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Ir-catalyzed distal branch- and enantioselective hydroarylation of internal alkenes using acetanilides via chain-walking and C—H activation☆

Mizuki Kadota, King Hung Nigel Tang, Takanori Shibata *

Department of Chemistry and Biochemistry, School of Science and Engineering, Waseda University, Shinjuku, Tokyo 169-8555, Japan

A B S T R A C T

This study presents the iridium-catalyzed branch- and enantioselective C—H alkylation of acetanilides with internal alkenes via chain-walking. This report addresses a key challenge in the selective C—C bond formation by using a newly developed electron-deficient TADDOL-based chiral ligand and we achieved an optimal balance between yield and enantiomeric ratio (up to 91:9 er). The use of 1.5 equivalent amounts of $[Ir(cod)_2]NTf_2$ relative to chiral ligands significantly improved the yields along with perfect regioselectivity and good enantioselectivity. The substrate scope demonstrated the broad applicability of the method across various acetanilide and alkene derivatives, including functionalized arenes and alkenes bearing aryl or aliphatic substituents.

Introduction

The direct functionalization of C—H bonds has become a powerful approach in organic synthesis, enabling streamlined routes to complex molecules with excellent atom- and step-economy [1]. Among them, C—H alkylation using alkenes realizes perfect atom-economy along with C—C bond formation [2]. In particular, enantioselective variants can offer a desirable strategy for the creation of stereocenters initiated by an inactive C—H bond [3]. We have been interested in Ir-catalyzed C—H activation since the early stage of our investigation [4], which has drawn increasing attention in the past decade [5]. Especially, aniline derivatives have garnered increasing interest as substrates because they are inexpensive and commercially available, and the aniline moiety offers opportunities for further functionalization of the products [6]. In 2017, we reported Ir-catalyzed enantioselective formal C—H conjugate addition of acetanilides to β-substituted acrylates (Scheme 1a) [7]. In 2018, Bower and co-workers demonstrated Ir-catalyzed branch- and enantioselective C—H alkylation of acetanilides using mainly styrene derivatives (R^2 = aryl) (Scheme 1b) [8].

Meanwhile, the chain-walking process, which relies on the successive migration of a metal along an alkyl chain via alkene isomerization, has emerged as a promising tool for remote functionalization [9] since the pioneering Pd-catalyzed cycloisomerization by Kochi and Kakiuchi's group in 2012 [10]. In particular, the merger of chain-walking and enantioselective C—H alkylation is attractive because it can achieve remote functionalization as well as asymmetric synthesis [11]. Iridium catalysts play a key role even in this difficult synthetic transformation (Scheme 2): Nishimura and co-workers developed an enantioselective hydroarylation of 2-phenylpyridines using benzyloxy-substituted terminal alkene (R' = H) along with chain-walking [12]. Zhang's group also used the pyridyl group as a directing group (DG) and achieved selective synthesis of branched products and showed an enantioselective reaction as a preliminary result [13]. In contrast, we focused on the use of the carbonyl moiety as DG from the synthetic aspect [14]. For example, benzamides were good substrates for achieving both chain-walking and branch-selective alkylation, along with a moderate enantiomeric ratio [15]. Recently, our group reported the enantioselective C2-alkylation of indoles bearing a piperidyl moiety as a DG [16]. The good enantioselectivity was accomplished by our original chiral diphosphite ligand derived from TADDOL. The slightly less equivalent amounts of the chiral ligand against the Ir catalyst was a key to success for the high yield.

Despite these advances, branch- and enantioselective C—H alkylation of anilides using internal alkenes remains undeveloped. We here examined an iridium-catalyzed C—H alkylation of anilides **1** using internal alkene **2** via chain-walking for the enantioselective formation of distal C—C bond (Scheme 3).

Results and discussion

As a preliminary study, we first determined the suitable chiral ligand for the branch- and enantioselective hydroarylation of terminal alkene **2a'** using acetanilide (**1a**) without chain-walking. The reactions were conducted using a chiral iridium catalyst in situ prepared from [Ir

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* Corresponding author.
E-mail address: tshibata@waseda.jp (T. Shibata).

