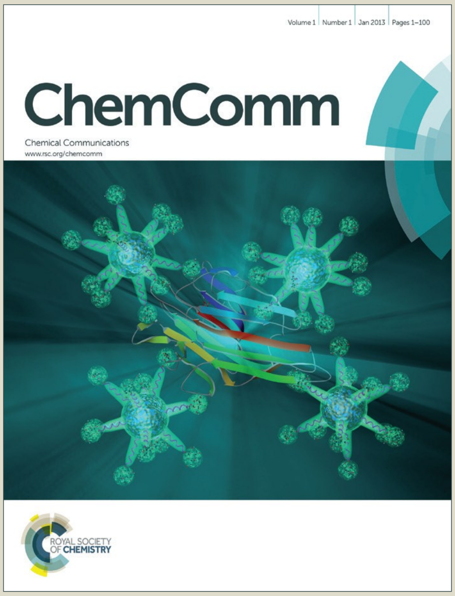
View Article Online
View Journal

ChemComm

This article can be cited before page numbers have been issued, to do this please use: X. Zhou, Z. Peng, H. Zhao, Z. Zhang, P. Lu and Y. Wang, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC05456K.



ROYAL SOCIETY OF CHEMISTRY

View Article Online
DOI: 10.1039/C6CC05456K

Journal Name

COMMUNICATION

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Rh-catalyzed annulations of N-methoxybenzamides and ketenimines: Synthesis of 3-aminoisoindolinones and 3-diarylmethyleneisoindolinones with strong aggregation induced emission properties

Xiaorong Zhou[†], Zhixing Peng[†], Hongyang Zhao, Zhiyin Zhang, Ping Lu*, Yanguang Wang*

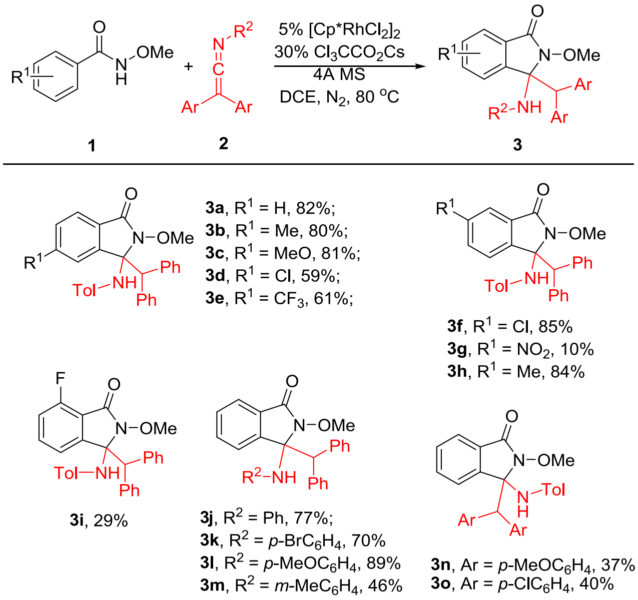
Rhodium-catalyzed C-H acitvation/annulations of ketenimines with N-methoxybenzamides furnished 3-aminoisoindolin-1-ones and 3-(diarylmethylene)isoindolin-1-ones. The synthesized 3-(diarylmethylene)isoindolin-1-ones exhibited aggregation induced emissions in aqueous tetrahydrofuran solution, and strong yellow or blue emissions both in nano-particles and in solids.

Ketenimines have been emerging as valuable and versatile synthetic intermediates in organic synthesis.[1] They can undergo a variety of reactions, including nucleophilic additions, [4+2] and [2+2] cycloadditions, and sigmatropic rearrangements. To the best of our knowledge, applications of ketenimine as a coupling partner in transition metal catalyzed C-H activation/annulations have not been reported although these reactions have been widely explored and applied in the preparation of a variety of carbocycles and heterocycles.[2] Herein, we report a Rh(III)-catalyzed cascade C-H activation/annulation reaction between *N*-methoxybenzamides and ketenimines, furnishing 3-aminoisoindolin-1-ones and 3-(diarylmethylene)isoindolin-1-ones.

