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N-Acylsulfonamide Assisted Tandem C−H Olefination/Annulation: Synthesis of Isoindolinones

Chen Zhu* and J. R. Falck

Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75390, United States

chen.zhu@utsouthwestern.edu

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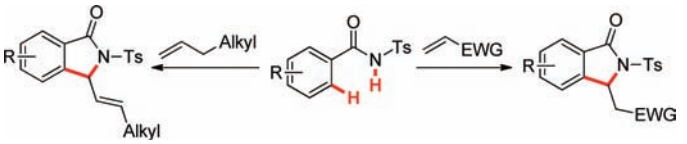
ABSTRACT



A tandem C−H olefination/annulation sequence directed by *N*-acylsulfonamides affords a variety of isoindolinones. This transformation is compatible with aliphatic alkenes as well as conjugated alkenes. Notably, molecular oxygen can be used as the sole, eco-friendly oxidant.

Pd(II)-mediated aromatic C(sp^2)−H olefinations (Fujiwara−Moritani reactions) have emerged as a powerful tool for C−C bond formation.[1,2] Indeed, the utility and unique characteristics of this reaction have been cogently demonstrated in the total synthesis of polyfunctional natural products of current interest and for the efficient construction of bioactive scaffolds.[3] Generally, nitrogen- or oxygen-containing directing groups are required for acceptable reactivity and selectivity using the Fujiwara−Moritani reaction.[4,5] Hence, it is apparent that both synthetic efficiency and atom economy would be greatly extended if the heteroatom served as both the directing group and precursor to a C−X bond (X = N, O). An early example of this concept was provided by Miura and co-workers who revealed benzoic acid could direct tandem C−H olefination and C−O formation, albeit in unsatisfying yields;[6] more recently, the Yu group demonstrated that a triflamide and tertiary hydroxyl were competent

(1) For initial reports, see: (a) Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119. (b) Fujiwara, Y.; Moritani, I.; Matsuda, M.; Teranishi, S. *Tetrahedron Lett.* **1968**, *9*, 633.

(2) For reviews, see: (a) Moritani, I.; Fujiwara, Y. *Synthesis* **1973**, 524. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (c) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(3) (a) Trost, B. M.; Godleski, S. A.; Genêt, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 3930. (b) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1993**, *115*, 9323. (c) Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904. (d) Garg, N. K.; Caspi, D. D.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 9552. (e) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004.

(4) For examples of Pd(II) catalyzed C−H olefination with directing groups, see: (a) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (b) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156. (c) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (d) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (e) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066. (f) García-Rubia, A.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511. (g) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (h) Shi, B. F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460. (i) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169. (j) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972. (k) García-Rubia, A.; Urones, B.; Arrayás, R. G.; Carretero, J. C. *Chem.—Eur. J.* **2010**, *16*, 9676.

(5) For examples of Pd(II) catalyzed C−H olefinations without directing groups, see: (a) Fujiwara, Y.; Maruyama, O.; Yoshidomi, M.; Taniguchi, H. *J. Org. Chem.* **1981**, *46*, 851. (b) Itahara, T.; Ikeda, M.; Sakakibara, T. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1361. (c) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (d) Beccalli, E. M.; Broggini, G. *Tetrahedron Lett.* **2003**, *44*, 1919. (e) Ma, S.; Yu, S. *Tetrahedron Lett.* **2004**, *45*, 8419. (f) Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250. (g) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. (h) Zhang, X.; Fan, S.; He, C.-Y.; Wan, X.; Min, Q.-Q.; Yang, J.; Jiang, Z.-X. *J. Am. Chem. Soc.* **2010**, *132*, 4506.

(6) (a) Miura, M.; Tsuda, T.; Satoh, T.; Pivsa-Art, S.; Nomura, M. *J. Org. Chem.* **1998**, *63*, 5211. Also see: (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (c) Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2007**, *72*, 5362.