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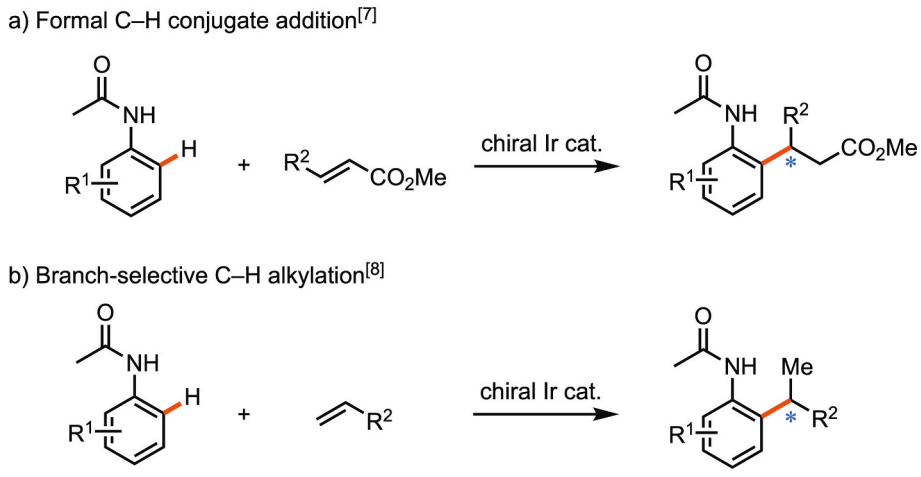
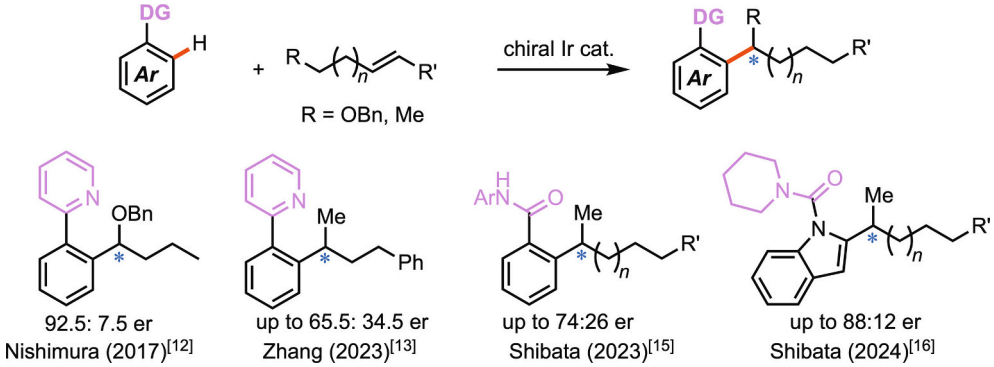
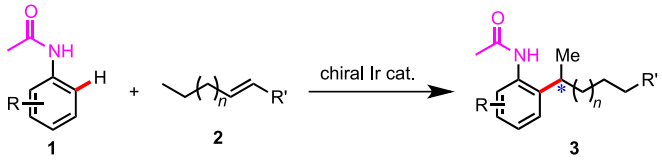


Scheme 1. Ir-catalyzed enantioselective C—H alkylation of anilides.



Scheme 2. Merger of chain-walking and enantioselective C—H alkylation.

