A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Palladium-Catalyzed Tandem Divergent Cyclopropanation via Solvent-Driven Regioselective C(sp3)-H Bond Activation

Authors: Da Sol Chung, Jae Sung Lee, Ho Ryu, Jiong Park, Hyunjoong Kim, Joo Hyun Lee, U Bin Kim, Won Koo Lee, Mu-Hyun Baik, and Sang-gi Lee

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201809133
Angew. Chem. 10.1002/ange.201809133

Link to VoR: http://dx.doi.org/10.1002/anie.201809133
http://dx.doi.org/10.1002/ange.201809133

WILEY-VCH

10.1002/anie.201809133

WILEY-VCH

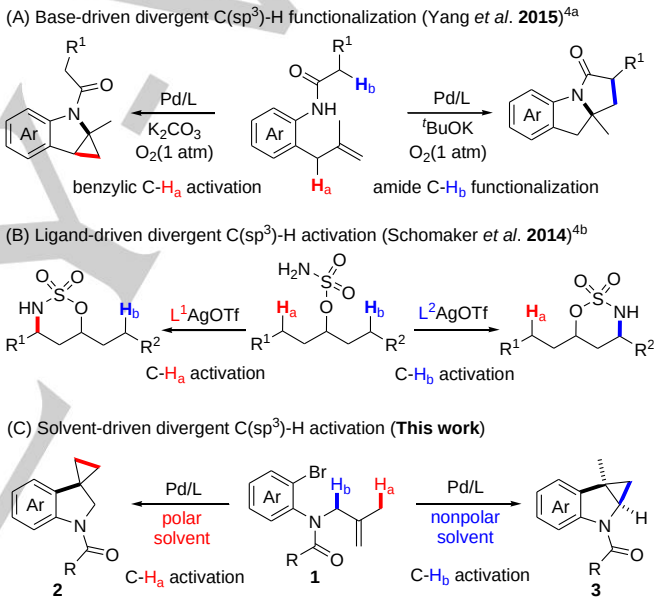
Palladium-Catalyzed Tandem Divergent Cyclopropanation via Solvent-Driven Regioselective C(sp^3)–H Bond Activation

Da Sol Chung[+], Jae Sung Lee[+], Ho Ryu, Jiyong Park, Hyunjoong Kim, Joo Hyun Lee, U Bin Kim, Won Koo Lee,* Mu-Hyun Baik,* and Sang-gi Lee*

Abstract: We report a palladium-catalyzed tandem Heck/regioselective C(sp^3)–H activation for divergent synthesis of spiro- and fused-cyclopropanated indolines from *N*-methallylated 2-bromoarylamides. The regioselectivity of the C–H bond activation of σ–alkylPd(II) intermediate could be controlled by the choice of the solvent used. DFT calculations suggest that the polarity of solvent molecules could influence the transition state energy, leading to a bifurcation of the C–H bond activation by the σ-alkylPd(II) intermediate.

Divergent catalysis, which can provide different products from a common precursor through intricate yet precise control of different catalytic pathways, is a highly attractive synthetic manoeuvre.[1] In particular, transition metal catalyzed C-H functionalization represents one of the most straightforward, powerful, and atom-economical methods to realize site-selective catalysis.[2] During last decades, the directing group-guided regioselective functionalization of (hetero)arene C(sp^2)-H bonds has been extensively studied.[3] However, the divergent activation of less reactive C(sp^3)-H bonds in a molecule remain far less demonstrated.[4] For example, Yang and co-workers reported base-controlled divergent C(sp^3)-H bond functionaliztions of σ-alkylPd(II) intermediates formed by Pd-catalyzed aminoalkylation of unsaturated anilides (Scheme 1A).[4a] Schomaker and co-workers utilized different ligands on Ag catalyst to tune for steric and electronic factors and regioselectively activate different C(sp^3)-H bonds of alkyl sulfamates (Scheme 1B).[4b] Herein, we report a conceptually distinctive solvent-driven regiodivergent C(sp^3)-H bond activation for tandem one-pot selective synthesis of spiro-(**2**) and fused-(**3**) cyclopropanated indolines from the same *N*-methallyl 2-bromoarylamides **1** (Scheme 1C).