To start with, we probed the reaction conditions for the envisioned rhodium-catalyzed C-H activation/annulation of N-methoxybenzamide (**1a**) with 2,2-diphenyl-*N*-(*p*-tolyl)ethen-1-imine (**2a**) (see Supporting Information, Table S1). In our primary test, the reaction of **1a** with **2a** under CsOAc (30 mol%) and [Cp*RhCl$_2$]$_2$ (5 mol%) in dichloroethene (DCE) at 80 °C afforded a [4+1] annulation product **3a** in 46% yield. We then screened catalysts ([Cp*RhCl$_2$]$_2$, [Cp*IrCl$_2$]$_2$, and [RuCl$_2$(cymene)]$_2$), solvents (DCE, CH$_3$CN, toluene, 1,4-dioxane, CH$_2$Cl$_2$, and acetone), bases (CsOAc, NaOAc, KOAc, Cl$_3$CCO$_2$Na, PivOCs, Cl$_3$CCO$_2$Cs, and Cl$_3$CCO$_2$K), reaction temperature (from room temperature to 100 °C), atmosphere (air, N$_2$, and O$_2$), the ratio of starting materials, and catalyst loading. The best result (82% yield) was obtained by the reaction of **1a** (0.36 mmol), **2a** (0.3 mmol), [Cp*RhCl$_2$]$_2$ (0.015 mmol), Cl$_3$CCO$_2$Cs (0.09 mmol), and 4Å MS (60 mg) in DCE (2 mL) at 80 °C for 10 hours.

With the optimized reaction conditions in hand, we examined the substrate scope using various *N*-methoxybenzamides **1** and ketenimines **2** (Table 1). Substituent (R^1) on the 4-position of *N*-methoxybenzamides **1** could either be electron-donating (Me, MeO) or electron-withdrawing (Cl, CF$_3$). Thus, **3b-e** were obtained at yields varying from 59% to 81%. Substituent on 3-position of *N*-methoxybenzamide could be Cl (**3f**), NO$_2$ (**3g**), and CH$_3$ (**3h**). 2-Fluoro-*N*-methoxybenzamide gave the desired product **3i** in low yield (29%). Substituent (R^2) on the nitrogen atom of ketenimines **2** could be *p*-BrC$_6$H$_4$ (**3k**[3]), *p*-MeOC$_6$H$_4$ (**3l**) and

Table 1 Synthesis of 3-aminoisoindolin-1-ones **3**[a]



[a] Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), [Cp*RhCl$_2$]$_2$ (0.015 mmol), Cl$_3$CCO$_2$Cs (0.09 mmol), 4Å MS (60 mg), DCE (2 mL), N$_2$, 80 °C, 10 h; Isolated yields refer to **2**.

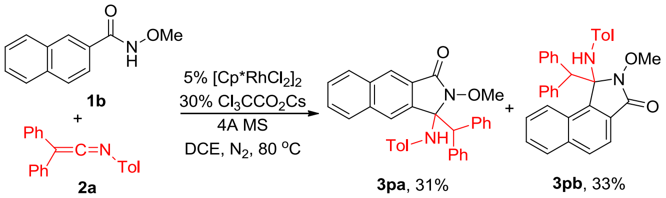
Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. China

† These authors contributed equally.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

DOI: 10.1039/C6CC05456K

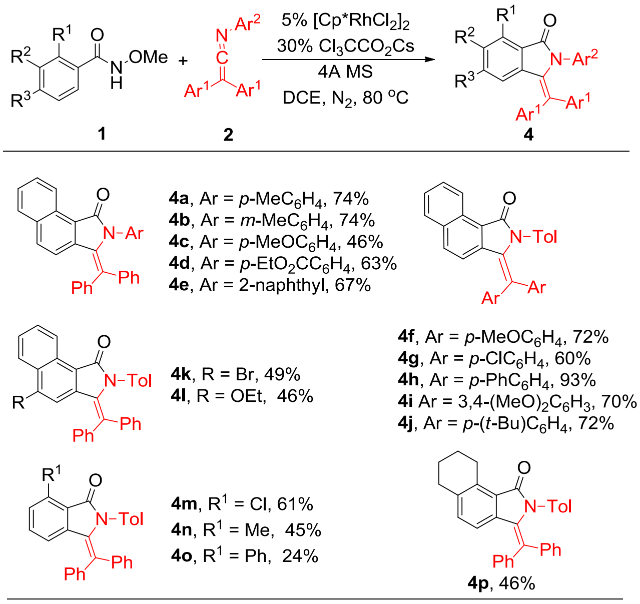
m-MeC$_6$H$_4$ (**3m**). Two aryls on the terminal carbon of ketenimines could be altered, and **3n** and **3o** were prepared at 37% and 40% yields, respectively. The reaction of N-methoxy-2-naphthamide (**1b**) with **2a** was also examined. In this case, **3pa** (31% yield) and **3pb** (33% yield) were obtained without regioselectivity (Scheme 1).