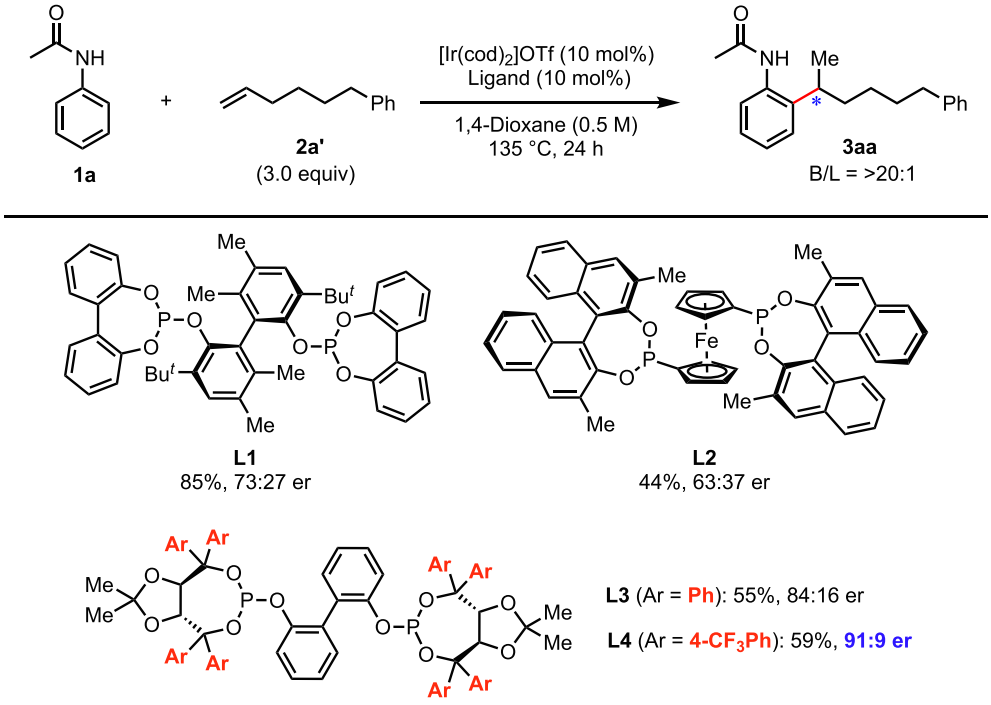


Scheme 3. This work.

$(cod)_2$]OTf and chiral ligand in 1,4-dioxane at 135 °C (Table 1). The BIPHEN-derived chiral ligand **L1** [17], which was used for branch- and enantioselective C—H alkylation of anilides with styrenes [8], realized perfect branch-selectivity and high catalytic activity, but the enantiomeric ratio was moderate. The ferrocenyl diphosphonite ligand **L2** with a chiral binaphthyl backbone, which induced high catalytic activity and regioselectivity in our report [15], resulted in a low enantiomeric ratio under the present conditions. We next evaluated a TADDOL-based ligand **L3**, which contains a more sterically congested chiral backbone originally developed by our laboratory [16]. As a result, **L3** provided the highest enantiomeric ratio. Encouraged by this result, we newly synthesized a series of chiral ligands based on the TADDOL scaffold, bearing various aryl substituents (see Supporting Information). Among the chiral ligands tested, **L4** bearing a trifluoromethyl group on the aryl ring, gave the highest enantiomeric ratio and a moderate yield for the desired product **3aa**. Other ligands showed either significantly lower yields or poor enantioselectivity. These results show the importance of both steric and electronic factors of the aryl moiety of the TADDOL scaffold for the control of the chiral induction.

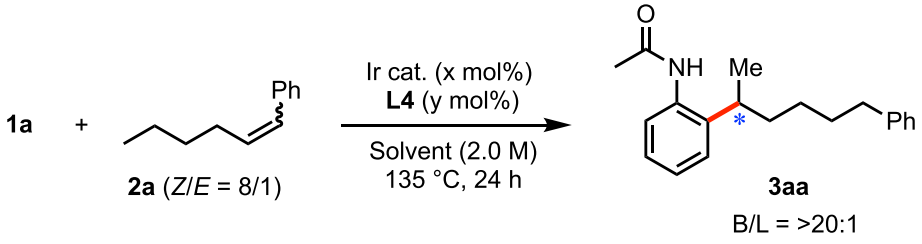
Next, we optimized the reaction conditions using internal alkene **2a** considering chain-walking (Table 2). When the chiral iridium catalyst prepared from the same equivalent amount of [Ir$(cod)_2$]OTf and **L4** was used, no reaction proceeded at all (Entry 1). Based on our previous study of hydroarylation of indoles [16], in which chain-walking can efficiently proceed with a slight excess amount of [Ir$(cod)_2$]OTf against the chiral ligand, we attempted the same ratio of the precatalyst to ligand. As expected, the reaction proceeded, yet in a very low yield (Entry 2). In order to facilitate the chain-walking and to improve the yield, a further excess amount of [Ir$(cod)_2$]OTf was added, i.e. 5 mol%: we observed both the improvement in the yield and the retention of the enantiomeric ratio of **3aa**, but most of **1a** still remained unreacted (Entry 3). We then investigated the counteranion of the iridium catalyst (Entries 4 and 5): bis(trifluoromethanesulfonyl)imide (NTf_2) was apparently suitable for the present reaction, and a moderate yield was achieved. We further screened the solvents with higher boiling points (Entries 6 and 7), and higher conversion of substrate was observed in *ortho*-dichlorobenzene (*o*-DCB). Finally, when the amount of alkene **2a** was increased to 6.0 equivalents, anilide **1a** was completely consumed, and the optically active **3aa** was quantitatively obtained with a good enantiomeric ratio (Entry 8).