Cyclopropanated *N*-heterocycles are ubiquitous scaffolds that feature prominently in natural products and bioactive molecules.[5] During our studies on divergent yet tandem catalytic processes involving σ-alkylPd (II) intermediates,[6] we envisioned a tandem Heck/regiodivergent C(sp^3)-H bond activation reaction where using a solvent "switch", manipulation of the spatial conformation of σ-alkylPd(II)-intermediate arising from Heck-type oxidative addition of **1** with Pd(0) catalyst would lead to a regiodivergent outcome. Although Heck-type palladium-catalyzed carbopalladation cascades have been utilized for construction of carbo- and heterocyclic motifs,[7] a regiodivergent activation of different C(sp^3)-H bonds mediated by the common σ-alkylPd(II)-intermediates remain unprecedented.



Scheme 1. Regiodivergent C(sp^3)–H Activations.

To effect the proposed solvent-controlled tandem Heck/regiodivergent C(sp^3)-H activation reaction, we employed **1a** as a test substrate under Pd catalysis (Table 1, for details see Tables S1 and S2 in SI). In polar coordinating solvents such as DMF and NMP, the C-H$_a$ bond of the methyl group was activated in presence of Pd(OAc)$_2$/PPh$_3$ to afford spiro-cyclopropanated **2a** as a major product along with significant amounts of dimethylated indoline **4a** (entries 1 and 2, Table 1). When 1.0 equivalent of pivalic acid was added, increased conversion was achieved, although the reaction was largely unselective, furnishing a mixture of **2a**:**3a**:**4a** with ratio of 48%:12%:21% (entry 3, Table 1). Replacing the polar NMP solvent with non-polar *p*-xylene altered the regioselectivity to result in the formation of **2a**/**3a** in a 9%:12% ratio, but undesired protonated compound **4a** (27%) was formed as the major product (entry 4, Table 1). Conversion and selectivity did not increase when using other bases such as Cs_2CO_3 in NMP or *p*-xylene (entries 5 and 6, Table 1) or when using bidentate

[*] D. S. Chung, J. H. Lee, Dr. U B. Kim, Prof. Dr. S.-g. Lee
Department of Chemistry and Nanoscience (BK21 PLUS)
Ewha Womans University, Seoul 03760 (Republic of Korea)
E-mail: sanggi@ewha.ac.kr

J. S. Lee, Prof. Dr. W. K. Lee
Department of Chemistry
Sogang University, Seoul 04107 (Republic of Korea)
E-mail: wonkoo@sogang.ac.kr

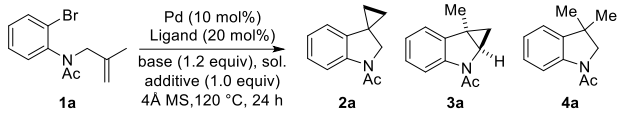
H. Ryu, Dr. J. Park, Hyunjoong Kim, Prof. Dr. M.-H. Baik
Department of Chemistry
Korea Advanced Institute of Science and Technology (KAIST),
Daejeon 34141 (Republic of Korea)
Center for Catalytic Hydrocarbon Functionalizations
Institute for Basic Science (IBS), Daejeon 34141 (Republic of Korea)
E-mail: mbaik2805@kaist.ac.kr

[+] These authors contributed equally to this work.
Supporting information and the ORCID identification numbers(s) for the author(s) of this article can be found under:

10.1002/anie.201809133

phosphine ligands such as Xantphos (see Tables S1 and S2 in SI). To our delight, when the reaction was carried out in the presence of 10 mol% $Pd(PPh_3)_4$ in polar NMP, the conversion and selectivity of the reaction was increased dramatically, furnishing **2a** as the major product in 75% yield along with 16% yield of **3a** (entry 7, Table 1). A further increase in selectivity was observed when the reaction was run in DMSO, where spiro-cyclopropanted indoline **2a** was isolated in 80% yield (entry 8, Table 1). Under such optimal conditions, only trace amounts of **3a** and **4a** were detected. Use of different acid additives such as 1-adamantyl carboxylic acid proved unfavourable for selective formation of **2a** (entry 9, Table 1).

