y.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 1092. (d) Duan, H.-F.; Jia, Y.-X.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 2567. (e) Wang, Z.-Q.; Feng, C.-G.; Xu, M.-H.; Lin, G.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (f) Okamoto, K.; Hayashi, T.; Rawal, V. H. *Chem. Commun.* **2009**, 4815. (g) Nishimura, T.; Noishiki, A.; Tsui, C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056. (h) Nishimura, T.; Noishiki, A.; Ebe, Y.; Hayashi, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 1777. (i) Wang, H.; Jiang, T.; Xu, M.-H. *J. Am. Chem. Soc.* **2013**, *135*, 971. (j) Chen, C.-C.; Gopula, B.; Syu, J.-F.; Pan, J.-H.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *J. Org. Chem.* **2014**, *79*, 8077. (k) Wang, H.; Li, Y.; Xu, M.-H. *Org. Lett.* **2014**, *16*, 3962. (l) Jiang, T.; Chen, W.-W.; Xu, M.-H. *Org. Lett.* **2017**, *19*, 2138. (m) Syu, J.-F.; Lin, H.-Y.; Cheng, Y.-Y.; Tsai, Y.-C.; Ting, Y.-C.; Kuo, T.-S.; Janmanchi, D.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *Chem. - Eur. J.* **2017**, *23*, 14515. (n) Shan, H.; Zhou, Q.; Yu, J.; Zhang, S.; Hong, X.; Lin, X. *J. Org. Chem.* **2018**, *83*, 11873.

(2) For seminal reviews, see: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Marques, C. S.; Burke, A. *ChemCatChem* **2011**, *3*, 635. (c) Tian, P.; Dong, H.-Q.; Lin, G.-Q. *ACS Catal.* **2012**, *2*, 95.

(3) *Chiral Amine Synthesis: Methods, Developments and Applications*; Nugent, T. C., Ed.; Wiley-VCH: Weinheim, Germany, 2010.

(4) For rhodium-catalyzed 1,2-alkenylation of aryl imines, see: (a) Shintani, R.; Takeda, M.; Soh, Y.-T.; Ito, T.; Hayashi, T. *Org. Lett.* **2011**, *13*, 2977. (b) Luo, Y.; Carnell, A. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 6762. (c) Gopula, B.; Chiang, C.-W.; Lee, W.-Z.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *Org. Lett.* **2014**, *16*, 632. (d) Cui, Z.; Chen, Y.- J.; Gao, W.-Y.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2014**, *16*, 1016. (e) Gopula, B.; Zeng, H.-W.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *J. Chin. Chem. Soc.* **2018**, *65*, 312.

(5) For seminal reviews, see: (a) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (b) Johnson, J. B.; Rovis, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 840. (c) Defieber, C.; Grützmacher, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4482. (d) Edwards, H. J.; Hargrave, J. D.; Penrose, S. D.; Frost, C. G. *Chem. Soc. Rev.* **2010**, *39*, 2093.

(6) For rhodium-catalyzed arylation of aliphatic imines, see: (a) Trincado, M.; Ellman, J. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5623. (b) Cui, Z.; Yu, H.-J.; Yang, R.- F.; Gao, W.-Y.; Feng, C.-G.; Lin, G.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 12394. (c) Kato, N.; Shirai, T.; Yamamoto, Y. *Chem. - Eur. J.* **2016**, *22*, 7739.

(7) For diastereoselective rhodium-catalyzed alkenylation of aliphatic imines, see: (a) Brak, K.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 3850. (b) Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 3147. For the enantioselective version, see: (c) Qian, X.-W.; Xue, Z.-J.; Zhao, Q.; Cui, Z.; Chen, Y.-J.; Feng, C.-G.; Lin, G.-Q. *Org. Lett.* **2017**, *19*, 5601.

(8) For rhodium-catalyzed allylation of cyclic sulfamate imines, see: (a) Luo, Y.; Hepburn, H. B.; Chotsaeng, N.; Lam, H. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8309. (b) Hepburn, H. B.; Chotsaeng, N.; Luo, Y.; Lam, H. M. *Synthesis* **2013**, *45*, 2649. (c) Hepburn, H. B.; Lam, H. M. *Angew. Chem., Int. Ed.* **2014**, *53*, 11605. (d) Martínez, J. I.; Smith, J. J.; Hepburn, H. B.; Lam, H. M. *Angew. Chem., Int. Ed.* **2016**, *55*, 1108.

(9) For a seminal review, see: (a) Puentes, C. O.; Kouznetsov, V. J. *J. Heterocycl. Chem.* **2002**, *39*, 595. (b) Ciufolini, M. A.; Hermann, C. W.; Whitmire, K. H.; Byrne, N. E. *J. Am. Chem. Soc.* **1989**, *111*, 3473. (c) Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 2003. (d) Nicolaou, K. C.; Mitchell, H. J.; van Delft, F. L.; Rubsam, F.; Rodriguez, R. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1871. (e) Felpin, F.-X.; Girard, S.; Vo-Thanh, G. R.; Robins, J.; Villieras, J.; Lebreton, J. *J. Org. Chem.* **2001**, *66*, 6305.

