Rhodium(III)-catalyzed internal oxidative coupling of *N*-hydroxyanilides with alkenes via C−H activation

Jing Wen, An Wu, Pei Chen, Jin Zhu

PII: S0040-4039(15)01234-4
DOI: http://dx.doi.org/10.1016/j.tetlet.2015.07.070
Reference: TETL 46559

To appear in: *Tetrahedron Letters*

Received Date: 3 June 2015
Revised Date: 15 July 2015
Accepted Date: 22 July 2015

Please cite this article as: Wen, J., Wu, A., Chen, P., Zhu, J., Rhodium(III)-catalyzed internal oxidative coupling of *N*-hydroxyanilides with alkenes via C−H activation, *Tetrahedron Letters* (2015), doi: http://dx.doi.org/10.1016/j.tetlet.2015.07.070

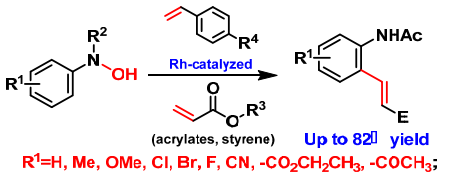
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Rhodium(III)-catalyzed internal oxidative coupling of *N*-hydroxyanilides with alkenes via C–H activation

Jing Wen, An Wu, Pei Chen and Jin Zhu

Leave this area blank for abstract info.



- Mild conditions
- Broad Substrate Scopes
- High Yields
- Pollution-free H_2O as by-product
- Internal oxidative olefination

R^1=H, Me, OMe, Cl, Br, F, CN, $-CO_2CH_2CH_3$, $-COCH_3$;
R^2=acyl; R^3=Me, Et, ^{n}Bu, ^{t}Bu, 2-methoxyethyl; R^4=H, Cl, F

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Rhodium(III)-catalyzed internal oxidative coupling of *N*-hydroxyanilides with alkenes via C–H activation

Jing Wen [a] , An Wu [b], Pei Chen [a] and Jin Zhu [a,*]

[a] *School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing National Laboratory of Microstructures, Nanjing University, Nanjing 210093, China.*
[b] *Kuang Yaming Honors School, Nanjing University, Nanjing 210093, China.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Rhodium
Anilides
Internal oxidation
Alkenes
C-H activation

ABSTRACT

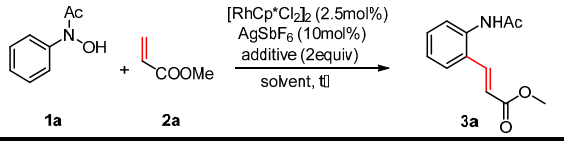
Described herein is an efficient new method for *ortho*-olefination of anilides in the presence of $AgSbF_6$ and NaOAc via rhodium(III)-catalyzed internal oxidative C–H bond activation based on hydroxyl as directing and oxidative group. A range of alkenes and functional groups on acetanilides is supported and a possible mechanism is proposed according to the experimental results.

A new C–C bond directly formed from two simple C–H bonds is supported by catalytic dehydrogenative cross-coupling such as oxidative Heck reaction pioneered by Fujiwara and Moritani, utilizing a C–C instead of a C–H bond.[1] This method has been rapidly developed and widely used in organic synthesis for the construction of C–X bond with advantages of atom economy, high selectivity and good toleration of unactivated substrates.[2] With the development in catalytic coupling reaction, there are lots of literatures involving the access to transition-metal-catalyzed *ortho*-functionalization of acetanilides, which is provided without the need for prefunctionalized partners.[3] Among them, using Rh catalysts, the coupling of acetanilides with diverse partners has proved to be efficient and versatile.[4] Since acetanilides could be easily hydrolyzed to anilines, these studies have realistic significance for derivation and modification of anilines that are the most important organic intermediates. Nevertheless, all the catalytic oxidative *ortho*-functionalization of acetanilides, even *ortho*-functionalization of anilides, occurs based on directing-acyl, most of which proceeds by external oxidation that requires additional oxidant such as copper(II) salts.[5] Therefore, developing a new way with novel directing group and internal oxidation to achieve the *ortho*-functionalization of anilides should be attractive. Here we report a study of the internal oxidative coupling of *N*-hydroxyanilides with alkenes catalyzed by $[Cp^*RhCl_2]_2$ ($Cp^* = C_5Me_5$) based on hydroxyl as directing and oxidative group with employing NaOAc and $AgSbF_6$ as additives. This study also shows broadening of substituted substrates, a possible mechanism and a kinetic test which identifies the rate determining step for this transformation. Moreover, catalytic C–H activation with using hydroxyl as directing group is seldom reported.

