J|A|C|S
COMMUNICATIONS

Ir-Catalyzed Cross-Coupling of Styrene Derivatives with Allylic Carbonates: Free Amine Assisted Vinyl C−H Bond Activation

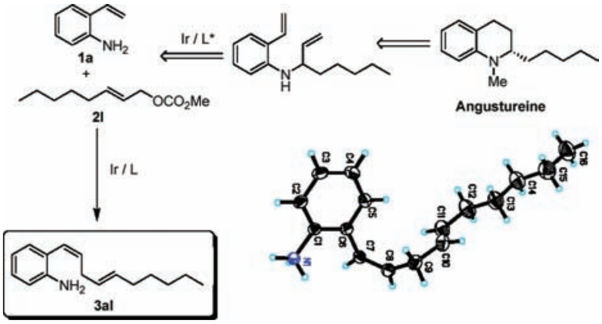
Hu He, Wen-Bo Liu, Li-Xin Dai, and Shu-Li You*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

Received February 23, 2009; E-mail: slyou@mail.sioc.ac.cn

The Heck reaction, one of the most elegant methods for the derivatization of C═C bonds, has found numerous applications in both academic and industrial laboratories.[1,2] However, most of the successful examples are carried out in the presence of a palladium catalyst and provide a C−C bond formation product with a characteristically *trans* double bond (*E* geometry).[2] As part of our ongoing efforts devoted to the development of Ir-catalyzed allylic substitution reactions,[3,4] we originally devised the synthesis of enantiopure tetrahydroquinolines via an Ir-catalyzed asymmetric allylic amination[5] of allylic carbonate **2l** with 2-vinylaniline **1a** and a subsequent ring-closing metathesis (RCM) reaction. To our great surprise, an unprecedented *cis*-Heck-type product **3al**, a skipped *Z*, *E* diene, was observed instead of the desired amination product (Scheme 1). More strikingly, a *cis* double bond was formed exclusively, as confirmed by an X-ray analysis and NMR study. Mechanistic studies disclose that this is a cross-coupling reaction via the amine assisted vinyl C−H bond activation.[6] This protocol serves as a complementary approach to the traditional Heck reaction which usually affords the *trans*-products. In this paper, we report the preliminary results.

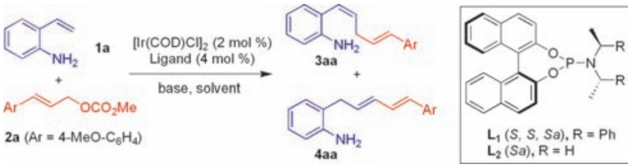
Scheme 1. Ir-Catalyzed Formation of **3al** and X-ray Structure of **3al** HCl Salt (Thermal Ellipsoids Are Set at 30% Probability)



For initial optimization of the reaction conditions, 2-vinylaniline (**1a**) and (*E*)-3-(4-methoxyphenyl)allyl methyl carbonate (**2a**) were chosen as the model substrates. The results are summarized in Table 1. Different ligands such as PPh_3, $P(OPh)_3$, dppe, Feringa's ligand (**L₁**), and **L₂** were tested in the presence of $[Ir(COD)Cl]_2$ (2 mol %) and DBU (110 mol %) in degassed THF at 60 °C, and only **L₁** proved to be an effective ligand (entries 1−5). Notably, byproduct **4aa** was also observed, which might be resulted from **3aa** through an Ir-catalyzed isomerization.[7] Fortunately, the formation of byproduct **4aa** can be reduced by altering the reaction conditions.

After examining various bases and solvents, the optimized conditions were obtained: 2 mol % of $[Ir(COD)Cl]_2$, 4 mol % of **L₁**, and 1.1 equiv of K_3PO_4 in THF at 60 °C (entry 9, Table 1). Under these conditions, various 2-vinylanilines and allyl carbonates were examined.

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	solvent	base	temp (°C)	*t* (h)	conv (%)[b]	**3aa/4aa**[c]
1	PPh_3	THF	DBU	60	12	−	−
2	$P(OPh)_3$	THF	DBU	60	12	−	−
3	dppe	THF	DBU	60	12	−	−
4	**L₂**	THF	DBU	60	12	−	−
5	**L₁**	THF	DBU	60	2	>95 (71)	80:20
6	**L₁**	THF	DABCO	60	3	>95 (69)	95:5
7	**L₁**	THF	Cs_2CO_3	60	2	>95 (84)	95:5
8	**L₁**	THF	KOAc	60	2	>95 (61)	95:5
9	**L₁**	**THF**	**K_3PO_4**	**60**	**2**	**>95 (87)**	**95:5**
10	**L₁**	THF	−	60	6	−	−
11	**L₁**	DCM	K_3PO_4	reflux	2	>95	81:19
12	**L₁**	dioxane	K_3PO_4	60	16	62	n.d.
13	**L₁**	toluene	K_3PO_4	60	16	33	n.d.
14	**L₁**	CH_3CN	K_3PO_4	60	4	>95 (86)	90:10
15	**L₁**	DME	K_3PO_4	60	2	>95 (85)	84:16
16	**L₁**	Et_2O	K_3PO_4	reflux	16	61	n.d.