(10) For diastereoselective allylation of aliphatic imines, see: (a) Foubelo, F.; Yus, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3823. (b) Li, S.-W.; Batey, R. A. *Chem. Commun.* **2004**, 1382. (c) Bertrand,

M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 2353. (d) Sun, X.-W.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2006**, *8*, 4979. (e) Reddy, L. R.; Hu, B.; Prashad, M.; Prasad, K. *Org. Lett.* **2008**, *10*, 3109. (f) Nishikawa, Y.; Kitajima, M.; Kogure, N.; Takayama, H. *Tetrahedron* **2009**, *65*, 1608. (g) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464. (h) Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1741. (i) Balasubramanian, N.; Mandal, T.; Cook, G. R. *Org. Lett.* **2015**, *17*, 314. For enantioselective allylation of aliphatic aldimines, see: (j) Lou, S.; Moquist, P. N.; Schaus, S. E. *J. Am. Chem. Soc.* **2007**, *129*, 15398. (k) Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 3332. (l) Shikora, J. M.; Chemler, S. R. *Org. Lett.* **2018**, *20*, 2133. (m) Liu, J.; Cao, C.-G.; Sun, H.-B.; Zhang, X.; Niu, D. *J. Am. Chem. Soc.* **2016**, *138*, 13103. (n) Wei, L.; Zhu, Q.; Xiao, L.; Tao, H.-Y.; Wang, C.-J. *Nat. Commun.* **2019**, *10*, 1.

(11) For seminal reviews on transition-metal-catalyzed allylation of imines, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984. (c) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600. (d) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (e) Friestad, G. K.; Ding, H. *Synthesis* **2005**, *2005*, 2815. (f) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541. (g) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626. (h) Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2011**, *111*, 7774. (i) Huo, H.-X.; Duvall, J. R.; Huang, M.-Y.; Hong, R. *Org. Chem. Front.* **2014**, *1*, 303.

(12) (a) Wei, W.-T.; Yeh, J.-Y.; Kuo, T.-S.; Wu, H.-L. *Chem. - Eur. J.* **2011**, *17*, 11405. (b) Huang, K.-C.; Gopula, B.; Kuo, T.-S.; Chiang, C.-W.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *Org. Lett.* **2013**, *15*, 5730. (c) Gopula, B.; Tsai, Y.-F.; Kuo, T.-S.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *Org. Lett.* **2015**, *17*, 1142. (d) Gopula, B.; Yang, S.-H.; Kuo, T.-S.; Hsieh, J.-C.; Wu, P.-Y.; Henschke, J. P.; Wu, H.-L. *Chem. - Eur. J.* **2015**, *21*, 11050. (e) Fang, J.-H.; Jian, J.-H.; Chang, H.-C.; Kuo, T.-S.; Lee, W.-Z.; Wu, P.-Y.; Wu, H.-L. *Chem. - Eur. J.* **2017**, *23*, 1830. (f) Jian, J.-H.; Hsu, C.-L.; Syu, J.-F.; Kuo, T.-S.; Wu, P.-Y.; Wu, H.-L. *J. Org. Chem.* **2018**, *83*, 12184. (g) Jian, J.-H.; Zeng, H.-W.; Kuo, T.-S.; Wu, P.-Y.; Wu, H.-L. *Org. Lett.* **2019**, *21*, 9468. (h) Chang, C.-A.; Uang, T.-Y.; Jian, J.-H.; Zhou, M.-Y.; Chen, M.-L.; Kuo, T.-S.; Wu, P.-Y.; Wu, H.-L. *Adv. Synth. Catal.* **2018**, *360*, 3381.

(13) Chiang, P.-F.; Li, W.-S.; Jian, J.-H.; Kuo, T.-S.; Wu, P.-Y.; Wu, H.-L. *Org. Lett.* **2018**, *20*, 158.

(14) (a) *See: International Conference on Harmonisation (ICH)*. Guideline Q3C (R5): Impurities: Guideline for Residual Solvents; ICH: Geneva, 2011. (b) Laird, T. *Org. Process Res. Dev.* **2012**, *16*, 1.

(15) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. - Eur. J.* **2012**, *18*, 6616.

(16) For the discussion of resulting stereochemical outcomes, please see Supporting Information.

(17) $[\alpha]_D^{21}$ +9.3 (*c* 0.3, EtOH). For comparison, see: Kondekar, N. B.; Kumar, P. *Synthesis* **2010**, *2010*, 3105. $[\alpha]_D^{25}$ −8.6 (*c* 0.25, EtOH) for *R*-isomer.

(18) $[\alpha]_D^{21}$ −1.2 (*c* 1.0, EtOH). For comparison, see: Zill, N.; Schoenfelder, A.; Girard, N.; Taddei, M.; Mann, A. *J. Org. Chem.* **2012**, *77*, 2246. $[\alpha]_D^{20}$ −1.5 (*c* 1.0, EtOH).

(19) $[\alpha]_D^{21}$ −98.3 (*c* 1.0, CH_2Cl_2). For comparison, see: Roa, L. F.; Gnecco, D.; Galindo, A.; Teran, J. L. *Tetrahedron: Asymmetry* **2004**, *15*, 3393. $[\alpha]_D^{20}$ +107.4 (*c* 1.0, CH_2Cl_2) for the enantiomeric isomer.

(20) Pinho, V. D.; Burtoloso, A. C. B. *Tetrahedron Lett.* **2012**, *53*, 876.

(21) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398.

(22) $[\alpha]_D^{22}$ −24.3 (*c* 1.0, EtOH). For comparison, see: Takahata, H.; Kubota, M.; Takahashi, S.; Momose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047. $[\alpha]_D^{25}$ −22.1 (*c* 4.1, EtOH)

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