We initiated our investigation with the optimization studies of the coupling. By the acidity of hydroxyl resulting from electron-withdrawing effect of *N*-acetyl and conjugated effect of phenyl, we predicted that base as additive, which tended to capture the protons of hydroxyl synergistically with formation of O-Rh bond, could be effective in catalytic system. Under this, we examined the effects of various bases as additive (2.0 equiv) toward the reaction of *N*-hydroxyacetanilide (1a) and methyl acrylate (2a, 1.2 equiv) in 1,4-dioxane at 100°C for 12 hours, using 1:4 $[RhCp^*Cl_2]_2$ (2.5 mol%)/$AgSbF_6$ (10 mol%) as the catalyst system. It was found that additive played a crucial role in the reaction efficiency (Table 1, entries 1-3, 8-13). Notably, the yields of 3a in the presence of NaOAc and KOAc exceeded 60% (Table 1, entries 3, 8) compared with that less than 55% in other additives, and 2.0 equiv of NaOAc was determined to be optimal (Table 1, entry 3). Among the set of representative solvents, *t*-AmOH was found to be optimal as well as 1,4-dioxane (Table 1, entries 3, 17). The reaction temperature of 100°C was determined to be the best by the results of that the lower yield of 3a was obtained at a temperature lower than 100°C and the yield of 3a did not increase at a temperature higher than 100°C (Table 1, entries 19-21). The reaction time more than 8 hours was unhelpful to increasing the yield of 3a (Table 1, entries 23, 24). Under these conditions, the satisfactory isolated yields of 76% and 77% were obtained respectively by increasing the concentration of Rh-catalyst to 3% and 4% (Table 1, entries 6, 7), and 75% isolated yield of 3a was obtained in *t*-AmOH as solvent instead of 1,4-dioxane (Table 1, entry 18). Given all this, the conditions in entry 6 was determined to be the optimal reaction

conditions and used as standard conditions in the following studies.

Table 1
Reaction Optimization[a]