Scheme 1 Formation of **3pa** and **3ph**.

When N-methoxy-1-naphthamide (**1c**) was used as substrate, a [3+2] annulation product, 3-(diarylmethylene)isoindolin-1-one **4a**,[3] was isolated in 74% yield (Table 2). Under the established reaction conditions, products **4b-j**[3] (46-93% yields) were prepared by the reaction of **1c** with a variety of ketenimines. The substituent on naphthalene substrate could be 4-Br (**4k**) and 4-ethoxy (**4l**). Then, we compared the reactivity of N-methoxy-2-chlorobenzamide (**1d**), N-methoxy-2-methyl-benzamide (**1e**), N-methoxy-2-phenylbenzamide (**1f**), and N-methoxy-5,6,7,8-tetrahydro-1-naphthamide (**1g**). Their reactions with **2a** afforded the corresponding products **4m-p** in 24-61% yields.

Table 2 Synthesis of 3-(diarylmethylene)isoindolin-1-ones **4**[a]

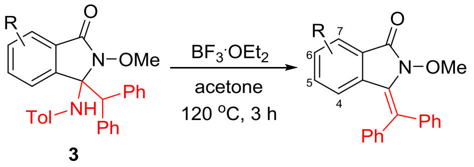


4a, Ar = p-MeC$_6$H$_4$, 74%
4b, Ar = m-MeC$_6$H$_4$, 74%
4c, Ar = p-MeOC$_6$H$_4$, 46%
4d, Ar = p-EtO$_2$CC$_6$H$_4$, 63%
4e, Ar = 2-naphthyl, 67%
4f, Ar = p-MeOC$_6$H$_4$, 72%
4g, Ar = p-ClC$_6$H$_4$, 60%
4h, Ar = p-PhC$_6$H$_4$, 93%
4i Ar = 3,4-(MeO)$_2$C$_6$H$_3$, 70%
4j, Ar = p-(t-Bu)C$_6$H$_4$, 72%
4k, R = Br, 49%
4l, R = OEt, 46%
4m, R^1 = Cl, 61%
4n, R^1 = Me, 45%
4o, R^1 = Ph, 24%
4p, 46%

[a] Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), [Cp*RhCl$_2$]$_2$ (0.015 mmol), Cl$_3$CCO$_2$Cs (0.09 mmol), 4Å MS (60 mg), DCE (2 mL), N$_2$, 80 °C, 10 h; Isolated yields refer to **2**.

The resulted 3-aminoisoindolin-1-ones **3** could also converted into 3-(diarylmethylene)isoindolin-1-ones. For example, **i**n the presence of trifluoroborane etherate, **3a** could be converted into **5a** in 83% yield. Similar eliminations could be done to produce **5b-d** in 76-86% yields (Scheme 2).

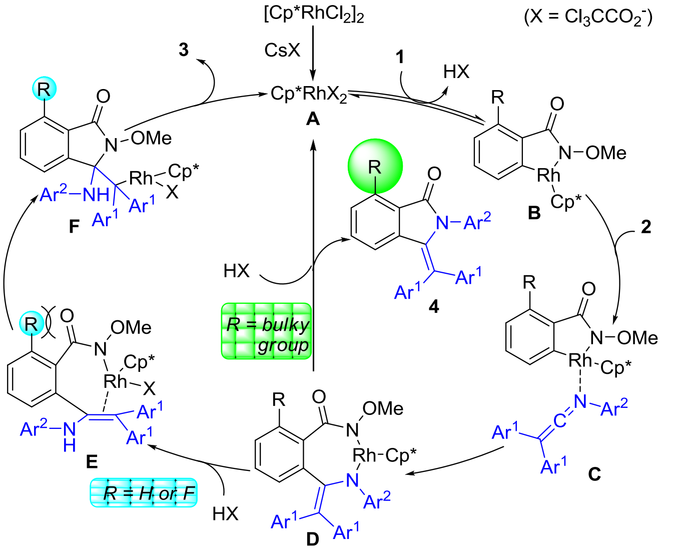
To probe the reaction mechanism, the reaction of **1a** with **2a** was examined using 5 mol % [Cp*RhCl$_2$]$_2$ and 15 mol % AgNTf$_2$ (see Supporting Information, Scheme S1, eq 1). We isolated a simple addition product **6** (96% yield), which is stable to the standard annulation conditions. In this case, the rhodium catalyst functioned as a Lewis acid and the C-H activation was effectively inhibited. When the reaction of **1a** was conducted with the addition of D$_2$O and in the absence of ketenimine, a deuterium incorporated product was obtained, indicating a reversible C-H activation (Scheme S1, eq 2). Kinetic isotope effect (KIE) was carried out in a parallel experiment (Scheme S1, eq 3). By treatment of **1a** or **1a-d_5** under standard reaction conditions for 30 min, KIE of the [4+1] reaction was determined to be 1.3. This result indicated that the C-H activation was not the rate determining step. When D$_2$O was added to the reaction of **1a** and **2a**, H$_a$ and H$_b$ were incorporated with deuterium in 22% and 18% ratios, respectively (Scheme S1, eq 4). The fact that H$_b$ was incorporated with deuterium implies that metal-H exchange occurred during the reaction.