Table 1. Selected Examples for Reaction Optimization.[a]



1a 2a 3a 4a

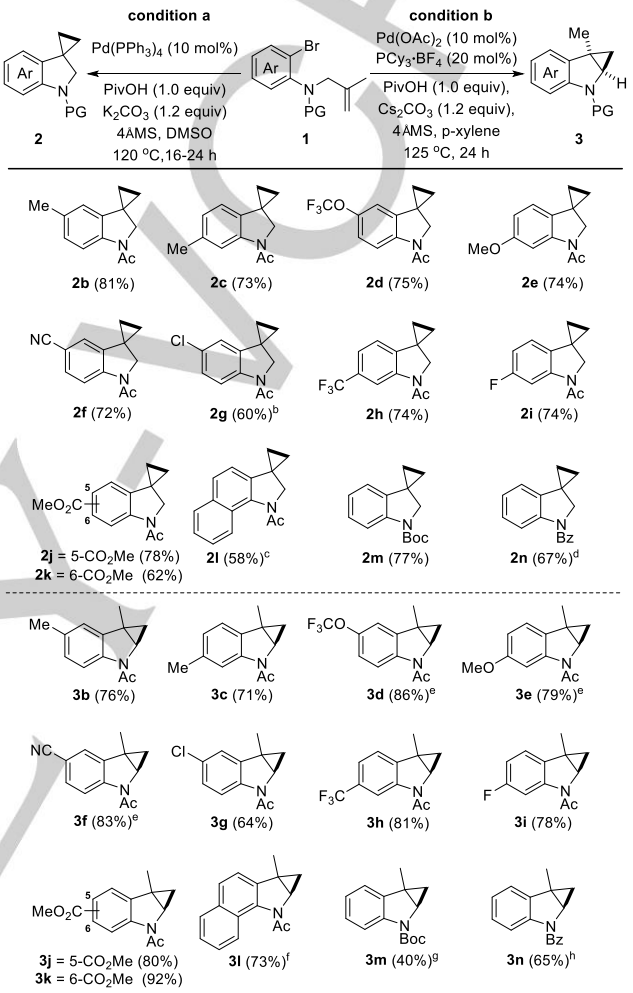
Entry	Pd/ligand	solvent	base	additive	Yield [%][b] 2a/3a/4a
1	$Pd(OAc)_2/PPh_3$	DMF	K_2CO_3	-	34/-/16
2	$Pd(OAc)_2/PPh_3$	NMP	K_2CO_3	-	43/>5/14
3	$Pd(OAc)_2/PPh_3$	NMP	K_2CO_3	PivOH	48/12/21
4	$Pd(OAc)_2/PPh_3$	*p*-xylene	K_2CO_3	PivOH	9/12/27
5	$Pd(OAc)_2/PPh_3$	NMP	Cs_2CO_3	PivOH	28/>5/12
6	$Pd(OAc)_2/PPh_3$	*p*-xylene	Cs_2CO_3	PivOH	16/39/19
7	$Pd(PPh_3)_4$	NMP	K_2CO_3	PivOH	75/16/8
8[c]	$Pd(PPh_3)_4$	DMSO	K_2CO_3	PivOH	80/9/-
9	$Pd(PPh_3)_4$	DMSO	K_2CO_3	AdOH	66/11/10
10	$Pd(PPh_3)_4$	*p*-xylene	K_2CO_3	PivOH	17/48/19
11	$Pd(PPh_3)_4$	*p*-xylene	Cs_2CO_3	PivOH	22/71/>5
12	$Pd(PPh_3)_4$	*p*-xylene	^{t}BuOK	PivOH	18/65/8
13	$Pd(OAc)_2$/ $P(p\text{-MeOPh})_3$	*p*-xylene	Cs_2CO_3	PivOH	-/5/9
14	$Pd[P^t(Bu)_3]_2$	*p*-xylene	Cs_2CO_3	PivOH	6/5/19
15[c],[d]	$Pd(OAc)_2$/ $PCy_3{\cdot}HBF_4$	*p*-xylene	Cs_2CO_3	PivOH	8/81/-
16	$Pd(PPh_3)_4$	DMF/H_2O	K_2CO_3	HCO_2NH_4	0/0/99

[a] Reaction conditions: **1a** (0.3 mmol), Pd (10 mol%), ligand (20 mol%), base (1.2 equiv), and additive (1.0 equiv) in a solvent (1.0 mL, 0.3 M) for 24 h at 120 °C. [b] Determined by ^{1}H NMR using 1,2-dimethoxy ethane as an internal reference. [c] Isolated yields of **2a** and **3a**. [d] Reaction at 125 °C.