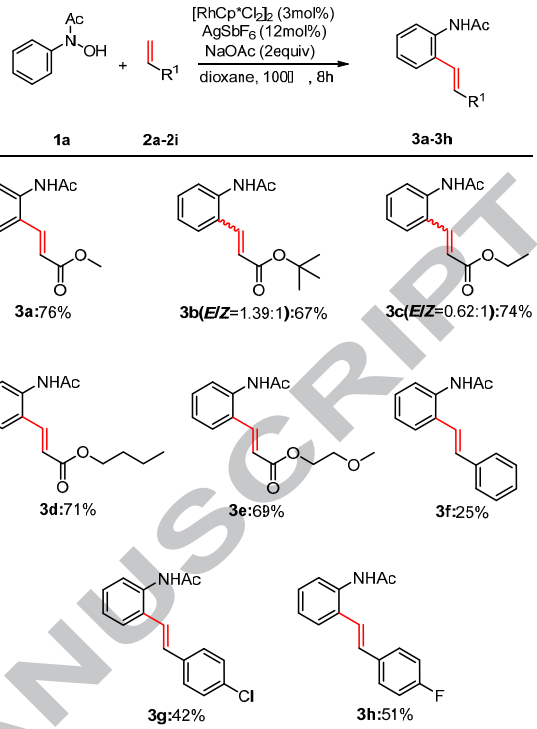
1a 2a 3a

entry	additive	solvent	temp(°C)	Time(h)	yield of **3a** (%)
1	AgOAc	1,4-dioxane	100	12	<5
2	$Cu(OAc)_2$	1,4-dioxane	100	12	23
3	NaOAc	1,4-dioxane	100	12	66
4	NaOAc[b]	1,4-dioxane	100	12	41
5	NaOAc[c]	1,4-dioxane	100	12	67
6[d]	NaOAc	1,4-dioxane	100	8	76
7[e]	NaOAc	1,4-dioxane	100	8	77
8	KOAc	1,4-dioxane	100	12	60
9	K_2CO_3	1,4-dioxane	100	12	<5
10	Na_2CO_3	1,4-dioxane	100	12	<5
11	PivONa	1,4-dioxane	100	12	55
12	NaOH	1,4-dioxane	100	12	19
13	PhONa	1,4-dioxane	100	12	31
14	NaOAc	DMF	100	12	13
15	NaOAc	Toluene	100	12	42
16[f]	NaOAc	DCE	100	12	<5
17	NaOAc	*t*-AmOH	100	12	65
18[d]	NaOAc	*t*-AmOH	100	8	75
19	NaOAc	1,4-dioxane	60	20	<5
20	NaOAc	1,4-dioxane	80	16	45
21[f]	NaOAc	1,4-dioxane	120	12	67
22	NaOAc	1,4-dioxane	100	6	54
23	NaOAc	1,4-dioxane	100	8	67
24	NaOAc	1,4-dioxane	100	16	65

[a] Typical conditions: 1a (0.237 mmol, 1.0 equiv), 2a (1.2 equiv), $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), additive (2.0 equiv), solvent (2.0 ml); Yields (<5%) estimated by TLC; Isolated yields estimated by weighing.
[b] NaOAc (1.0 equiv). [c] NaOAc (3.0 equiv).
[d] $[RhCp^*Cl_2]_2$ (3 mol%), $AgSbF_6$ (12 mol%).
[e] $[RhCp^*Cl_2]_2$ (4 mol%), $AgSbF_6$ (16 mol%).
[f] Experiment in the pressure tube.