5a, R = H, 83%
5b, R = 6-Me, 76%
5c, R = 5-Cl, 86%
5d, R = 5-MeO, 81%

Scheme 2 Preperation of **5a-d**.

On the basis of these results, a possible reaction mechanism is proposed in Scheme 3. In the presence of Cl$_3$CCO$_2$Cs, [Cp*RhCl$_2$]$_2$ is activated to species **A**. Then, the activation of **I** and subsequent coordination with **2** afford σ-complex **C**, which undergoes migration insertion to C=N bond to form complex **D**. When the *ortho* position of benzamide is occupied by H or F with less steric hindrance, the C=C bond in **D** can coordinate to center metal to form **E**. **E** undergoes a migration insertion and metal-H exchange to generate **3** in a [4+1] annulation manner. In the cases where the *ortho* position of benzamide is occupied by a bulky group (i.e., R ≠ H or F), it is difficult for the coordination of the C=C bond to metal to form **E** due to more steric hindrance between R and amido groups, but **D** can undergoes an intramolecular nucleophilic substitution to produce **4** in a [3+2] annulation manner.



Scheme 3 Proposed mechanism.

During the preparation of 3-(diarylmethylene)isoindolin-1-ones **4,** we serendipitously found that this class of compounds exhibited strong aggregation-induced emissions (AIE)[4] properties. Delighted by the potential applications of AIE active molecules in optoelectronic devices, luminescent sensors, biomedical imaging and smart materials,[5] and as an continuation of our work on developing new AIE fluorophores,[6] we investigated the photophysical properties of these compounds. The results are summarized in Table S2 (see Supporting Information).

Absorption of the selected compounds **4a**-**p** and **5a**-**d** were measured in dilute solution of THF in a concentration scale of 10^{-5} M. Compounds **4a**-**e** absorbed light at about 375 nm with molar absorptivities varying from 17800 to 23700. By installing substituent on *para*-position of 3-diarylmethylene, electron-donating group (MeO) could tune the maximum absorption wavelength. **4i** and **4f** absorbed light at 405 nm and 412 nm, respectively. The highest absorptivity was achieved when the substituent is phenyl (**4h**). Either electron-withdrawing (Br, **4k**) or electron-donating (EtO, **4l**) on 4-position of naphthalene influenced the absorption and gave rise to a blue-shifted absorption. Compounds **4m**-**p** absorbed light at about 370 nm with molar absorptivities ranging from 18100 to 19500. Compared with **4**, the absorption of **5a**-**b** shifted to about 346 nm. Theoretical HOMO and LUMO orbitals were calculated by B3LYP/6-31G+ method on Guassian 09 program. The calculated HOMO-LUMO gaps were in good agreement with the experimental observations based on the relative errors shown in Table S3 (see Supporting Information).

Dilute solutions of compounds **4a**-**p** were not emissive with quantum yields up to 0.077% (**4h**) referring to the standard of quinine sulfate (Φ =0.54 in 0.1M H_2SO_4). Quantum yields of **5a**-**d** were slightly higher up to 0.514% (**5a**). The situation changed by just adding water. For example, solutions of **4d** were not emissive as the water fraction gradually changed to 80% (Fig. 1). Further tuning the water fraction to 85%, the solution was lit up under UV-irradiation. As water fraction increased to 95%, the quantum yield increased to 87.3 times the initial quantum yield. The results indicated that all of these compounds were AIE active. The quantum yields of **4a**-**p** could be magnified in a range of 18 to 163 folds. In comparison with the reported AIE-active molecules, such as tetraphenylethene (40 folds),[7] 9-(diphenylmethylene)-9*H*-fluorene (35 folds)[8] and 3,4-diphenylisoquinolin-1(2*H*)-one (8 folds)[9], the AIE effect of the synthesized compounds **4a** and **4h** was obvious (Fig. 2).