Table 1
Ligand screening.[a]



[a] The yield was determined by ^{1}H NMR with dibromomethane as an internal standard. The enantiomeric ratio was determined by chiral HPLC. cod = cycloocta-1,5-diene, OTf = trifluoromethanesulfonate.

Table 2
Optimization of reaction conditions.



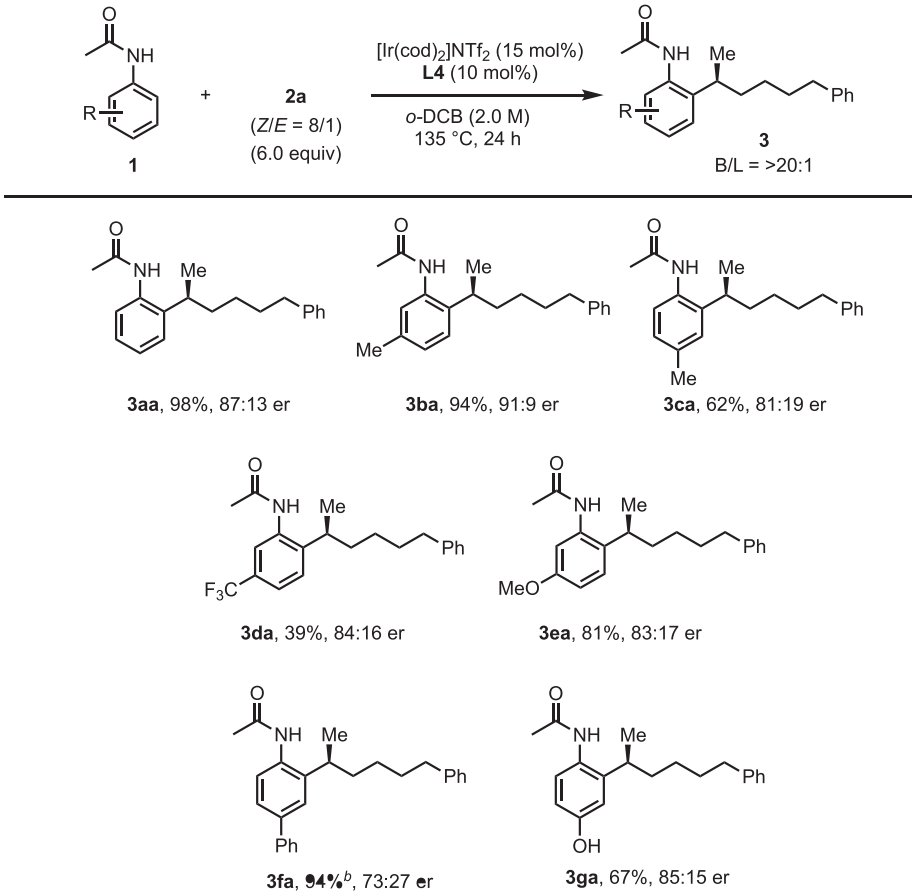
Entry	x	y	Ir cat.	Solvent	NMR yield (%)[a]	er[b]
1	10	10	$[Ir(cod)_2]OTf$	1,4-Dioxane	NR	–
2	10	9	$[Ir(cod)_2]OTf$	1,4-Dioxane	4	–
3	15	10	$[Ir(cod)_2]OTf$	1,4-Dioxane	17	90:10
4	15	10	$[Ir(cod)_2]NTf_2$	1,4-Dioxane	60	87:13
5	15	10	$[Ir(cod)_2]BF_4$	1,4-Dioxane	46	88:12
6	15	10	$[Ir(cod)_2]NTf_2$	Toluene	55	86:14
7	15	10	$[Ir(cod)_2]NTf_2$	*o*-DCB	77	86:14
8[c]	15	10	$[Ir(cod)_2]NTf_2$	*o*-DCB	>99	86:14

[a] Determined by ^{1}H NMR using dibromomethane as an internal standard. [b] Determined by chiral HPLC analysis. [c] The reaction was conducted using 6.0 equivalents of **2a**.