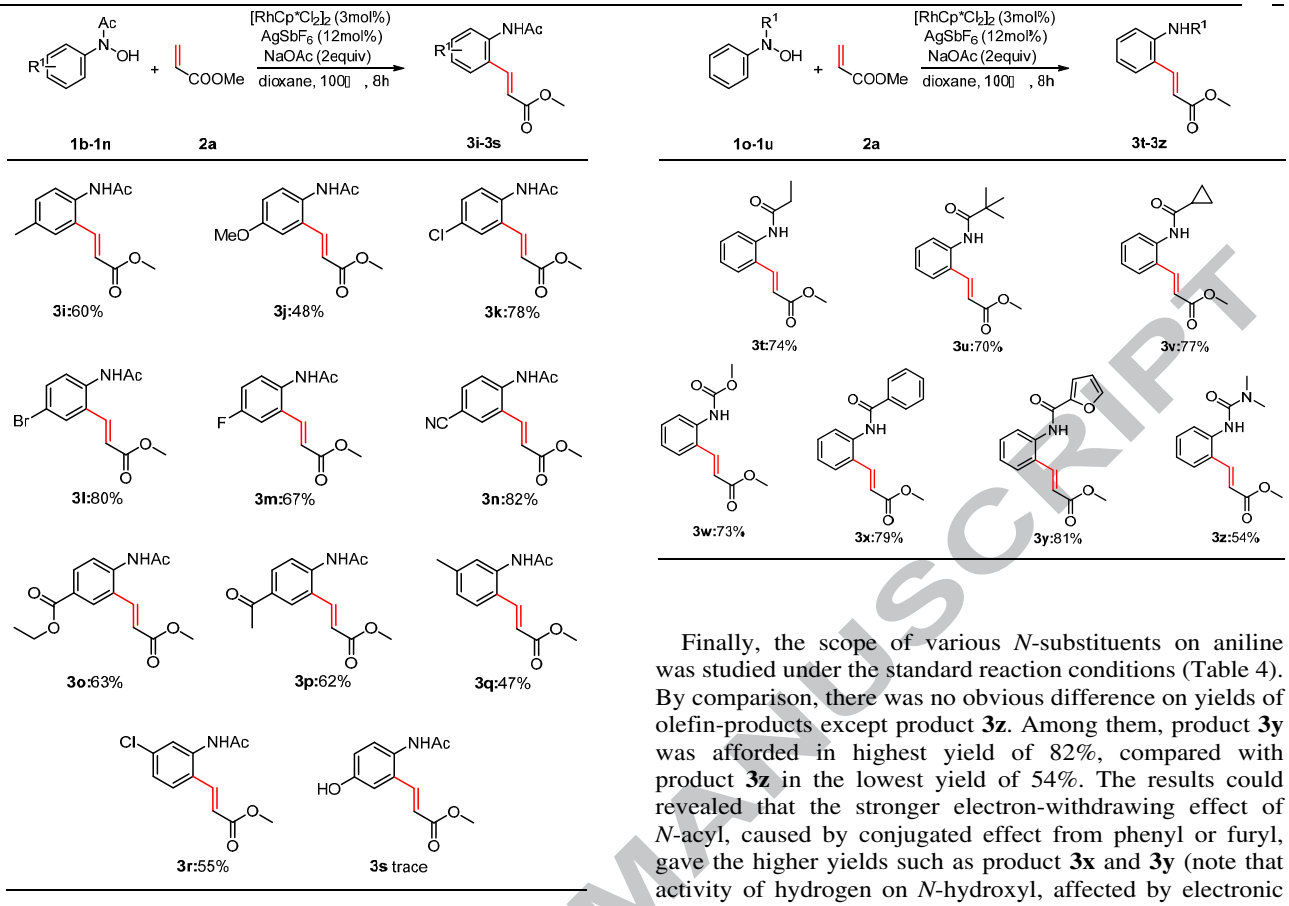
With an optimized catalytic system in hand, we proceeded to evaluate the generality of the standard reaction conditions with a variety of alkenes as shown in Table 2. The reactions of alkenes **2** and *N*-hydroxyacetanilide **1a** assessed initially showed that only terminal alkenes such as acrylates and substituted styrenes could react with *N*-hydroxyacetanilide. The standard reaction conditions, which was optimized for the Rh-catalyzed oxidative coupling of acrylates affording products **3a**-**3e** in yields of 67-76%, afforded products **3f**-**3h** in lower yields of 25-51% with substituted styrenes. The electron-donating substituted styrene did not react with *N*-hydroxyacetanilide, probably resulted from that electron-donating group on styrenes is unfavourable to stabilization for PhC^- formed from migratory insertion of double bond into the Rh-C bond. In all these cases, (*E*)-configuration of all products was mainly observed, except that the conversion of (*E*)-configuration to (*Z*)-configuration was observed in products **3b** and **3c**.

Table 2
Scope of Alkenes[a]



[a] conditions: **1a** (0.237 mmol, 1.0 equiv), **2a** (1.2 equiv), $[RhCp^*Cl_2]_2$ (3 mol%), $AgSbF_6$ (12 mol%), NaOAc (2.0 equiv), dioxane (2.0 ml), 100°C.