Adding water to the solution of **4d** in THF resulted in the aggregation of solutes and the formation of nano-particles. The shape and size distribution of nano-particles were determined by TEM and DLS (Fig. 3). As the water fraction increased from 85% to 99%, the diameter of nano-particles changed from 164 nm to 72 nm. As a result, a smaller diameter corresponds to a stronger emission.[10]

View Article Online
DOI: 10.1039/C6CC05456K

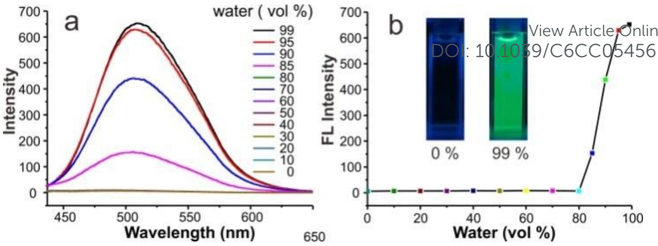


Fig. 1 (a) Emission spectra of **4d** in THF/water mixtures. (b) Fluorescence intensity of **4h** in THF/water mixtures. Excited width = 3 mm, emission width = 10 mm.

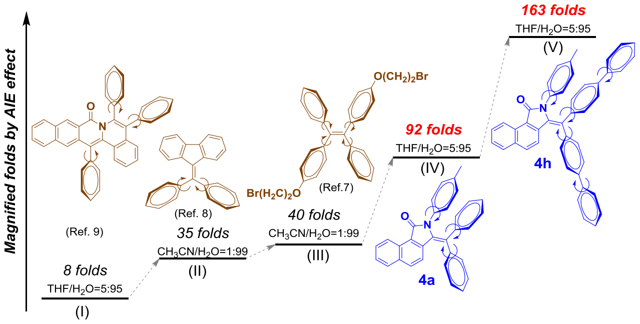


Fig. 2 Magnified folds of quantum yields by AIE effect.

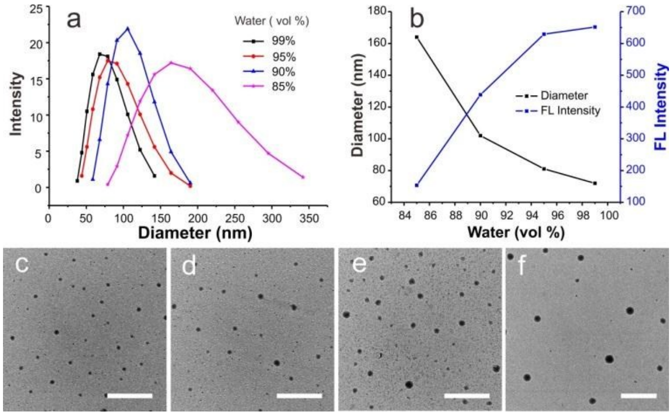


Fig. 3 The size distribution and shape of nano-particles of compound **4d** in H_2O-THF (99;1, 95:5, 90:10, and 85:15, v/v). (a) Particle size distribution. (b) Particle size in peak value and relationship of particle size in peak value and the corresponding maximum fluorescence intensity. (c)-(f) TEM of particles in 99;1, 95:5, 90:10, and 85:15 H_2O-THF, respectively (Scare bar = 1 μm)

The stronger emission in nano-suspension could be explained by aggregation induced emission.[4] The restriction of intramolecular rotation (RIR) of phenyl and phenylene rings in aggregates might be the main reason.[11] Because **4h** has two more phenylene rings conjugated by sigma bonds, the quantum yield of **4h** was magnified to 163 folds. Compounds **4a**-**p** and **5a**-**d** are strong emissive not only in nano-suspension but also in solids. Comparative figures, before and after UV-irradiation on **4a**, **4d**, **4h**, **4n**, and **5c**, are shown in Fig. 4. These compounds are shining in solids.

