ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 1674–1676

www.rsc.org/chemcomm

COMMUNICATION

Rhodium catalyzed C–H olefination of *N*-benzoylsulfonamides with internal alkenes†

Chen Zhu* and John R. Falck

Received 9th November 2011, Accepted 26th November 2011
DOI: 10.1039/c2cc16963k

An annulation *via* tandem rhodium catalyzed C–H olefination of *N*-benzoylsulfonamides with internal olefins followed by C–N bond formation is disclosed. A *N*-substituted quaternary center is formed during the reaction thus providing efficient access to a series of 3,3-disubstituted isoindolinones.

Isoindolinones represent a significant class of nitrogen-containing heterocycles, which are ubiquitous in natural products and biologically active compounds.[1] As depicted in Fig. 1, Pestalachloride A **1** is a strongly antifungal metabolite isolated from the plant endophytic fungus *Pestalotiopsis adusta*;[2] Pagoclone **2** has been commercialized as an anxiolytic drug;[3] spirocyclic compound **3** is described as an aldose reductase inhibitor.[4] Consequently, the development of efficient methods to construct such scaffolds is of great importance.

C–H olefination has evolved into a powerful tool for C–C bond formation and offers a straightforward approach to the construction of various heterocycles.[5] Despite the versatility of C–H olefination, the transformation is still mostly limited to terminal olefins (eqn (1)). Only a few examples involving internal olefins have been reported in intramolecular settings and only one example has been achieved in intermolecular settings.[6] Therefore, the establishment of a general method for intermolecular C–H olefination with internal olefins is strongly desired. Herein, we disclose a tandem approach of rhodium catalyzed C–H olefination of *N*-benzoylsulfonamides with internal olefins followed by subsequent annulation (eqn (2)). More importantly, a *N*-substituted quaternary center constructed during the process affords a series of intriguing 3,3-disubstituted isoindolinones.

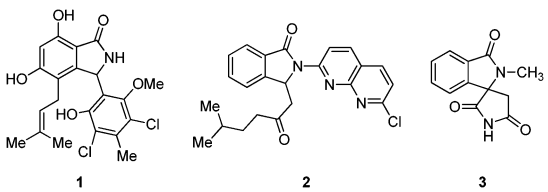
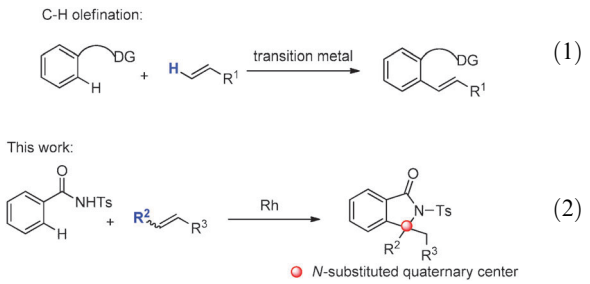
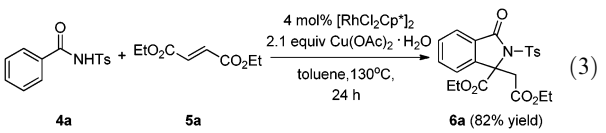


Fig. 1 Representative structures involving isoindolinone.



We have reported the palladium catalyzed C–H olefination of *N*-benzoylsulfonamides with terminal olefins.[7] These results prompted us to explore C–H olefinations using internal (1,2-disubstituted) olefins as coupling partners. Very recently, rhodium catalyst [{$RhCl_2Cp^*$}$_2$] has been successfully applied in the reaction of amide-directed C–H activation.[8] For instance, the annulation of amides with alkynes *via* C–H activation has been developed by several groups, respectively.[9] In addition, Li *et al.* and Glorius *et al.* reported C–H activation of amides with alkenes using the same rhodium catalyst.[10] However, in their chemistry, the scope of olefin was as well limited to the terminal olefins. Our initial investigation was performed with electron-deficient diethyl fumarate as the olefin of choice. Gratifyingly, the desired transformation proceeded readily in the presence of catalyst [{$RhCl_2Cp^*$}$_2$].[11] As shown in eqn (3), the optimized conditions afforded the annulated product **6a** in high chemical yield, and the newly formed *N*-substituted quaternary center was unambiguously assigned *via* the X-ray crystal structure of **6a**.[12]