Table 3
Scope of *N*-hydroxyacetanilides

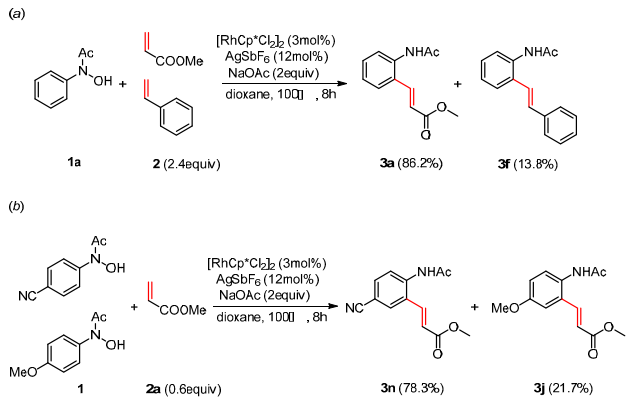


Subsequently, the scope of variously substituted *N*-hydroxyacetanilides **1a**-**1n** with methyl acrylate **2a** was studied under the standard reaction conditions (Table 3). The electronic properties and position of substituents proved to have an impact on the yields of products. Evidently, it was found that *para*-substituted *N*-hydroxyacetanilides gave higher yields than *meta*-substituted ones and electron-poor *N*-hydroxyacetanilides were more favorable for coupling reaction than electron-rich ones. With cyan-substituted substrate, the reaction afforded product **3n** in highest yield of 82%. Notably, *meta*-substituted substrates exhibited good regioselectivity that the coupling occurred at a defined position on aryl. In addition, the reaction mainly delivered trans-products. The trace of **3s** was observed, which was probably caused by resistance to Rh-catalyzed C–H activation from acidic property of hydroxyl substituent. No reaction with *ortho*-substituted substrates occurred as a result of steric hindrance. Clearly, all of the coupling reactions via C-H activation occurred at the *ortho*-position on aryl, which demonstrated the key role of directing group.

Table 4
Scope of *N*-substituents

Finally, the scope of various *N*-substituents on aniline was studied under the standard reaction conditions (Table 4). By comparison, there was no obvious difference on yields of olefin-products except product **3z**. Among them, product **3y** was afforded in highest yield of 82%, compared with product **3z** in the lowest yield of 54%. The results could revealed that the stronger electron-withdrawing effect of *N*-acyl, caused by conjugated effect from phenyl or furyl, gave the higher yields such as product **3x** and **3y** (note that activity of hydrogen on *N*-hydroxyl, affected by electronic properties of *N*-acyl, could be understood based on chemical shift of hydrogen in NMR). In addition, the substrate with hydroxyl protected by acetyl could not work in this catalytic system, illustrating the key role of *N*-hydroxyl.

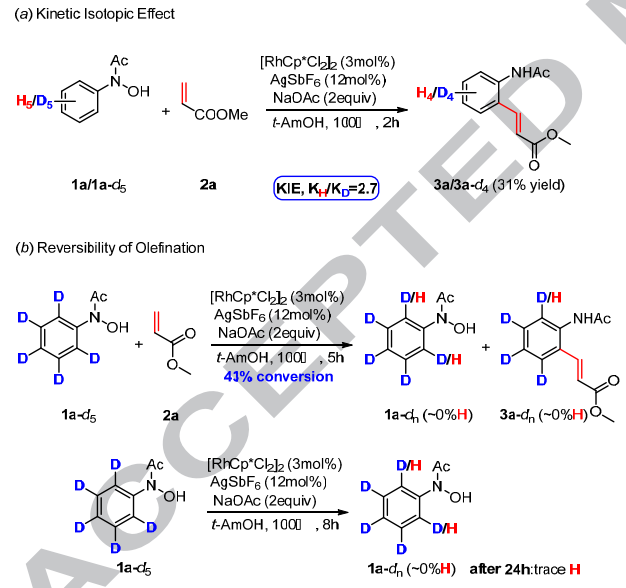
On the basis of the scope, the chemoselectivity of the rhodium catalysis in the standard conditions was preliminarily understood. Intermolecular competition experiments of different alkenes further revealed that acrylates as coupling partners were converted preferentially to products compared with styrenes (Scheme 1a). Additionally, electron-withdrawing substituted *N*-hydroxyacetanilides were converted preferentially (Scheme 1b). The results are essentially in accord with yield data of products **3a-3r**, which suggested that electron-withdrawing groups on aryl as well as *N*-acetyl and NaOAc could promote the cleavage of O-H bond and C-H activation probably followed concerted metalation-deprotonation rather than electrophilic aromatic substitution (EAS).[6]