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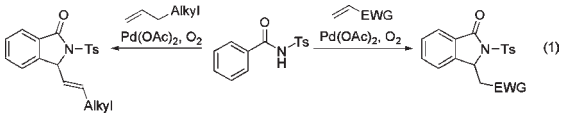
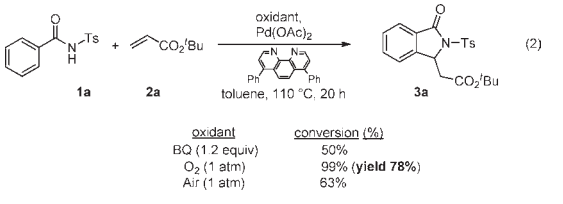
directing groups for the cascade process of C−H olefination/C−X bond formation resulting in six-membered heterocycles.[7,8] However, in those cases, the annulation was strictly limited to electron-deficient olefins. Herein, we disclose tosyl amide as a new directing group that affords the isoindolinone motif via a sequence of C−H olefination followed by C−N bond formation. Another notable feature is the use of molecular oxygen as the sole oxidant and shows the preference for the Pd^{II}/Pd^{0} redox cycle. Importantly, this transformation is broadly compatible with aliphatic alkenes as well as activated alkenes; the specific type of adduct formed is dictated by the electronic properties of the alkene (eq 1).

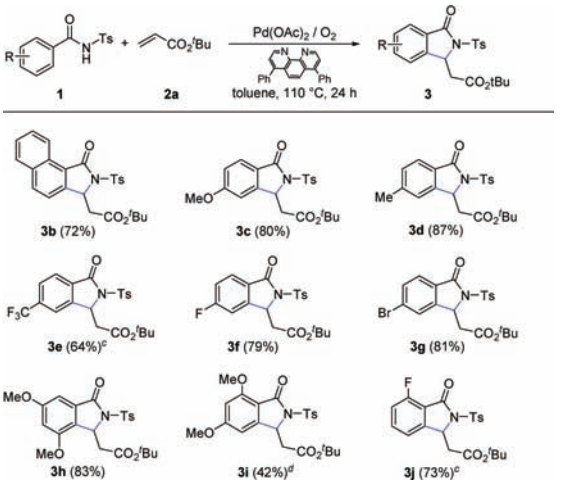


For the initial survey of reaction conditions and optimization, *N*-tosylbenzamide and *tert*-butyl acrylate were selected as model substrates since they were commercially available and amenable to deprotection and/or manipulation following annulation. Subsequent screening campaigns established some important reaction parameters:[9] (i) $Pd(OAc)_2$ performed as well or better than other commercial Pd(II)-catalysts, (ii) bathophenanthroline was much superior to other intermediaries of the catalytic Pd^{II}/Pd^{0} redox cycle, and (iii) toluene furnished better yields than THF, CH_3CN, DMSO, and other common solvents. While benzoquinone (BQ) is one of the most commonly used oxidants for Pd(II)-catalyzed C−H activations, and also works in our reaction, we were delighted to discover eco-friendly molecular oxygen had a higher turnover number than BQ and could function as the sole oxidant in the absence of other co-oxidants.[10] Indeed, the anticipated annulation adduct **3a** was isolated in good chemical yield when the optimized conditions were employed (eq 2).



Encouraged by this result, we applied the method to a variety of substituted *N*-tosylbenzamides (Scheme 1). The tandem process readily provided isoindolinones regardless

Scheme 1. Reaction Scope Using Various *N*-Tosylbenzamides[a,b]



[a] **1** (0.1 mmol), alkene (0.12 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.012 mmol) and O_2 (1 atm). [b] Isolated yield. [c] 72 h. [d] Performed for 80 h using 20 mol % $Pd(OAc)_2$ and 24 mol % bathophenanthroline.

of the electronic properties of the aryl substituent(s). For instance, the electron-donating methoxy (**3c**) and methyl group (**3d**) as well as fluoride (**3f**) all furnished their respective adducts in high yields. The chemoselective formation of **3g**, without a competitive Heck reaction by the aryl bromide, is noteworthy, as the latter provides functionality for subsequent Pd(0)-mediated cross-coupling reactions. Acceptable yields of adduct when strong electron-withdrawing groups were present, e.g., CF_3, generally required prolonged reaction times (**3e**). The facile annulation of **3h** compared with the somewhat sluggish closure of the regioisomeric **3i** is also of interest and can be attributed to the torsional hindrance from the *ortho*-methoxy in **3i**, which prevents the amide from achieving optimum overlap with the aromatic ring. To confirm this hypothesis, a comparable experiment was carried out by replacing the bulky *ortho*-methoxy with an *ortho*-fluoro group. As might be anticipated from the foregoing discussion, the annulation of **3j** proceeded with an obviously better reaction rate and in higher yield than **3i**.