Under the optimal conditions (Entry 8 in Table 2), we examined the scope of acetanilides (Table 3). 3-Methylacetanilide (**1b**) provided **3ba** in the highest enantiomeric ratio. The C—C bond formation proceeded at the less hindered *ortho* position, probably due to the steric environment around the ligand, which plays a critical role in determining regioselectivity. In contrast, substrates bearing substituents at the *para* position closer to the reaction site, such as 4-methylacetanilide (**1c**), resulted in a moderate yield. Electron-donating substituents on the aryl ring were well tolerated and gave **3ea** with comparable reactivity to the non-substituted analogue. Of particular note is that the reaction conditions could also be used for a protic functional group, as demonstrated by the successful conversion of acetaminophen to the corresponding product **3ga**.

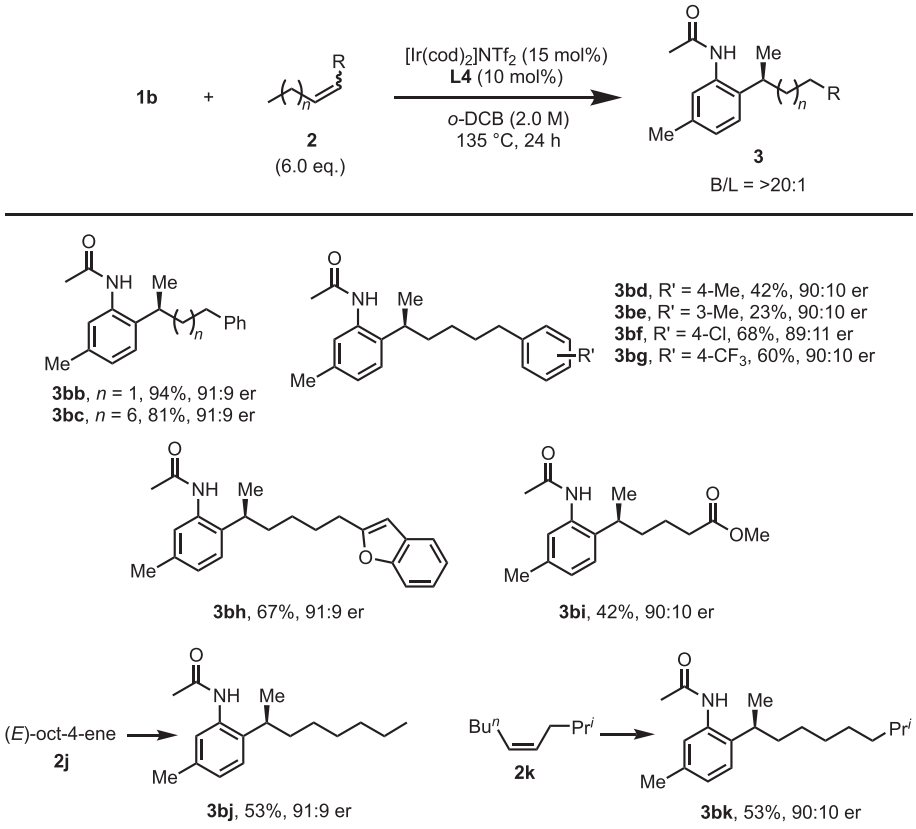
Subsequently, the scope of alkenes was examined using 3-methylacetanilide (**1b**) as the model substrate (Table 4). Alkenes **2b** and **2c** bearing either shorter or longer alkyl chain were successfully converted to the corresponding products with consistently high reactivity and good enantiomeric ratios. Several aryl-substituted alkenes were also well tolerated, affording the desired branched products **3bd–3bg** with good enantioselectivity. Furthermore, both an *α, β*-unsaturated ester and an

Table 3
Scope of acetanilides.[a]



[a] Reactions were conducted on a 0.10 mmol scale with acetanilide derivative **1** (0.10 mmol, 1.0 equiv), **2a** (0.60 mmol, 6.0 equiv), $[Ir(cod)_2]NTf_2$ (0.015 mmol, 15 mol %), and **L4** (0.010 mmol, 10 mol%) in *o*-DCB (0.05 mL, 2.0 M) at 135 °C under argon. [b] Reaction time was 72 h.

