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Low-Temperature Heck Reactions of Axially Chiral *o*-Iodoacrylanilides Occur with Chirality Transfer: Implications for Catalytic Asymmetric Heck Reactions

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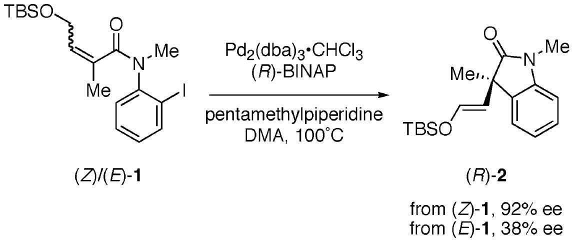
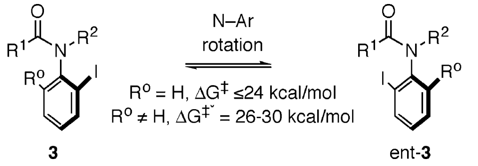
Asymmetric Heck reactions promoted by chiral palladium catalysts were among the first catalytic asymmetric carbon−carbon bond forming reactions to be explored, and they have frequently been harnessed in natural product synthesis.[1] Cyclizations of *o*-iodoanilides, pioneered by Overman and co-workers, have proven value in alkaloid synthesis.[2] For example, cyclization of (*Z*)- or (*E*)-**1** under "neutral conditions"[2c] with Pd$_2$(dba)$_3$ and (*R*)-BINAP provides (*R*)-**2** in up to 92% ee despite the high reaction temperatures (eq 1). In this and other asymmetric Heck reactions, it is assumed that the insertion of the aryl (or alkenyl) palladium species into the carbon−carbon bond is the stereocontrolling step.



(1)

Subsequent to the discovery of these asymmetric Heck reactions, the rotational dynamics and thermodynamics of *o*-iodoanilides **3** have become rather well understood (eq 2).[3] These anilides are axially chiral and have N−Ar rotation barriers that vary from <20 to 30 kcal/mol, depending on the size of the ortho-substituent R°. In favorable cases, pure enantiomers can be obtained and onward reactions such as radical cyclizations can occur with very high levels of chirality transfer.[3c−e,g]



(2)

Mapping the new understanding of the rotational features of **3** over the prior results on Heck reactions with chiral palladium catalysts, we suggested in passing[3e] that Heck reactions like that in eq 1 might be dynamic kinetic resolutions. In this view, the stereocontrolling step is oxidative addition to the carbon−iodine bond, rather than C═C complexation or insertion. Very recently, Stephenson hybridized the two limiting suggestions to propose that both oxidative addition and C═C complexation were important stereocontrolling events.[4] We report herein the generation of highly enantioenriched, axially chiral organopalladium intermediates, and we show that these intermediates cyclize with high fidelity. We interpret the results as supporting oxidative addition as the stereocontrolling step in this class of asymmetric Heck reaction.

The standard method to conduct an asymmetric Heck reaction involves treatment of a racemic *o*-iodoacrylanilide with a chiral palladium catalyst (eq 1). We supposed that if oxidative addition were the stereocontrolling step in such reactions, then cyclization of a single enantiomer of an *o*-iodoacrylanilide with an achiral palladium catalyst would produce an enantioenriched product. To test this supposition, we prepared racemates **4a**,**b** (Table 1) and resolved them into their enantiomeric components by preparative chiral HPLC (see Supporting Information). A racemization experiment provided a rotation barrier of 26.0 kcal/mol for interconversion of the enantiomers of **4a**. This barrier is sufficiently high for resolution and handling under ambient lab conditions; however, under high-temperature conditions, racemization is likely to compete with the Heck reaction. We thus took advantage of recent developments of room-temperature Heck reactions promoted by bulky phosphine ligands.[5]

In a typical experiment (Table 1, entry 1), a toluene solution of (*M*)-(−)-**4a** (99.5/0.5 er), 10% Pd$_2$(dba)$_3$, and 20% (*t*-Bu)$_3$P (generated in situ from Et$_3$N and (*t*-Bu)$_3$PH•BF$_4$) was stirred at 25 °C for 24 h. After standard workup and chromatographic purification, (*R*)-(+)-**5a** was isolated in 95% yield in 85.5/14.5 er (assayed by chiral HPLC). Likewise, cyclization of (*P*)-(+)-**4a** (entry 2) gave **5a** in comparable yield but reversed enantiomer ratio. The two enantiomeric bromides (*M*)-(−)-**4b** and (*P*)-(+)-**4b** were also cyclized to provide the corresponding products **5b** in slightly lower isolated yields (77 and 69%) but slightly higher enantiopurities (both 89/11 er). These results show that axial chirality can be transferred from a precursor to a product in a Heck reaction without intervention of a chiral ligand or catalyst.