The range of acceptable alkenes was also investigated. When subjected to the preceding reaction conditions, electron-deficient alkenes, e.g., a conjugated ester (**4a**), ketone (**4b**), and amide (**4c**), smoothly evolved adducts **4** (Scheme 2). Even 2,4-pentadienoate and the α-branched olefin methacrylate were suitable, affording **4d** and **4e**, respectively.

Despite the otherwise rare participation of simple aliphatic alkenes in C−H olefinations owing to their poor reactivity, we found terminal aliphatic alkenes were readily converted into annulated adducts (Table 1). Not only simple alkene (**5a**) but also functionalized alkenes such as aliphatic ester (**5b**), aliphatic chloride (**5c**), and aryl substituted alkene (**5d**) were suitable substrates for the annulation cascade. An intriguing example of specificity

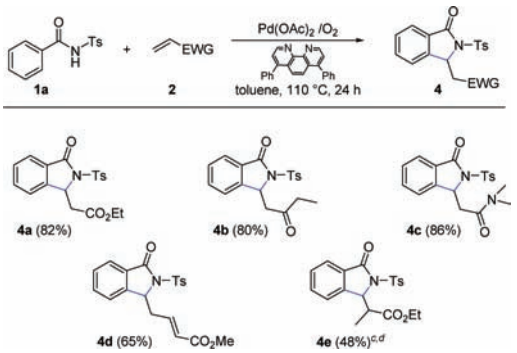
(7) (a) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (b) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916.

(8) For an example of tandem C(sp^3)−H olefination/C−N formation, see: Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680.

(9) See Supporting Information for details of reaction parameter screening.

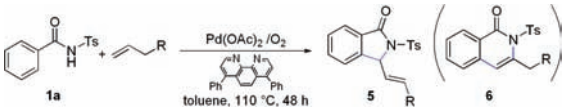
(10) For examples of using O_2 as an oxidant in C−H olefination, see: (a) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (b) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137.

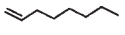
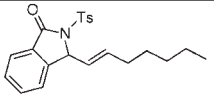
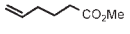
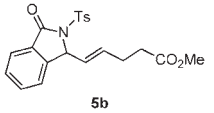
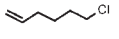
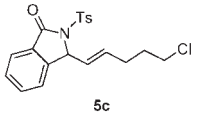
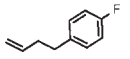
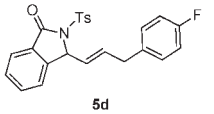
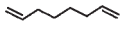
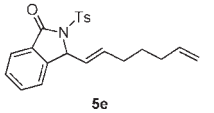
Scheme 2. Reaction Scope with Activated Alkenes[a,b]



[a] **1** (0.1 mmol), alkene (0.12 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.012 mmol), and O_2 (1 atm). [b] Isolated yield. [c] Reaction performed for 72 h using 20 mol % $Pd(OAc)_2$ and 24 mol % bathophenanthroline. [d] dr = 1.4:1, separated by preparative TLC.

Table 1. Reaction Scope with Nonconjugated Alkenes[a]

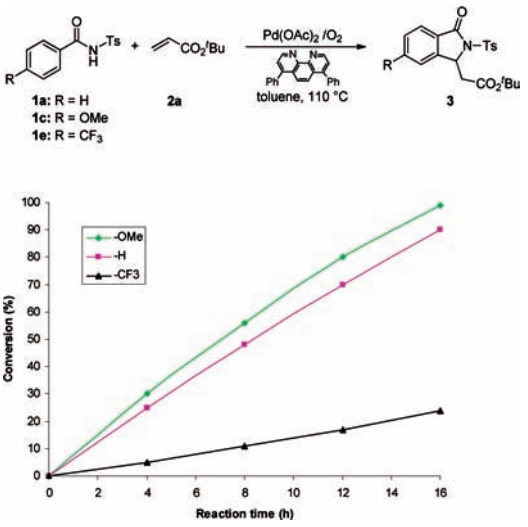


entry	alkene	isoindolinone	combined yield (%)[b]
1		 **5a**	68 (**5a**/**6a** 3.1/1)[c]
2		 **5b**	65 (**5b**/**6b** 3.0/1)
3		 **5c**	60 (**5c**/**6c** 3.1/1)
4		 **5d**	63 (**5d**/**6d** 2.7/1)
5		 **5e**	38[d]