Interestingly, the regioselectivity of C-H activation could be inversely altered by using non-polar, non-coordinating *p*-xylene as solvent to afford fused-cyclopropanated indoline **3a** as a major product, but this was accompanied by moderate selectivity (entry 10, Table 1). Varying the base and carboxylic acid additives did not improve the selectivity. Propitiously, after screening different palladium catalyst/ligand combinations, it was found that treating **1a** with 10 mol% $Pd(OAc)_2$ and 20 mol% $PCy_3{\cdot}HBF_4$ in *p*-xylene led to highly selective activation of the *endo* C-H_b bond, furnishing **3a** in 81% isolated yield (entry 15, Table 1). It was also possible to achieve efficient reductive trapping of the σ-alkylPd(II)-intermediate by using ammonium formate as an additive in a mixture of DMF/H_2O to produce **4a** as the sole product in almost quantitative yield (entry 16, Table 1). The structures of both **2a** and **3a** were established unambiguously by X-ray analysis.[8]

With the two-different optimal reaction parameters, *i.e.,* conditions **a** (entry 8, Table 1) and **b** (entry 15, Table 1), in hand for selectively activating different C(sp^3)-H bonds, a variety of spiro- **2** and fused-cyclopropanated indolines **3** were selectively synthesized from common starting material **1** (Table 2).

Table 2. Regiodivergent Synthesis of Cyclopropanated Indolines **2** and **3**.[a]

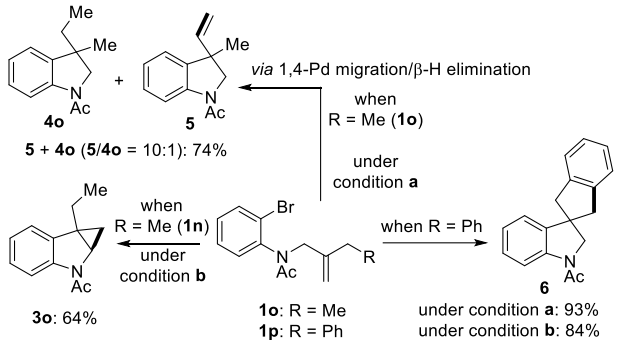


[a] Reaction conditions: **1** (0.3 mmol) and solvent (1.0 mL, 0.3 M). Isolated yields. [b] **3g** was also isolated in 15% yield. [c] **3l** was also isolated in 29% yield. [d] **3n** was also isolated in 10% yield. [e] Reaction at 115 °C. [f] Reaction at 120 °C. [g] **2m** was also isolated in 11% yield. [h] **2n** was also isolated in 12% yield.

In general, substrates showed excellent regioselectivity, and under condition **a** selectively afforded **2** (top in Table 2) and **3** under condition **b** (bottom in Table 2). Although the use of substrates **1g** and **1l** under condition **a** did produce noticeable amounts of minor products **3g** and **3l** alongside expected major products **2g** and **2l**, these were easily separated by silica column chromatography. The utility of this methodology was demonstrated by preparing spiro-cyclopropanated indoline **2k**, which is a key intermediate towards various PDE4 enzyme inhibitors.[9] Analogous fused-cyclopropanated indoline **3k** was prepared in high yield under condition **b**. Replacement of the *N*-Ac group with *N*-Boc (**1m**) or *N*-Bz groups (**1n**) showed a similar trend of regioselectivity and efficiency under established optimal conditions, resulting in the corresponding **2m-2n** and **3m-3n**.