The absolute configurations of **4b** and **5b** were assigned by X-ray crystallography, as detailed in the Supporting Information. The second-eluting enantiomer of **4b** on an (*S,S*)-Whelk-O1 column was levorotatory and proved to have the (*P*) absolute configuration. On Heck cyclization, this yielded predominantly the second-eluting, levorotatory enantiomer of **5b**, which proved to be (*S*). The same correlation of rotation sign and elution order was observed for the conversion of **4a** to **5a**, so the absolute configurations of this series were assigned by analogy.

We interpret these results within the mechanistic framework shown in Figure 1. Insertion of palladium into the carbon iodide bond of (*M*)-**4** with retention of axial chirality provides aryl palladium intermediate **6**. Though N−Ar axially chirality is retained in its formation, **6** can still potentially provide either enantiomer of **5** because the alkene must twist for insertion of the carbon−palladium bond to occur. This twisting can expose either of the alkene's two diastereotopic faces for reaction.

In addition to the twisted N−Ar bond (*b*), methacrylanilides like **4** have a second element of axial chirality owing to their twisted C(O)−C(CH$_3$)CH$_2$ bond (*a*).[6] Stephenson proposed that complexation and insertion of palladium take place on the exposed alkene face as deduced from X-ray crystallography.[4] However, in our crystal structure of **4b**, the alkene face that is exposed to the iodine (and hence later the palladium) is not the face upon which the Heck

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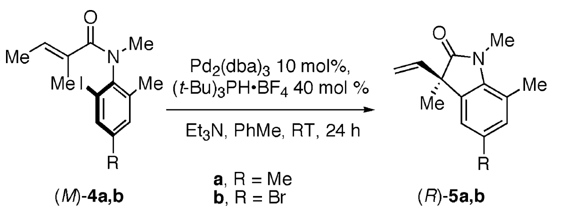
Table 1. Yields and Enantiomer Ratios (er) in Room-Temperature Heck Cyclizations of Axially Chiral *o*-Iodoacrylanilides



entry	R	precursor	er **4**	product	er **5**	yield %	% chirality transfer
1	Me	(*M*)-(−)-**4a**	99.5/0.5	(*R*)-(+)-**5a**	85.5/14.5	95	86
2	Me	(*P*)-(+)-**4a**	98.5/1.5	(*S*)-(−)-**5a**	86.5/13.5	92	88
3	Br	(*M*)-(−)-**4b**	99.5/0.5	(*R*)-(+)-**5b**	89/11	77	89
4	Br	(*P*)-(+)-**4b**	97.5/2.5	(*S*)-(−)-**5b**	89/11	69	91

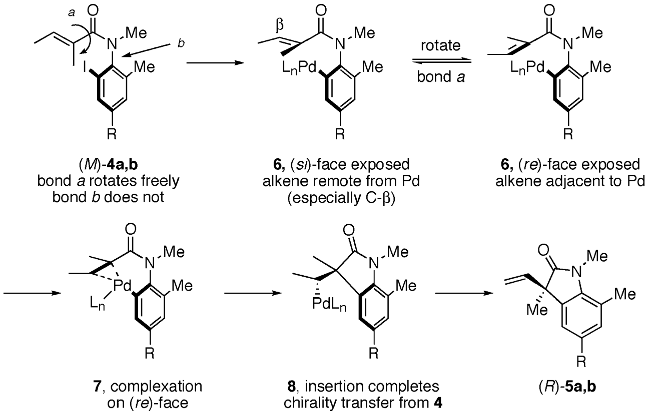


Figure 1. Model for transfer of axial chirality in room-temperature Heck reactions of **4**.

reaction occurs. Accordingly, we propose that the axial chirality of the acryloyl group of **4** is not important because this group exists in two (or more) low energy conformers that rapidly interconvert because of the low-rotation barrier of bond *a*.

Instead, the geometric requirements of the alkene/palladium complex **7** dictate which face of alkene **6** reacts; complexation on the *re*-face of the alkene can occur without undue strain to give **7**, which in turn suffers C−Pd bond insertion and β-hydride elimination to provide (*R*)-**5** via **8**. Complexation on the *si*-face of **6** and onward reaction cannot occur directly because the palladium atom is not positioned over the alkene π-orbitals. To establish this positioning would impose an energy penalty associated with significant distortion of the amide.

Implications of this work for asymmetric Heck reactions of *o*-iodoacrylamides are summarized in Figure 2. In such reactions, there is typically no other ortho substituent besides the iodine, so the racemic (not achiral) precursors **9**/*ent*-**9** will be in rapid equilibration under typical high-temperature Heck conditions.[3f,g] Insertion of the chiral palladium catalyst into the carbon−iodine bond **9** to give **10** is a dynamic kinetic resolution step that dictates both the sense and magnitude of the asymmetric induction of the overall transformation.[7] Subsequent face-selective insertion of **10** to provide **11** is now more rapid than N−Ar bond rotation of **10** (not shown).[8] The insertion is important because it relays the configuration to **13**, but this relay is inherent in the axial chirality of **10** and the chiral ligands on palladium are not required.