[a] Percentage in bracket estimated by ^{1}H NMR meaning proportion of each product in total not yield

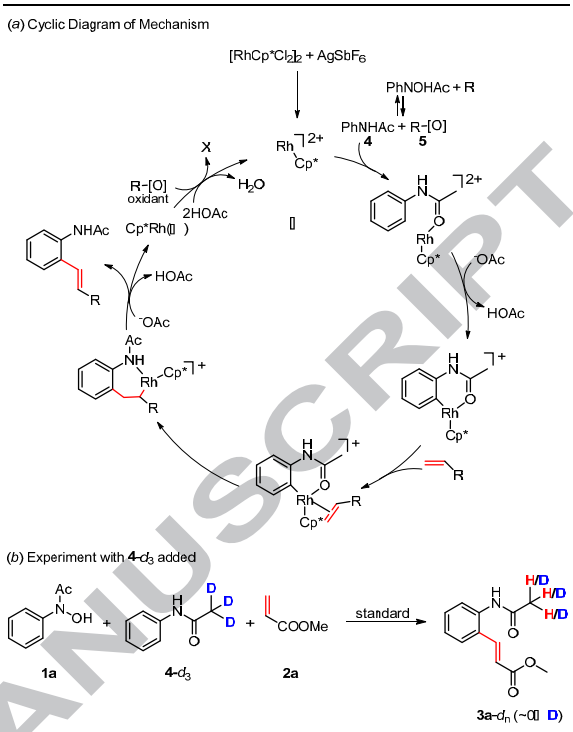
Scheme 1. Competition Experiment[a]

Further mechanistic studies showed that the kinetic isotope effect (KIE) measured by using **1a** and **1a**-d_5 as substrates revealed a reaction involving a rate-limiting C–H bond activation (Scheme 2a).[7] Additionally, an H/D exchange was not observed with employing *t*-AmOH as the solvent and deuterated *N*-hydroxyacetanilide **1a**-d_5 as substrate, which revealed the irreversibility of C–H activation and migratory insertion of double bond (Scheme 2b) (note that a trace of H was observed after 24 hours under the conditions without **2a**).



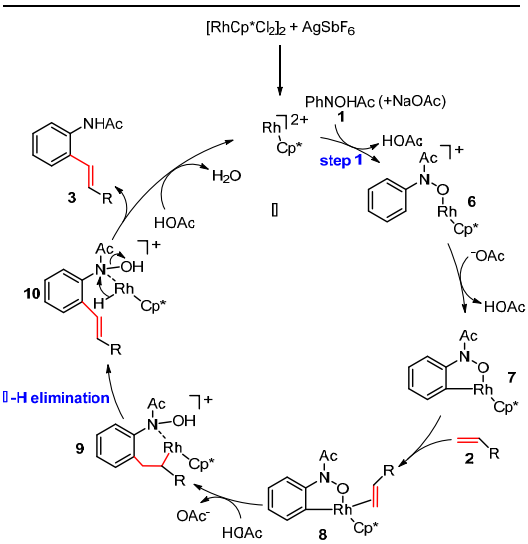
Scheme 2. Deuterium Experiments

To understand the conversion of substrate, we did a pre-study on the side reaction, and observed a certain amount of acetanilide **4** at the end of the reaction. Further studies showed that the translation from *N*-hydroxyacetanilide **1a** to acetanilide **4** via oxidation-reduction process occurred under the standard conditions without alkenes. The above findings are compatible with the mechanism sketched in Scheme 3a. In this cycle, the rhodacycle is formed with using acetanilide **4** as the starting reactant and Rh(I) is oxidized to Rh(III) by external oxidant **5.** However, the product **3a**-d_n (~0% D) refutes the proposed mechanism **I** (Scheme 3b).