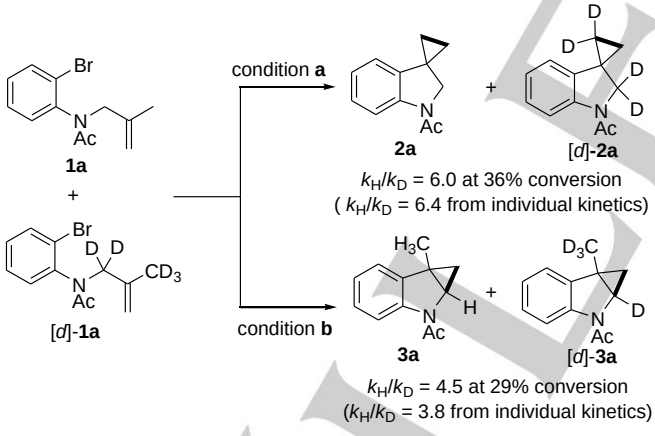
10.1002/anie.201809133

Interestingly, ethylallylated 2-bromoarylamide **1o** exhibited modified reactivity under condition **a**, furnishing inseparable mixture of vinylated indoline **5** and protonated **4o** (**5**/**4o** = 10:1, determined by ^{1}H NMR analysis) in 74% yield (Scheme 2). This observation suggested that σ-alkylPd(II)-intermediate, generated from **1o**, underwent 1,4-Pd migration followed by β-H elimination to afford **5** as a major product.[10] In contrast, subjecting **1o** under the condition **b** led to the expected fused-cyclopropanated indoline **3o** in 64% yield, alongside **5** in 21% yield. When using substrate **1p** (R = Ph) however, the phenyl C(sp^2)-H bond proved to be more activated than C(sp^3)-H bonds, affording **6** as the sole product under both conditions **a** and **b**.



Scheme 2. Modified reactivity of ethylallylated and benzylallylated 2-bromoarylamides under optimized conditions **a** and **b**.

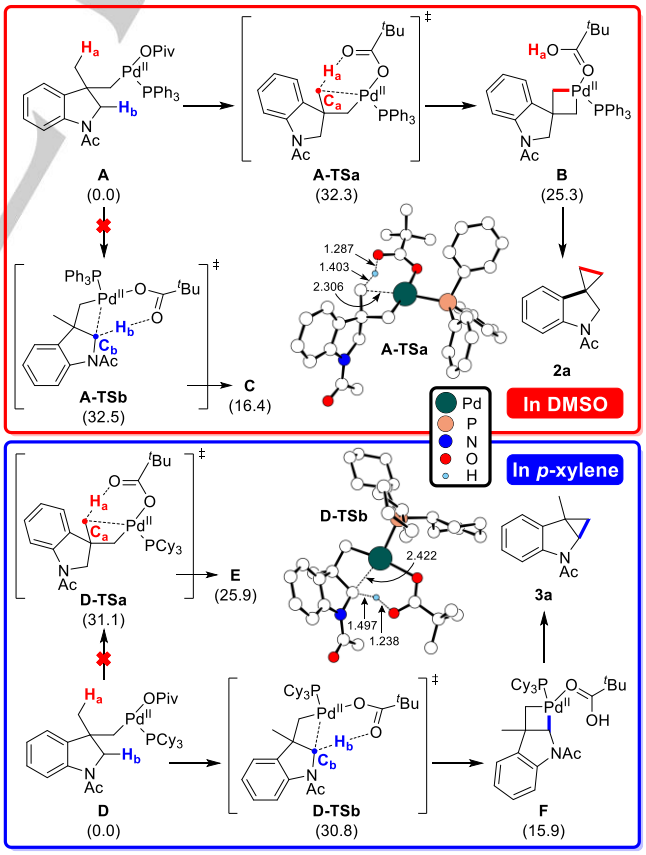
To discern the rate-determining step of these tandem Heck /C(sp^3)-H bond activation reactions,[11] intermolecular kinetic isotope effect (KIE) experiments were carried out with a 1 :1 molar mixture of **1a** and deuterated [*d*]-**1a** (Scheme 3).



Scheme 3. Kinetic Isotope Effects.