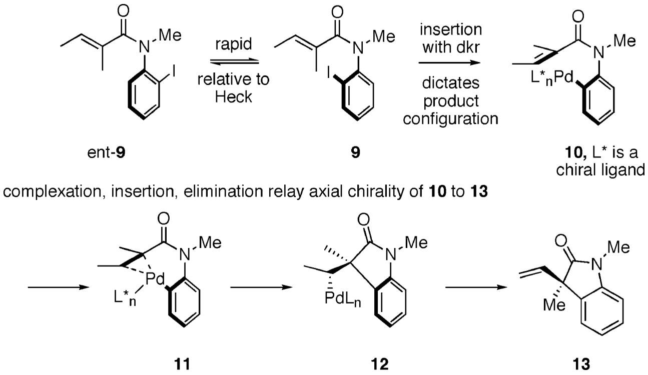


Figure 2. Dynamic kinetic resolution (dkr) model for Heck reactions of Pd complexes with chiral ligands (L*).

In short, low-temperature Heck reactions of chiral *o*-iodoacrylanilides with achiral palladium catalysts occur with efficient transfer of chirality from the chiral axis of the precursor to the new stereocenter of the product. The results suggest that the stereocontrolling step in asymmetric Heck reactions is a dynamic kinetic resolution (oxidative addition to the C−I) bond and not a face selective reaction (complexation or insertion to the alkene). This knowledge should help advance such reactions by aiding catalyst design and by guiding the selection of appropriate substrates and reaction conditions. Indeed, in asymmetric Heck reactions, the use of substrates with high N−Ar rotation barriers and low reaction temperatures may actually be undesirable because the dynamic kinetic resolution is spoiled if the Heck process becomes faster than precursor racemization.

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Note Added after ASAP Publication. After ASAP publication on December 29, 2006, a compound number was corrected in Table 1. The corrected version was published ASAP on January 4, 2007.

Supporting Information Available: Details of experiments and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453−3516. (b) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533−1552. (c) Guiry, P. J.; Kiely, D. *Curr. Org. Chem.* **2004**, *8*, 781−794. (d) Shibasaki, M.; Miyazaki, F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley; New York, 2002; Vol. 1, p 1283−1315. (e) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963. (f) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371−7395.

(2) (a) Ashimori, A.; Bachand, B.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6477−6487. (b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499. (c) Cyclizations under “cationic conditions” with silver additives often provide very different results.

(3) (a) Horne, S.; Taylor, N.; Collins, S.; Rodrigo, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3047−3051. Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955−3975. (b) Curran, D. P.; Geib, S.; DeMello, N. *Tetrahedron* **1999**, *55*, 5681−5704. (c) Curran, D. P.; Liu, W. D.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012−11013. (d) Curran, D. P.; Chen, C. H. T.; Geib, S. J.; Lapierre, A. J. B. *Tetrahedron* **2004**, *60*, 4413−4424. (e) Petit, M.; Geib, S. J.; Curran, D. P. *Tetrahedron* **2004**, *60*, 7543−7552. (f) Adler, T.; Bonjoch, J.; Clayden, J.; Font-Bardia, M.; Pickworth, M.; Solans, X.; Sole, D.; Vallverdu, L. *Org. Biomol. Chem.* **2005**, *3*, 3173−3183. (g) Petit, M.; Lapierre, A. J. B.; Curran, D. P. *J. Am. Chem. Soc.* **2005**, *127*, 14994−14995.

(4) McDermott, M. C.; Stephenson, G. R.; Hughes, D. L.; Walkington, A. J. *Org. Lett.* **2006**, *8*, 2917−2920.

(5) Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677−2678.

(6) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585−4595.

(7) The figures illustrate the insertion occurring before formation of the π-complex; however, it is also possible that the π-complex reversibly forms first, or that the two steps occur together.

(8) Evidence suggests that related (albeit cationic) insertion reactions are fast relative to N−Ar rotation of anilides bearing bulky *o*-substituents (ref 3b). See (a) Brown, J. M.; Pérez-Torrente, J. J.; Alcock, N. W.; Clase, H. J. *Organometallics* **1995**, *14*, 207−213. (b) Brown, J. M.; Hii, K. K. *Angew. Chem., Int. Ed.* **1996**, *35*, 657−659. Alternatively, if N−Ar rotation of **10** is faster than insertion, then axial chirality dictates product configuration in a dynamic thermodynamic resolution.

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