[a] Reaction conditions: 0.2 mmol of **1a**, 0.22 mmol of **2a**, 0.22 mmol of base in solvent (2 mL). [b] Isolated yield in the parentheses. [c] Determined by ^1H NMR.

As summarized in Table 2, reaction of different aryl allylic carbonates bearing either electron-donating groups (*p*-OMe, *p*-Me, *m*-OMe, *o*-OMe) (entries 1−2, 6−7) or electron-withdrawing groups (*p*-F, *m*-Cl, *p*-Br, *p*-CF_3) (entries 3−5, 8) with 2-vinylaniline **1a** all led to their corresponding cross-coupling products in excellent yields (86−99%). In addition, the reaction of 1-naphthyl-substituted and 2-furyl-substituted allyl carbonates with **1a** led to their corresponding products in excellent yields (98% and 92%, entries 10−11). To our delight, various aliphatic carbonate substrates **2l**−**2r** derived from *γ*-alkylallyl alcohols were well tolerated and afforded the cross-coupling products in excellent yields with exclusive formation of product **3** (90−95%, entries 12−17). The simple allyl carbonate **2r** gave the product **3ar** in slightly lower yield (75%, entry 18).

Different 2-vinylaniline derivatives were also tested under the above optimized conditions. Substrates bearing either electron-withdrawing groups (**1b**−**d**) or electron-donating group (**1e**) were well tolerated (78−93%, entries 19−26). In general, less isomerized byproducts are observed with aliphatic allylic carbonates. Interestingly, when disubstituted alkene **5** was used, the desired alkylation products **6** were obtained without the formation of isomerized byproducts (entries 27−28). 2-Methyl allylcarbonate is also well tolerated (entry 29).

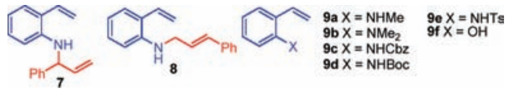
10.1021/ja901384j CCC: $40.75

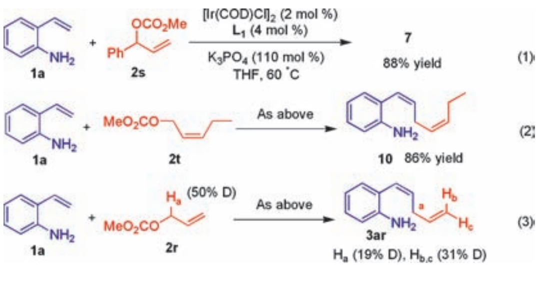
Table 2. Examination of the Reaction Substrate Scope[a]

entry	**1**, R¹ or **5**	**2**, R²	time (h)	yield (%)	**3/4**
1	**1a**, H	**2a**, 4-MeO-C_6H_4	2	**3aa**, 87	95:5
2	**1a**, H	**2b**, 4-Me-C_6H_4	4	**3ab**, 93	98:2
3	**1a**, H	**2c**, 4-CF_3-C_6H_4	3	**3ac**, 95	97:3
4	**1a**, H	**2d**, 4-F-C_6H_4	4	**3ad**, 93	99:1
5	**1a**, H	**2e**, 4-Br-C_6H_4	2	**3ae**, 99	96:4
6	**1a**, H	**2f**, 2-MeO-C_6H_4	4	**3af**, 86	99:1
7	**1a**, H	**2g**, 3-MeO-C_6H_4	2	**3ag**, 92	97:3
8	**1a**, H	**2h**, 3-Cl-C_6H_4	4	**3ah**, 99	95:5
9	**1a**, H	**2i**, Ph	4	**3ai**, 94	96:4
10	**1a**, H	**2j**, 1-naphthyl	4	**3aj**, 98	96:4
11	**1a**, H	**2k**, 2- furyl	4	**3ak**, 92	97:3
12	**1a**, H	**2l**, n-C_5H_{11}	2	**3al**, 95	>99:1
13	**1a**, H	**2m**, n-C_4H_9	2	**3am**, 92	>99:1
14	**1a**, H	**2n**, n-C_3H_7	2	**3an**, 93	>99:1
15	**1a**, H	**2o**, n-C_2H_5	2	**3ao**, 94	>99:1
16	**1a**, H	**2p**, n-CH_3	2	**3ap**, 94	>99:1
17	**1a**, H	**2q**, $CH_3CH{=}CH$	2	**3aq**, 90	>99:1
18	**1a**, H	**2r**, H	2	**3ar**, 75	>99:1
19	**1b**, 5-Br	**2a**, 4-MeO-C_6H_4	6	**3ba**, 91	95:5
20	**1b**, 5-Br	**2n**, n-C_3H_7	4	**3bn**, 93	>99:1
21	**1c**, 4,5-Br, Br	**2e**, 4-Br-C_6H_4	3	**3ce**, 73	91:9
22	**1c**, 4,5-Br, Br	**2n**, n-C_3H_7	3	**3cn**, 83	97:3
23	**1d**, 4-Cl	**2a**, 4-MeO-C_6H_4	4	**3da**, 82	97:3
24	**1d**, 4-Cl	**2n**, n-C_3H_7	3	**3dn**, 78	>99:1
25	**1e**, 5-Me	**2e**, 4-Br-C_6H_4	3	**3ee**, 86	96:4
26	**1e**, 5-Me	**2n**, n-C_3H_7	3	**3en**, 83	99:1
27	**5**	**2e**, 4-Br-C_6H_4	4	**6e**, 80	>99:1
28	**5**	**2n**, n-C_3H_7	3	**6n**, 51	>99:1
29	**1a**, H	$CH_2{=}C(Me)CH_2OCO_2Me$	6	**3au**, 96	>99:1