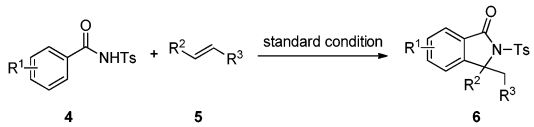


With the optimized conditions in hand, we then evaluated the scope of the reaction (Table 1). The satisfactory outcome lasted in the investigation of substrate scope, and was compatible with various substituents regardless of the electronic or steric properties. When a 2-naphthyl substrate was used, notably, the conversion to **6b** occurred with excellent regioselectivity as only the β-positional product was observed (entry 2). Surprisingly, during

Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, Texas 75390-9038, USA. E-mail: chen.zhu@utsouthwestern.edu

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, NMR spectra, and X-ray crystallographic information of **6a** (CIF). CCDC 843998. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc16963k

Table 1 Reaction scope of the annulation[a]



4 5 6

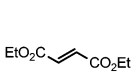
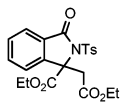
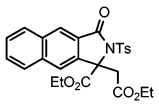
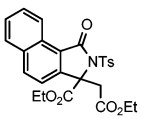
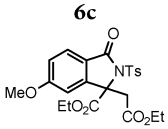
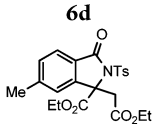
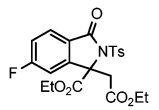
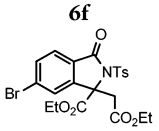
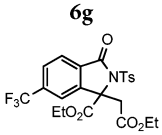
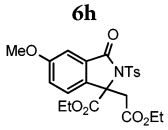
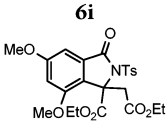
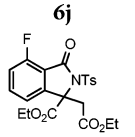
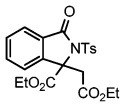
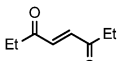
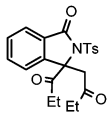
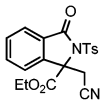
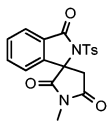
Entry	4	5	Product	Yield[b] (%)
1	**4a**	 **5a**	 **6a**	82
2[c]	**4b**	**5a**	 **6b**	81[d]
3[e]	**4c**	**5a**	 **6c**	85[e]
4	**4d**	**5a**	 **6d**	76
5	**4e**	**5a**	 **6e**	80
6	**4f**	**5a**	 **6f**	84
7	**4g**	**5a**	 **6g**	70
8	**4h**	**5a**	 **6h**	76
9[c]	**4i**	**5a**	 **6i**	72[f]
10[c]	**4j**	**5a**	 **6j**	46
11[c]	**4k**	**5a**	 **6k**	84

Table 1 (*continued*)

Entry	4	5	Product	Yield[b] (%)
12	**4a**	 **5b**	 **6a**	80
13	**4a**	 **5c**	 **6l**	51
14	**4a**	 **5d**	 **6m**	66
15[c]	**4a**	 **5e**	 **6n**	73

[a] Standard condition: **4** (0.10 mmol), **5** (0.12 mmol), $[RhCl_2Cp^*]_2$ (0.004 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (0.21 mmol) in 0.8 mL toluene, 130 °C for 24 h. [b] Isolated yield. [c] 48 h. [d] Regioisomeric ratio: β/α > 19 : 1. [e] Combined yield (**6c**/**6b** = 1 : 1). [f] Regioisomeric ratio: *para*/*ortho* = 16 : 1.

the examination of a 1-naphthyl substrate, the rearranged product **6b** was isolated concurrently with the expected product **6c** (entry 3).[13] The electron-donating methoxy and methyl groups, as well as fluoride, all furnished their respective adducts in high yields (entries 4–6). The chemoselective formation of **6g**, without competitive reaction by the aryl bromide is noteworthy, as the latter provides the functionality for subsequent cross-coupling reactions (entry 7). Good yields were also achieved when strong electron-withdrawing groups were present, *e.g.*, CF_3 (entry 8). Finally, both *meta*- and *ortho*-occupied substrates afforded the products in useful yields, albeit prolonged reaction times were required (entries 9–11). Once again good regioselectivity was exhibited and the *para*-positional product **6i** was predominant in high yield (entry 9).