[a] **1** (0.1 mmol), alkene (0.12 mmol), $Pd(OAc)_2$ (0.01 mmol), ligand (0.012 mmol), and O_2 (1 atm). [b] Isolated yield. [c] Ratio of **5**/**6** calculated from isolated yields. [d] Trace of **6e** only detected by ^{1}H NMR.

was found in 1,7-octadiene wherein one terminal alkene underwent annulation while the other survived (**5e**). A distinguishing feature of the adducts in Table 1, as opposed to those in Scheme 2, is the retention and positional shift of the olefin (exclusively *E*-configuration by ^{1}H NMR) indicating a significant variation in the termination step.

Scheme 3. Electronic Effects on Reaction Rate



Additionally, a small amount of isoquinolinone **6** was also produced. The overall process represents an unprecedented tandem C−H olefination/annulation involving simple aliphatic alkenes.

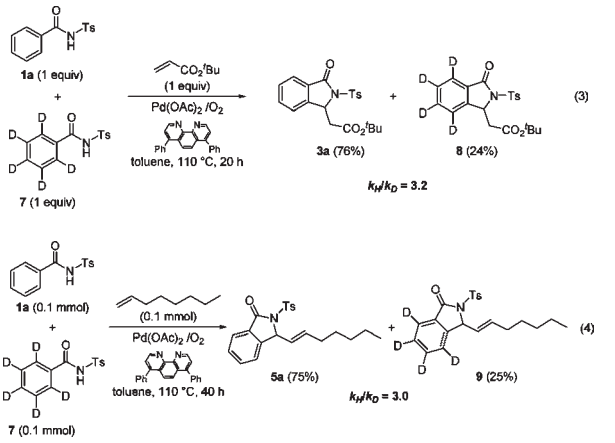
While the mechanism of Pd(II)-mediated C(sp^2)−H cleavage has attracted considerable attention in past decades, the precise details remain controversial.[11] However, the data gained from the competitive reactions agree with an electrophilic palladation mechanism as originally proposed by Ryabov and co-workers (Scheme 3).[11a] Specifically, tosyl amides bearing substituents with various electronic properties were subjected to parallel experiments in which the conversion ratio was determined by ^{1}H NMR. Substrates with electron-donating groups, e.g., **1c**, showed the highest reaction rates while an unsubstituted case (**1a**) was intermediate and the electron-deficient substrate (**1e**) had the lowest reactivity. These results are consistent with the pathway of an arenium (Wheland) intermediate of which the efficacy is highly reliant on the electronic property of arene.[11a]

To further study the C−H cleavage step, we prepared deuterium-labeled compound **7** and subjected it to competitive, intermolecular experiments (eqs 3 and 4). An equimolar mixture of **1a** and **7** was treated with 1 equiv of electron-deficient alkene (or aliphatic alkene); the measured product isotope effect of 3.2 (or 3.0) might suggest

(11) For mechanistic studies of Pd(II)-mediated C−H cleavages, see: (a) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Chem. Soc., Dalton Trans.* **1985**, 2629. (b) Canty, A. J.; van Koten, G. *Acc. Chem. Res.* **1995**, *28*, 406. (c) Gómez, M.; Granell, J.; Martinez, M. *Organometallics* **1997**, *16*, 2539. (d) Gómez, M.; Granell, J.; Martinez, M. *J. Chem. Soc., Dalton Trans.* **1998**, 37. (e) Biswas, B.; Sugimoto, M.; Sakaki, S. *Organometallics* **2000**, *19*, 3895. (f) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754. (g) Tunge, J. A.; Foresee, L. N. *Organometallics* **2005**, *24*, 6440.

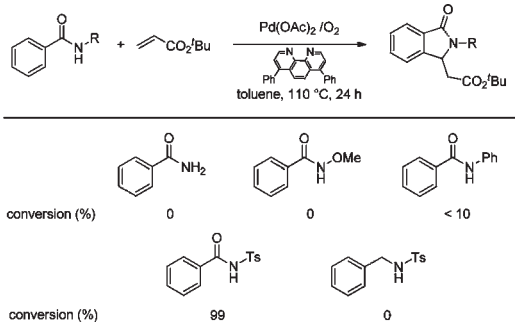
(12) (a) Davidson, J. M.; Triggs, C. *J. Chem. Soc. A* **1968**, 1324. (b) Shue, R. S. *J. Am. Chem. Soc.* **1971**, *93*, 7116. (c) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (d) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581.

that the deprotonation was involved as the rate-limiting step.[4a,j,12]



To clarify the influence of the acidic N−H sulfonamide, control experiments, utilizing the standard reaction conditions, were conducted using benzamides in which the tosyl group was replaced by H, Ph, or OMe.[13] The results cogently showed that the acid N−H was essential and could dramatically improve the reactivity (Scheme 4).