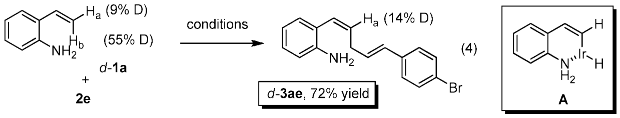
[a] Ratio of **3/4** was determined by ^1H NMR.

Initial experiments have been carried out to understand the reaction mechanism. To test whether the products are formed from allylic amination product via double [3, 3′] sigmatropic rearrangements, the amination products **7** and **8** were synthesized and tested under the optimized conditions respectively. The fact that no desired product was observed suggests that the reaction through double [3, 3′] sigmatropic rearrangements is less likely. No reaction occurred when styrene or **9a−c** was used, while allylic substitution reactions proceeded when substrates **9d−f** (X = NHBoc, NHTs, OH) were used.





The reactions of **1a** with **2s** and **2t** led to the allylic amination product **7** and *Z*, *Z* diene **10**, respectively (eqs 1−2), and the latter is in accord with the report by Takeuchi.[4c] When monodeuterated **2r** was used (eq 3), a deuterium label was distributed at both the allyl termini suggesting the existence of π-allyl-Ir in the cross-coupling with simple allyl carbonate. In addition, when substrate *d*-**1a**, 9 atom % (H_a) and 55 atom % (H_b) deuterated at the terminal alkene, was used, product *d*-**3ae** was obtained with 14 atom % deuterated at H_a (eq 4).[8] Since the deuterated ratio of H_a does not change significantly, the reaction occurring through the Heck reaction or direct allylic alkylation by 2-vinylaniline acting as a conjugated enamine is also excluded. For either of the last two cases, the ratio of the deuterated H_a should be highly increased and exclusive *cis* double bond formation is difficult to be explained. On the basis of the above experiments, an iridium-catalyzed amine-assisted vinyl C−H bond activation process is proposed,[9] through an intermediate A.



In summary, we have found that $[Ir(COD)Cl]_2$/Feringa’s ligand efficiently catalyzes the cross-coupling of *o*-amino styrene derivatives with allylic carbonates. The reaction affords unprecedented skipped *Z*, *E* dienes with the exclusive formation of a *cis* double bond and is complementary to the traditional Heck reaction. Further studies on the reaction mechanism are currently underway in the lab.

Acknowledgment. We thank the NSFC (20872159, 20821002), National Basic Research Program of China (973 Program 2009CB825300), and the STCSM (07pj14106, 07JC14063) for generous financial support.

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

References

(1) (a) Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083. (b) Heck, R. F. *Org. React.* **1982**, 27.
(2) (a) For recent reviews: Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev* **2000**, *100*, 3009. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (c) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (e) Koopmans, C.; Iannelli, M.; Kerep, P.; Klink, M.; Schmitz, S.; Sinnwell, S.; Ritter, H. *Tetrahedron* **2006**, *62*, 4709. (f) Arisawa, M. *Chem. Pharm. Bull.* **2007**, *55*, 1099.
(3) (a) He, H.; Zheng, X.-J.; Li, Y.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2007**, *9*, 4339. (b) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815.
(4) (a) For reviews: Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349. (b) Helmchen, G.; Dahnz, A.; Dübon, P.; Schelwise, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. For an early report: (c) Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647.
(5) (a) For recent examples: Weihofen, R.; Tverskoy, O.; Helmchen, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5546. (b) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem.—Eur. J.* **2006**, *12*, 3596. (c) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508. (d) Defieber, C.; Ariger, M. A.; Moriel, P.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 3139. (e) Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 11680. (f) Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949. (g) Spiess, S.; Welter, C.; Franck, G.; Taquet, J.; Helmchen, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 7652.
(6) For a recent example: Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082.
(7) (a) Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, *125*, 13000. (b) Trost, B. M.; Zhang, T. *Org. Lett.* **2006**, *8*, 6007. (c) Nelson, S. G.; Wang, K. *J. Am. Chem. Soc.* **2006**, *128*, 4324.
(8) The increased deuterated ratio is likely due to Ir-catalyzed H/D exchange: Zhou, J.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2008**, *47*, 5783.
(9) (a) Selected recent examples for the protected amine-assisted C−H activation: Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (b) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (c) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (e) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560.

JA901384J