Table 4
Scope of alkene.[a]



[a] Reactions were conducted on a 0.10 mmol scale with acetanilide derivative **1** (0.10 mmol, 1.0 equiv), **2a** (0.60 mmol, 6.0 equiv), $[Ir(cod)_2]NTf_2$ (0.015 mmol, 15 mol%), and **L4** (0.010 mmol, 10 mol%) in *o*-DCB (0.05 mL, 2.0 M) at 135 °C under argon.

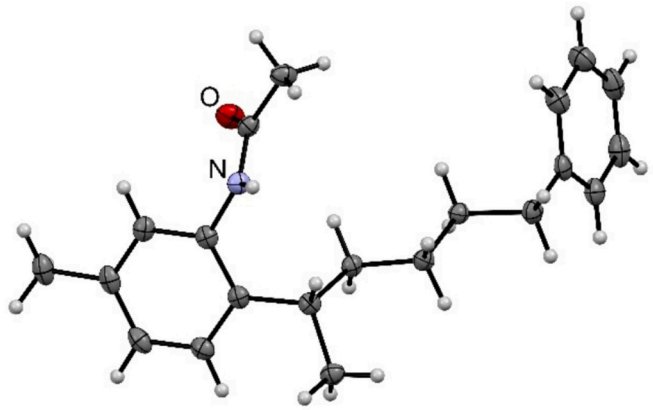
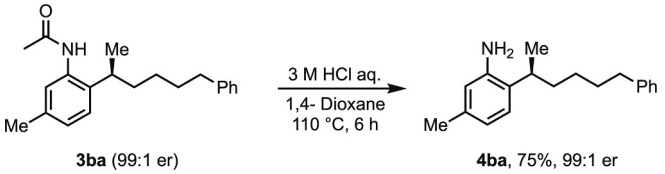


Fig. 1. ORTEP diagram of enantiomerically pure **3ba** (thermal ellipsoids shown at 50 % probability).



Scheme 4. Deprotection without loss of enantiomeric purity.

unactivated aliphatic alkene could also be used under these reaction conditions, delivering the corresponding products **3bi–3bk** with over 90:10 er.

Compound **3ba** was recrystallized from hexane/ethyl acetate to afford almost enantiomerically pure product (>99.5:<0.5 er), and its single-crystal X-ray analysis revealed that the absolute configuration of the obtained **3ba** was *S* (Fig. 1).

Compound **3ba** was subjected to deprotection under acidic conditions. Treatment with 3 M HCl aq. in 1,4-dioxane (1:1) at 110 °C for 6 h successfully hydrolyzed the amide group, affording the corresponding chiral aniline **4ba (**Scheme 4**)**. The enantiopurity was perfectly retained during the deprotection process, as the enantiomeric ratio of **4ba** remained identical to that of **3ba**. This transformation provides direct access to optically active aniline scaffolds, which are valuable intermediates in pharmaceuticals and fine chemicals.

Conclusions

We have developed a branch- and enantioselective hydroalkylation of acetanilides with internal alkenes via iridium-catalyzed chain-walking and C(sp^2)–H activation. The C—H alkylated products were obtained in perfect branch-selectivity and good enantioselectivity by using the newly synthesized electron-deficient chiral diphosphite ligand.

Experimental section

To a flame-dried 5 mL sealed tube equipped with a magnetic stirrer, acetanilide derivative (0.10 mmol), $[Ir(cod)_2]NTf_2$ (0.015 mmol, 15 mol %), and **L4** (0.010 mmol, 10 mol%) were added, and the tube was

capped with a rubber septum. The reaction vessel was evacuated and backfilled with argon three times. Internal alkene (0.60 mmol) and degassed *o*-dichlorobenzene (0.05 mL) were added to the reaction vessel. The rubber septum was rapidly replaced with a screw cap under argon flow, and then the reaction mixture was heated at 135 °C with a preheated oil bath. After 24 h, the reaction mixture was filtered through a pad of silica gel (hexane, then hexane/ethyl acetate 1:1). The filtrate was concentrated in vacuo and purified by preparative TLC to give the pure product.

CRediT authorship contribution statement

Mizuki Kadota: Writing – original draft, Methodology, Data curation. **King Hung Nigel Tang:** Writing – review & editing, Conceptualization. **Takanori Shibata:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2025.155823.

Data availability

Data will be made available on request.