The range of acceptable olefins was also investigated (Table 1, entries 12–15). The adaptability of other electron-deficient internal olefins to this transformation provides the capacity to construct diverse quaternary centers. Furthermore, the olefin configuration was observed to be unimportant to the reaction, since replacing **5a** with diethyl maleate **5b** provided the same product **6a** without diminishing the chemical yield (entry 12). *E*-1,2-Diketone conjugated olefin **5c** was also a suitable substrate affording the corresponding product **6l** in useful outcome (entry 13). Interestingly, the transformation demonstrated excellent electronic discrimination with respect to the unsymmetric olefin **5d** so that the regioisomeric product **6m** was exclusively generated (entry 14). Cyclic olefins were also compatible with the reaction conditions (entry 15). Coupling with maleimide **5e** offered a facile access to the spiroisoindolinone **6n**, the scaffold of bioactive compound **3** described

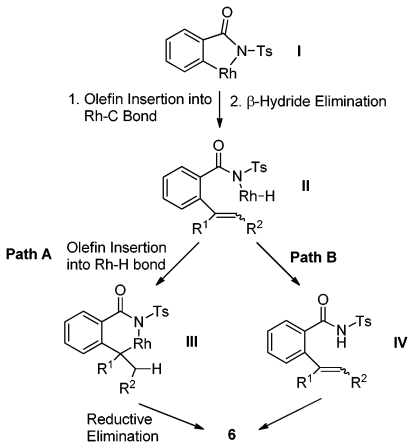
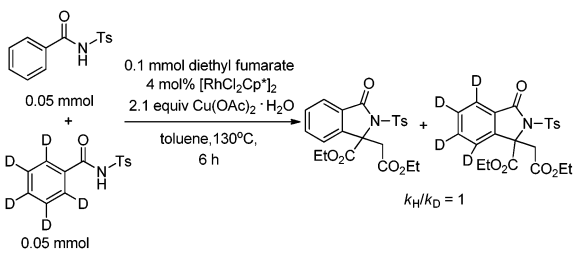


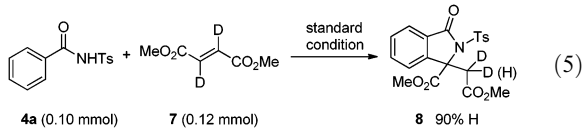
Fig. 2 Plausible mechanism.

above. However, the conversion did not proceed when ethyl crotonate was used.

The KIE value (k_H/k_D = 1) of the C–H olefination might suggest that the C–H cleavage is fast, thus not involved as the rate-limiting step (eqn (4)). The postulated mechanism is summarized in Fig. 2. Rapid C–H activation of **4** generates a five-membered rhodacycle (**I**), which subsequently undergoes the well-established mechanistic route of C–H olefination to generate a Rh–H complex (**II**). Two pathways (A and B) could possibly lead to the desired product **6**. Path B is the commonly accepted C–H olefination/C–N bond formation sequence, however, without experimental evidence.[14] To probe this pathway, deuterium-labelled olefin **7** was synthesized and subjected to the standard conditions (eqn (5)). The appearance of proton on the methylene position indicates that the adduct **8** might come from the intermediate **IV** (Fig. 2), since the acidic N–H (or N–D) is exchangeable with external protons.



(4)



(5)

In summary, we describe a tandem rhodium catalyzed C–H olefination of *N*-benzoylsulfonamides with internal olefins followed by C–N bond formation. A new *N*-substituted quaternary centre is formed during the reaction thus providing efficient access to a series of 3,3-disubstituted isoindolinones. Other applications of this methodology are currently ongoing in our laboratory.

We thank the NIH (GM31278) and the Robert A. Welch Foundation (GL625910) for financial support.

Notes and references

1 (*a*) M. Anzini, A. Capelli, S. Vomero, G. Giorgi, T. Langer, G. Bruni, M. R. Romero and A. S. Basile, *J. Med. Chem.*, 1996, **39**, 4275; (*b*) L. C. Chang, K. P. L. Bhat, E. Pisha, E. J. Kennelly, H. H. S. Fong, J. M. Pezzuto and A. D. Kinghorn, *J. Nat. Prod.*, 1998, **61**, 1257; (*c*) T. R. Belliotti, W. A. Brink, S. R. Kesten, J. R. Rubin, D. J. Wustrow, K. T. Zoski, S. Z. Whetzel, A. E. Corbin, T. A. Pugsley, T. G. Heffner and L. D. Wise, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 1499; (*d*) J. L. Wood, D. T. Petsch, B. M. Stoltz, E. M. Hawkins, D. Elbaum and D. R. Stover, *Synthesis*, 1999, 1529; (*e*) T. Honma, K. Hayashi, T. Aoyama, N. Hashimoto, T. Machida, K. Fukasawa, T. Iwama, C. Ikeura, M. Ikuta, I. Suzuki-Takahashi, Y. Iwasawa, T. Hayama, S. Nishimura and H. Morishima, *J. Med. Chem.*, 2001, **44**, 4615; (*f*) C. Riedinger, J. A. Endicott, S. J. Kemp, L. A. Smyth, A. Watson, E. Valeur, B. T. Golding, R. J. Griffin, I. R. Hardcastle, M. E. Noble and J. M. McDonnell, *J. Am. Chem. Soc.*, 2008, **130**, 16038.