[a] The structure of compound **5** was not definite.

Scheme 3. Mechanism proposall[a]



[a] **Step 1** follows the concerted metalation-deprotonation of hydroxyl.

Scheme 4. Mechanism proposalll[a]

Finally, a possible catalytic cycle is proposed in Scheme 4. We hypothesize that the catalytic cycle initiates with formation of the rhodacycle intermediate **7** via [RhCp*]-catalyzed C–H activation.[8] Immediately, migratory insertion of double bond into the Rh-C bond works synergistically with cleavage of O-Rh bond to deliver a six-membered rhodacycle **9**.[9] Subsequently, intermediate **10** formed by β-H elimination simultaneously delivers product

3, H_2O and Rh(III) derived from internal oxidation by hydroxyl (note that H_2O was observed by ^1H NMR; Since NaOAc can not react with *N*-hydroxyacetanilide **1a** to form a sodium salt of **1a**, **step 1** in the catalytic cycle should follow the concerted metalation-deprotonation of hydroxyl).

In summary, we have developed an efficient new methodology to achieve the direct *ortho*-olefination of acetanilides with acrylates and aryl alkenes via Rh-catalyzed internal oxidative C-H activation, and brought forth new hydroxyl as both directing group and internal oxidant. This methodology, which is attractive with high efficiency of Rh-catalyst, easily prepared NaOAc, absence of external oxidant and pollution-free H_2O as by-product, supports a range of differently substituted substrates. The results shows that electron-withdrawing substrates were more effective than electron-donating substrates in the coupling reaction with generation of product **3n** in the highest yield of 82%. The above features in the coupling of acetanilides with alkenes obtained should lead to many applications, especially in organic synthesis involving aromatic amines.

Acknowledgements

J.Z. gratefully acknowledges support from the National Natural Science Foundation of China (21425415, 21274058) and the National Basic Research Program of China (2015CB856303, 2011CB935801).

Notes and references

1 (a) Moritanl, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, *8*, 1119; (b) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992; (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633; (d) Asano, R.; Moritani, I.; Fujiwara, Y.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2910.

2 (a) Urkalan, K. B.; Sigman, M. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 3146; (b) Hyster, T. K.; Rovis, T. *Chem. Sci.* **2011**, *2*, 1606; (c) Yu, S.; Wan, B.; Li, X. *Org. Lett.* **2013**, *15*, 3706; (d) Zhou, B.; Du, J.; Yang, Y.; Feng, H.; Li, Y. *Org. Lett.* **2014**, *16*, 592; (e) Ng, K.-H.; Zhou, Z.; Yu, W.-Y. *Chem. Commun.* **2013**, *49*, 7031; (f) Lohr, T. L.; Piers, W. E.; Parvez, M. *Chem. Sci.* **2013**, *4*, 770; (g) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204; (h) Qi, Z.; Li, X. *Angew. Chem. Int. Ed.* **2013**, *52*, 8995; (i) Ye, X.; He, Z.; Ahmed, T.; Weise, K.; Akhmedov, N. G.; Petersen, J. L.; Shi, X. *Chem. Sci.* **2013**, *4*, 3712; (j) Yang, Y.; Hou, W.; Qin, L.; Du, J.; Feng, H.; Zhou, B.; Li, Y. *Chem. Eur. J.* **2014**, *20*, 416. (k) Wang, L.; Qu, X.; Li, Z.; Peng, W.-M. *Tetrahedron Lett.* **2015**, *56*, 3754; (l) Matsuda, T.; Tomaru, Y. *Tetrahedron Lett.* **2014**, *55*, 3302; (m) Muraoka, T.; Hiraiwa, E.; Abe, M.; Ueno, K. *Tetrahedron Lett.* **2013**, *54*, 4309.