References

[1] (a) E.M. Carreira, J.-Q. Yu, C.P. Decicco, A. Fürstner, G. Koch, G.A. Molander, E. Schaumann, M. Shibasaki, E.J. Thomas, B.M. Trost, Catalytic Transformations via C–H Activation 1, Georg Thieme Verlag, Stuttgart (2016), https://doi.org/10.1002/anie.201606502;
(b) J.H. Docherty, T.M. Lister, G. McArthur, M.T. Findlay, P. Domingo-Legarda, J. Kenyon, S. Choudhary, I. Larrosa, Transition-metal-catalyzed C–H bond activation for the formation of C–C bonds in complex molecules, Chem. Rev. 123 (2023) 7692–7760, https://doi.org/10.1021/acs.chemrev.2c00888.

[2] (a) Z. Dong, Z. Ren, S.J. Thompson, Y. Xu, G. Dong, Transition-metal-catalyzed C–H alkylation using alkenes, Chem. Rev. 117 (2017) 9333–9403, https://doi.org/10.1021/acs.chemrev.6b00574;
(b) H.N. Lim, D. Xing, G. Dong, Transition-metal-catalyzed ketone α-alkylation and alkenylation with simple alkenes and alkynes through a dual activation strategy, Synlett 30 (2019) 674–684, https://doi.org/10.1055/s-0037-1610315.

[3] (a) S.L. You, Asymmetric Functionalization of C–H Bonds (RSC). https://pubs.rsc.org/en/, 2015 content/ebook/978–1–78262-102-7#! divbookcontent;
(b) C.G. Newton, S.-G. Wang, C.C. Oliveira, N. Cramer, Catalytic enantioselective transformations involving C–H bond cleavage by transition-metal complexes, Chem. Rev. 117 (2017) 8908–8976, https://doi.org/10.1021/acs.chemrev.6b00692;
(c) T.K. Achar, S. Maiti, S. Jana, D. Maiti, Transition metal catalyzed enantioselective C(sp^2)–H bond functionalization, ACS Catal. 10 (2020) 13748–13793, https://doi.org/10.1021/acscatal.0c03743.

[4] (a) S. Pan, K. Endo, T. Shibata, Ir(I)-catalyzed enantioselective secondary sp^3 C–H bond activation of 2-(alkylamino)pyridines with alkenes, Org. Lett. 13 (2011) 4692–4695, https://doi.org/10.1021/ol201907w;
(b) S. Pan, K. Endo, T. Shibata, Ir(I)-catalyzed intermolecular regio- and enantioselective hydroamination of alkenes with heteroaromatic amines, Org. Lett. 14 (2012) 780–783, https://doi.org/10.1021/ol203318z;
(c) S. Pan, Y. Matsuo, K. Endo, T. Shibata, Cationic iridium-catalyzed enantioselective activation of secondary sp^3 C–H bond adjacent to nitrogen atom, Tetrahedron 68 (2012) 9009–9015, https://doi.org/10.1016/j.tet.2012.08.071;
(d) S. Pan, N. Ryu, T. Shibata, Ir(I)-catalyzed C–H bond alkylation of C2-position of indole with alkenes: selective synthesis of linear or branched 2-alkylindoles, J. Am. Chem. Soc. 134 (2012) 17474–17477, https://doi.org/10.1021/ja308585u.

[5] (a) D.F. Fernández, J.L. Mascareñas, F. López, Catalytic addition of C–H bonds across C–C unsaturated systems promoted by iridium(I) and its group IX congeners, Chem. Soc. Rev. 49 (2020) 7378–7405, https://doi.org/10.1039/D0CS00359J;
(b) Ł. Woźniak, J.-F. Tan, Q.-H. Nguyen, A. Madron du Vigné, V. Smal, Y.-X. Cao, N. Cramer, Catalytic enantioselective functionalizations of C–H bonds by chiral iridium complexes, Chem. Rev. 120 (2020) 10516–10543, https://doi.org/10.1021/acs.chemrev.0c00559.

[6] (a) A. Ricci, Amino group chemistry: from synthesis to the life sciences, John Wiley & Sons (2008), https://doi.org/10.1002/9783527621262;
(b) M. Anjalin, N. Kanagathara, A.B. Suganthi, A brief review on aniline and its derivatives, Mater. Today Proc. 33 (2020) 4751–4755, https://doi.org/10.1016/j.matpr.2020.08.358;
(c) S. Zhou, G. Huang, G. Chen, Synthesis and biological activities of local anesthetics, RSC Adv. 9 (2019) 41173–41191, https://doi.org/10.1039/C9RA09287K.