2 (*a*) E. Li, L. Jiang, L. Guo, H. Zhang and Y. Che, *Bioorg. Med. Chem.*, 2008, **16**, 7894; (*b*) N. Slavov, J. Cvengros, J.-M. Neudoerfl and H.-G. Schmalz, *Angew. Chem., Int. Ed.*, 2010, **49**, 7588.

3 (*a*) L. A. Sorbera, P. A. Leeson, J. Silvestre and J. Castaner, *Drugs Future*, 2001, **26**, 651; (*b*) T. L. Stuk, B. K. Assink, R. C. Bates, Jr., D. T. Erdman, V. Fedij, S. M. Jennings, J. A. Lassig, R. J. Smith and T. L. Smith, *Org. Process Res. Dev.*, 2003, **7**, 851.

4 J. Wrobel, A. Dietrich, S. A. Woolson, J. Millen, M. McCaleb, M. C. Harrison, T. C. Hohman, J. Sredy and D. Sullivan, *J. Med. Chem.*, 1992, **35**, 4613.

5 For selected reviews of C–H olefination, see: (*a*) I. Moritani and Y. Fujiwara, *Synthesis*, 1973, 524; (*b*) C. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633; (*c*) E. M. Beccalli, G. Broggini, M. Martinelli and S. Sottocornola, *Chem. Rev.*, 2007, **107**, 5318; (*d*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*e*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*f*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*g*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215.

6 For intramolecular examples, see: (*a*) B. M. Trost, S. A. Godleski and J. P. Genêt, *J. Am. Chem. Soc.*, 1978, **100**, 3930; (*b*) P. S. Baran and E. J. Corey, *J. Am. Chem. Soc.*, 2002, **124**, 7904; (*c*) N. K. Garg, D. D. Caspi and B. M. Stoltz, *J. Am. Chem. Soc.*, 2004, **126**, 9552; (*d*) E. M. Beck, R. Hatley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2008, **47**, 3004; (*e*) A. L. Bowie, Jr. and D. Trauner, *J. Org. Chem.*, 2009, **74**, 1581; for intermolecular example, see: (*f*) F. W. Patureau, T. Besset and F. Glorius, *Angew. Chem., Int. Ed.*, 2011, **50**, 1064.

7 (*a*) C. Zhu and J. R. Falck, *Org. Lett.*, 2011, **13**, 1214; also see: (*b*) C. Zhu, W. Xie and J. R. Falck, *Chem.–Eur. J.*, 2011, **17**, 12591.

8 For review, see: T. Satoh and M. Miura, *Chem.–Eur. J.*, 2010, **16**, 11212.

9 (*a*) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908; (*b*) T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.*, 2010, **132**, 10565; (*c*) S. Mochida, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Lett.*, 2010, 744; (*d*) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree and X. Li, *J. Org. Chem.*, 2010, **75**, 7487.

10 (*a*) F. Wang, G. Song and X. Li, *Org. Lett.*, 2010, **12**, 5430; (*b*) S. Rakshit, C. Grohmann, T. Resset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2350; also see: (*c*) F. W. Patureau and F. Glorius, *J. Am. Chem. Soc.*, 2010, **132**, 9982; (*d*) T. Besset, N. Kuhl, F. W. Patureau and F. Glorius, *Chem.–Eur. J.*, 2011, **17**, 7167; (*e*) J. Willwacher, S. Rakshit and F. Glorius, *Org. Biomol. Chem.*, 2011, **9**, 4736.

11 For details, see ESI†.

12 For X-ray crystallographic information of **6a**, see ESI† (CIF).

13 HNMR spectrum of crude reaction as the proof is attached in ESI†.

14 For selected examples, see: (*a*) M. Miura, T. Tsuda, T. Satoh, S. Pivsa-Art and M. Nomura, *J. Org. Chem.*, 1998, **63**, 5211; (*b*) M. Wasa, K. M. Engle and J.-Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3680; (*c*) B. S. Kim, S. Y. Lee and S. W. Youn, *Chem.–Asian J.*, 2011, **6**, 1952.