3 (a) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 5524; (b) Ng, K.-H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862; (c) Liu, X.; Hii, K. K. *J. Org. Chem.* **2011**, *76*, 8022; (d) Wang, S.; Yang, Z.; Liu, J.; Xie, K.; Wang, A.; Chen, X.; Tan, Z. *Chem. Commun.* **2012**, *48*, 9924; (e) Yang, F.; Song, F.; Li, W.; Lan, J.; You, J. *RSC Adv.* **2013**, *3*, 9649; (f) Ackermann, L.; Wang, L.; Wolfram, R.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 728; (g) Manikandan, R.; Jeganmohan, M. *Org. Lett.* **2014**, *16*, 912; (h) Padala, K.; Jeganmohan, M. *Chem. Commun.* **2013**, *49*, 9651; (i) Chinnagolla, R. K.; Jeganmohan, M. *Chem. Commun.* **2014**, *50*, 2442;

4 (a) Hoshino, Y.; Shibata, Y.; Tanaka, K. *Adv. Synth. Catal.* **2014**, *356*, 1577; (b) Kim, M.; Park, J.; Sharma, S.; Han, S.; Han, S. H.; Kwak, J. H.; Jung, Y. H.; Kim, I. S. *Org. Biomol. Chem.* **2013**, *11*, 7427; (c) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326; (d) Cajaraville, A.; López, S.; Varela, J. A.; Saá, C. *Org. Lett.* **2013**, *15*, 4576; (e) Gong, T.-J.; Cheng, W.-M.; Su, W.; Xiao, B.; Fu, Y. *Tetrahedron Lett.* **2014**, *55*, 1859; (f) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982; (g) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474; (h) Zhang, G.; Yu, H.; Qin, G.; Huang, H. *Chem. Commun.* **2014**, *50*, 4331; (i) Moon, Y.; Jeong, Y.; Kook, D.; Hong, S. *Org. Biomol. Chem.* **2015**, *13*, 3918; (j) Shi, Z.; Boultadakis-Arapinis, M.; Glorius, F. *Chem. Commun.* **2013**, *49*, 6489.

5 (a) Nishikata, T.; Abela, A. R.; Huang, S.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2010**, *132*, 4978; (b) Xue, D.; Li, J.; Liu, Y.-X.; Han, W.-Y.; Zhang, Z.-T.; Wang, C.; Xiao, J. *Synlett* **2012**, *23*, 1941; (c) Zhou, J.; Li, B.; Hu, F.; Shi, B.-F. *Org. Lett.* **2013**, *15*, 3460; (d) 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; (e) Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem. Int. Ed.* **2009**, *48*, 1830; (f) Cajaraville, A.; López, S.; Varela, J. A.; Saá, C. *Org. Lett.* **2013**, *15*, 4576; (g) Haridharan, R.; Muralirajan, K.; Cheng, C.-H. *Adv. Synth. Catal.* **2015**, *357*, 366.

6 (a) Juribašić, M.; Budimir, A.; Kazazić, S.; Ćurić, M. *Inorg. Chem.* **2013**, *52*, 12749; (b) Solomon, E. I.; Light, K. M.; Liu, L. V.; Srnec, M.; Wong, S. D. *Acc. Chem. Res.* **2013**, *46*, 2725; (c) Nedd, S.; Alexandrova, A. N. *Phys. Chem. Chem. Phys.* **2015**, *17*, 1347.

7 (a) Madix, R. J.; Telford, S. G. *Surf. Sci.* **1992**, *277*, 246; (b) Gómez-Gallego, M.; Sierra, M. A. *Chem. Rev.* **2011**, *111*, 4857; (c) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 4814.

8 Li, L.; Brennessel, W. W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492.

9 Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449.