Under the optimized conditions **a** and **b** affording **2a** and **3a** respectively, significant KIEs were observed in the NMR analysis at low conversion, *i.e.*, k_H/k_D = 6.0 at 36% conversion for **2a** and k_H/k_D = 4.5 at 29% conversion for **3a**. Similar KIEs have also been observed in the early stage kinetics obtained from the independent reactions of **1a** and [*d*]-**1a** under conditions **a** and **b** affording indolines **2a** (k_H/k_D = 6.4) and **3a** (k_H/k_D = 3.8), respectively (Figure S1 in SI). These results clearly implicate C-H bond cleavage to be the turnover limiting step in both conditions **a** and **b**. In addition, the optimal reaction conditions suggest that both of C(sp^3)-H$_a$ and C(sp^3)-H$_b$ activation reactions likely follow the inner-sphere pivalate-assisted concerted-metalation-deprotonation (CMD) mechanistic pathway, which was proposed for related Pd-catalyzed C(sp^3)-H activation reactions.[12]

Initially we anticipated that the intramolecular coordination between Pd(II) and the amide carbonyl may affected by the solvent polarity, controlling the regioselectivity in C-H activation. Therefore, we initially monitored the amide C=O absorption bands of the σ-alkylPd(II)-complexes generated by reaction of **1a** and 1.0 equivalent of Pd(PPh$_3$)$_4$ at 100 °C in both DMSO and *p*-xylene using time-resolved infrared spectroscopy. The amide carbonyl stretching vibration in **1a** was slightly shifted to shorter wave numbers ($\Delta\nu$ = 11 cm^{-1} in p-xylene, $\Delta\nu$ = 4 cm^{-1} in DMSO) (see SI), but these shifts are too small to imply that Pd(II) coordinates to the amide carbonyl, leading to the observed regioselectivity. Next, we carried out density functional theory (DFT) calculations and located the transition states leading to both products. Surprisingly, these calculations indicate that the indoline skeleton is too rigid to allow the σ-alkylPd(II)-moiety to reach across the five-membered ring to bind to the amide-carbonyl. Instead, a subtle effect based on the polarity of the solvents is suggested. The observed selectivity indicates that the energy difference governing the divergence of these reactions is small, within ~1 kcal/mol. Solvation corrected quantum chemical calculations, including DFT-methods, are not accurate enough to reliably model these effects, but some plausible insight can be derived nonetheless.



Scheme 4. DFT-calculated transition states and energies. The unit of energy is kcal/mol.

As summarized in Scheme 4 and Figure 1, our calculations show that the transition state **A-TSa** leading to the spiro-cyclopropanated product is slightly disfavored over **A-TSb**, which gives the fused-cyclopropanated product, by 0.3 kcal/mol in gas phase. This energy difference is slightly increased to 0.6 kcal/mol between **D-TSa** and **D-TSb**, when the PCy_3 ligand is used instead of PPh_3. Interestingly, the molecular surface areas of the two transition states are quite different and we found that the transition states leading to the spiro-cyclopropanated products **A/D-TSa** have larger surface areas of 543 and 548 Å^2, whereas 526 and 545 Å^2 are found in **A/D-TSb**, respectively. Consequently, **A/D-TSa** have slightly higher solvation energy than **A/D-TSb**, as illustrated in Figure 1. In *p*-Xylene with a dielectric constant of 2.27, the difference in solvation energy is not enough to reverse the order of the two transition states, and **D-TSb** is calculated to be at 30.8 kcal/mol, which is slightly lower than **D-TSa** at 31.1 kcal/mol. As the DMSO solvent is more polar, the solvation energy difference becomes larger and ultimately renders **A-TSa** slightly lower in energy than **A-TSb**, as illustrated in Figure 1. Whereas these energy differences are too small to be trusted in a quantitative sense, the qualitative rationale behind these numbers is plausible, namely, the regioselectivity is connected to the molecular surface area of the transition states leading to the spiro-cycloproanated product being favored in the more polar DMSO solvent.

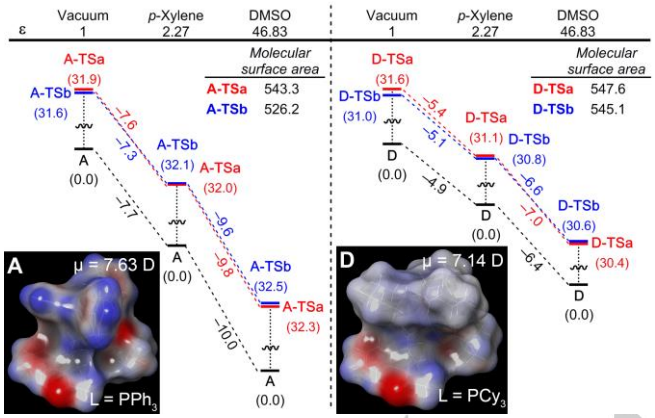


Figure 1. DFT-calculated energies and solvation energy corrections. The unit of energy is kcal/mol.