[7] T. Shibata, M. Michino, H. Kurita, Y. Tahara, K.S. Kanyiva, Enantioselective formal C–H conjugate addition of acetanilides to β-substituted acrylates by chiral iridium catalysts, Chem. Eur. J. 23 (2017) 88–91, https://doi.org/10.1002/chem.201604962.

[8] S. Grélaud, P. Cooper, L.J. Feron, J.F. Bower, Branch-selective and enantioselective iridium-catalyzed alkene hydroarylation via anilide-directed C–H oxidative addition, J. Am. Chem. Soc. 140 (2018) 9351–9356, https://doi.org/10.1021/jacs.8b04627.

[9] H. Sommer, F. Juliá-Hernández, R. Martin, I. Marek, Walking metals for remote functionalization, ACS Cent. Sci. 4 (2018) 153–165, https://doi.org/10.1021/acscentsci.8b00005.

[10] T. Kochi, T. Hamasaki, Y. Aoyama, J. Kawasaki, F. Kakiuchi, Chain-walking strategy for organic synthesis: catalytic cycloisomerization of 1,n-dienes, J. Am. Chem. Soc. 134 (2012) 16544–16547, https://doi.org/10.1021/ja308377u.

[11] (a) M. Zhang, Y. Ji, C. Zhang, Transition metal catalyzed enantioselective migratory functionalization reactions of alkenes through chain-walking, Chin. J. Chem. 40 (2022) 1608–1622, https://doi.org/10.1002/cjoc.202200072;
(b) X.X. Chen, H. Luo, Y.W. Chen, Y. Liu, Z.T. He, Enantioselective palladium-catalyzed directed migratory allylation of remote dienes, Angew. Chem. Int. Ed. 62 (2023) e202307628, https://doi.org/10.1002/ange.202307628;
(c) M. Jiao, J. Long, J. Chen, H. Yang, T. Wang, X. Fang, Nickel-catalyzed regio- and enantioselective migratory hydrocyanation of internal alkenes: expanding the scope to α,ω-diaryl internal alkenes, Angew. Chem. Int. Ed. 63 (2024) e202402390, https://doi.org/10.1002/anie.202402390.

[12] Y. Ebe, M. Onoda, T. Nishimura, H. Yorimitsu, Iridium-catalyzed regio- and enantioselective hydroarylation of alkenyl ethers by olefin isomerization, Angew. Chem. Int. Ed. 56 (2017) 5607–5611, https://doi.org/10.1002/anie.201702286.

[13] F. Li, Y. Luo, J. Ren, Q. Yuan, D. Yan, W. Zhang, Iridium-catalyzed remote site-switchable hydroarylation of alkenes controlled by ligands, Angew. Chem. Int. Ed. 62 (2023) e202309859, https://doi.org/10.1002/anie.202309859.

[14] K.H.N. Tang, K. Uchida, K. Nishihara, M. Ito, T. Shibata, Ir-catalyzed remote functionalization by the combination of deconjugative chain-walking and C–H activation using a transient directing group, Org. Lett. 24 (2022) 1313–1317, https://doi.org/10.1021/acs.orglett.1c04321.

[15] K.H.N. Tang, R. Tokutake, M. Ito, T. Shibata, Ir-catalyzed distal branch-selective hydroarylation of unactivated internal alkenes with benzanilides via C–H activation along with consecutive isomerization, Org. Lett. 25 (2023) 5197–5202, https://doi.org/10.1021/acs.orglett.3c01619.

[16] K.H.N. Tang, H. Takahashi, R. Tokutake, T. Shibata, Unconventional ligand-to-catalyst ratio for the distal C–C bond formation via C–H activation and chain-walking, Adv. Synth. Catal. 366 (2024) 3610–3615, https://doi.org/10.1002/adsc.202400535.

[17] I. Ojima, M. Takai, T. Takahashi, Mitsubishi Chemical Corporation, The Research Foundation of State University of New York, World Intellectual Property Organization Optically active phosphites and phosphoramidites bearing biphenol skeletons with axial chirality, and their use in catalytic asymmetric reaction WO2004078766 A1, 2004.