Scheme 4. Dependency of Reactivity on N−H Acidity

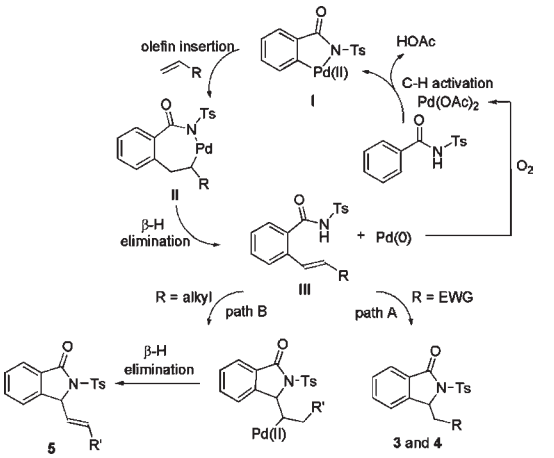


Illuminated by the preceding investigations, the postulated mechanism is depicted in Scheme 5. We speculate that the increased acidity of the N−H, a consequence of the combined inductive effects of the carbonyl and tosyl, facilitates the formation of the Pd−N bond that in turn promotes the formation of a palladacycle (**I**). Alkene insertion leads to intermediate **II** from which **III** is derived via β-H elimination. The electronic properties of the alkenes determines the ultimate fate of **III**. Electron-deficient alkenes likely participate by a Michael addition (path A),[6a,7a,8] while nonconjugated alkenes are annulated in a Wacker-type amination (path B).[14] Confirmation was obtained by

(13) For examples of Pd(II)-mediated C−H activation involving benzamides, see: (a) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett*. **2000**, *41*, 2655. (b) Shabashov, D.; Daugulis, O. *Org. Lett*. **2006**, *8*, 4947. (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc*. **2008**, *130*, 7190. (d) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc*. **2008**, *130*, 14058. (e) Yeung, C. S.; Zhao., X.; Borduas, N.; Dong, V. M. *Chem. Sci*. **2010**, *1*, 331.

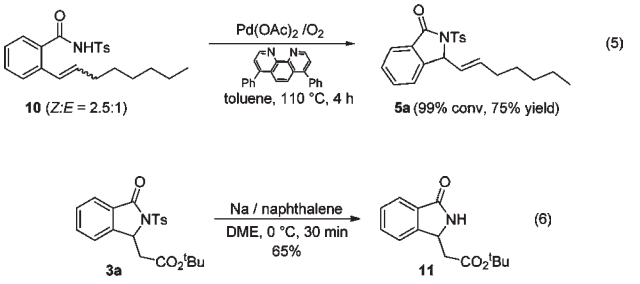
(14) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc*. **2005**, *127*, 17778.

Scheme 5. Proposed Mechanism



subjecting **10** (mixture of *Z*/*E*-olefins) to the standard annulation conditions (eq 5). The Wacker amination was complete within a few hours and afforded the anticipated product **5a** irrespective of the original olefin configuration.[15]

If the parent nitrogen heterocycle is desired, the tosyl can be conveniently removed in just 0.5 h using sodium naphthalenide, e.g., **3a** to isoindolinone **11** (eq 6).



In summary, a tandem process of C−H olefination/annulation for heterocyclic synthesis is described. Tosyl amides were employed as a novel directing group to afford a series of isoindolinones. Impressively, this transformation is broadly compatible with electron-rich and -deficient alkenes. For more eco-friendly transformations, molecular oxygen or even atmospheric air could be used without the need of other co-oxidants. From a practical point of view, the only waste is water and thus this transformation meets the goal of green chemistry. Further applications are ongoing in our group.

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

(15) Formation of byproduct isoquinolinone **6** was not observed in the experiment. It presumably derived from intermediate **II** via reductive elimination and subsequent dehydrogenation.