In summary, we have developed a conceptually distinctive tandem Heck/regiodivergent C(sp^3)-H bond activation reaction to selectively construct both spiro- and fused-cyclopropanated indolines starting from the same *N*-methallylated *N*-acyl-2-bromoanilines. DFT-calculations suggest that the regioselectivity is governed by the fact that the fused-product is favored in gas phase and also in low dielectric media, where the solvation energies are relatively small. The transition state leading to the spiro-fused product shows a larger molecular surface and becomes more favorable in high dielectric media. Further studies on other solvent-driven divergent catalytic reactions are currently underway.

Acknowledgements

This work was made possible by the support of the National Research Foundation (NRF-2016R1A2B2013727). D. S. Chung thanks to the Solvay Fellowship. We thank Dr Y. Kim for X-ray analysis. We also thank Prof. S. Chang at KAIST for sharing time-resolved infrared spectrometry. MHB acknowledges the financial support from the Institute for Basic Science (IBS-R10-D1).

Keywords: Divergent catalysis • Palladium • C-H activation • Cyclopropanation • Indolines

[1] a) L. Li, Z. Chen, X. Zhang, Y. Jia, *Chem. Rev.* **2018**, *118*, 3752-3832; b) J. Hou, A. Ee, W. Feng, J.-H. Xu, Y. Zhao, J. Wu, *J. Am. Chem. Soc.* **2018**, *140*, 5257-5263; c) H. Zhou, W. Chen, Z. Chen, *Org. Lett.* **2018**, *20*, 2590-2594; d) F. A. Cruz, V. M. Dong, *J. Am. Chem. Soc.* **2017**, *139*, 1029-1032; e) Q.-Q. Cheng, M. Lankelma, D. Wherritt, H. Arman, M. P. Doyle, *J. Am. Chem. Soc.* **2017**, *139*, 9839-9842; f) T.-R. Li, L.-Q. Lu, Y.-N. Wang, B.-C. Wang, W.-J. Xiao, *Org. Lett.* **2017**, *19*, 4098-4101; g) Y. Wei, M. Shi, *ACS Catal.* **2016**, *6*, 2515-2524; h) J.-Y. Liao, P.-L. Shao, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 628-631.

[2] a) N. Della Ca', M. Fontana, E. Motti, M. Catellani, *Acc. Chem. Res.* **2016**, *49*, 1389-1400; b) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.* **2015**, *115*, 12138-12204; c) L. Yang, H. Huang, *Chem. Rev.* **2015**, *115*, 3468-3517; d) J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369; e) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009; f) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879-5918; g) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740-4761; h) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902-4911; i) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890-931; j) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624-655; k) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654-2672.

[3] a) L. Ping, D. S. Chung, J. Bouffard, S.-g. Lee, *Chem. Soc. Rev.* **2017**, *46*, 4299-4328; b) J. A. Leitch, Y. Bhonoah, C. G. Frost, *ACS Catal.* **2017**, *7*, 5618-5627; c) O. Daugulis, J. Roane, L. D. Tran, *Acc. Chem. Res.* **2015**, *48*, 1053-1064; d) Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong, *Chem. Soc. Rev.* **2015**, *44*, 7764-7786; e) M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li, W. Su, *Org. Chem. Front.* **2014**, *1*, 843-895; f) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726-11743; g) G. Rousseau, B. Breit, *Angew. Chem. Int. Ed.* **2011**, *50*, 2450-2494; h) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147-1169.

[4] a) W. Du, Q. Gu, Z. Li, D. Yang, *J. Am. Chem. Soc.* **2015**, *137*, 1130-1135; b) J. M. Alderson, A. M. Phelps, R. J. Scamp, N. S. Dolan, J. M. Schomaker, *J. Am. Chem. Soc.* **2014**, *136*, 16720-16723; c) J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 10954-10990; d) A. Renaudat, L. Jean-Gérard, R. Jazzar, C. E. Kefalidis, E. Clot, O. Baudoin, *Angew. Chem. Int. Ed.* **2010**, *49*, 7261-7265; e) A. Kros, W. Jesse, G. A. Metselaar, J. J. L. M. Cornelissen, *Angew. Chem. Int. Ed.* **2005**, *44*, 4349-4352.

[5] a) S. Arai, M. Nakajima, A. Nishida, *Angew. Chem. Int. Ed.* **2014**, *53*, 5569-5572; b) M. Zhang, F. Jovic, T. Vickers, B. Dyck, J. Tamiya, J. Grey, J. A. Tran, B. A. Fleck, R. Pick, A. C. Foster, C. Chen, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3682-3686.

[6] J. H. Kim, J. Bouffard, S.-g. Lee, *Angew. Chem. Int. Ed.* **2014**, *53*, 6435-6438.

[7] a) T. Yao, D. He, *Org. Lett.* **2017**, *19*, 842-845; b) H. Yoon, A. Lossouarn, F. Landau, M. Lautens, *Org. Lett.* **2016**, *18*, 6324-6327; c) A. Düfert, D. B. Werz, *Chem. Eur. J.* **2016**, *22*, 16718-16732; d) K. Yuan, J.-F. Soulé, V. Dorcet, H. Doucet, *ACS Catal.* **2016**, *6*, 8121-8126; e) W. Kong, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 16028-16031; f) H. Ohno, *Asian J. Org. Chem.* **2013**, *2*, 18-28.

[8] X-ray data: 2a (CCDC: 1473532) and 3a (CCDC: 1473531), for details, see SI. CIF files are also available free from charge on http://www.ccdc.cam.ac.uk

[9] A. Nardi, F. Jakob, I. Konetzki, T. Craan, C. Hesslinger, R. Doodeman, WO2016008593A1, **2014**. For details of **2k** preperation please see supporting information.

[10] a) F. Shi, R. C. Larock, in *C-H Activation* (Eds.: J.-Q. Yu, Z. Shi), Springer Berlin Heidelberg, Berlin, Heidelberg, **2010**, pp. 123-164; b) T.-J. Hu, M.-Y. Li, Q. Zhao, C.-G. Feng, G.-Q. Lin, *Angew. Chem. Int. Ed.* **2018**, *57*, 5871-5875; c) T. Kesharwani, R. C. Larock, *Tetrahedron* **2008**, *64*, 6090-6102; d) S. Ma, Z. Gu, *Angew. Chem. Int. Ed.* **2005**, *44*, 7512-7517.

[11] a) H. Wang, C. Grohmann, C. Nimphius, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 19592-19595; b) Y. Wei, I. Deb, N. Yoshikai, *J. Am. Chem. Soc.* **2012**, *134*, 9098-9101; c) E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2012**, *51*, 3066-3072.

[12] a) T. Saget, N. Cramer, *Angew. Chem. Int. Ed.* **2013**, *52*, 7865-7868; b) E. Larionov, M. Nakanishi, D. Katayev, C. Besnard, E. P. Kündig, *Chem. Sci.* **2013**, *4*, 1995-2005; c) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066-1067; d) M. Lafrance, C. N. Rowley, T. K. Woo, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 8754-8756.

10.1002/anie.201809133

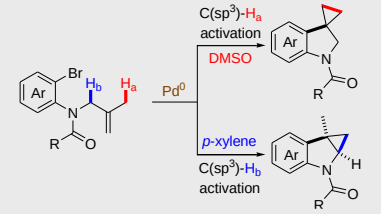
WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Solvent paves the way: Choice of solvent for Pd-catalyzed tandem Heck/regiodivergent C(sp^3)-H bond activation enables construction of different C-C bonds selectively from a common precursor, affording spiro- or fused cyclopropanated indolines at will.



Da Sol Chung+, Jae Sung Lee+, Ho Ryu, Jiyong Park, Joo Hyun Lee, U Bin Kim, Won Koo Lee, Mu-Hyun Baik* and Sang-gi Lee**

Page No. – Page No.

Palladium-Catalyzed Tandem Divergent Cyclopropanation via Solvent-Driven Regioselective C(sp^3)–H Bond Activation