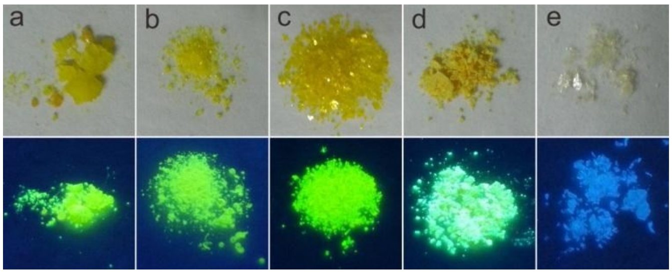


Fig. 4 Image of compounds **4a** (a), **4d** (b), **4h** (c), **4n** (d), and **5c** (e) before (top) and after (bottom) UV-irradiation.

Mechanochromic fluorescent materials have attracted much attention due to their promising applications. They can be applied in fields including mechanosensors,[12] security inks[13] and optical storage.[14] Therefore, compound **4h** was tested for such possibilities. As showed in Fig. 5 , **4h** in crystal shown green with emission at 525 nm. However, it changed colour from green to yellow with emission at 541 nm after grounding. Fluorescence spectra agreed well with the pictures. The different phenomenon may be ascribed to the change of configuration. After grounding, it altered from crystal to amorphous state. SXRD also verified the assumption.

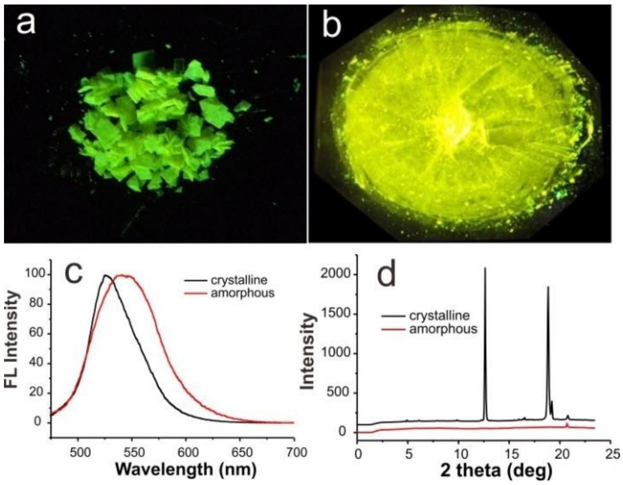


Fig. 5 Fluorescent images of compound **4h** in crystalline (a) and amorphous (b). (c) Emission spectra of **4h** in crystalline and amorphous. (d) SXRD patters of **4h** in crystalline and amorphous

In conclusion, we have developed a rhodium-catalyzed C-H activation/annulation of ketenimines with N-methoxybenzamides. Two types of annulations have been revealed based on the structure variation of N-methoxybenzamides. Thus, 3-aminoisoindolin-1-ones and 3-(diarylmethylene)isoindolin-1-ones were constructed through [4+1] and [3+2] annulation manners, respectively. Furthermore, the synthesized 3-(diarylmethylene)isoindolin-1-ones were found to exhibit strong aggregation-induced emission effect. Strong yellow or blue emissions were observed for these compounds existing both in nano-particles and in solids.

We thank the National Natural Science Foundation of China (Nos. 21272204, 21272203 and J1210042) for finacial support.

Notes and references

View Article Online
DOI: 10.1039/C6CC05456K

1 For recent reviews on ketenimines, see: (a) P. Lu and Y. Wang, *Synlett* **2010**, *2010*, 165; (b) S. H. Kim, S. H. Park, J. H. Choi and S. Chang, *Chem. Asian J.* **2011**, *6*, 2618; (c) P. Lu and Y. Wang, *Chem. Soc. Rev.* **2012**, *41*, 5687; (d) M. Alajarin, M. Marin-Luna and A. Vidal, *Eur. J. Org. Chem.* **2012**, *2012*, 5637.

2 For recent reviews on Rh^{III}-catalyzed C-H activation: (a) T. Satoh and M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212; (b) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; (c) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.* **2012**, *45*, 814; (d) F. W. Patureau,J.Wencel-Delordand and F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31; (e) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; (f) N. Kuhl, N. Schröder and F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443; (g) G. Song and X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007; (h) B. Ye and N. Cramer, *Acc. Chem. Res.* **2015**, *48*, 1308; (i) Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu and Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107.

3 For ORTEPs of products **3k**, **4a**, and **4h** please see the SupportingInformation. CCDC 1405389 (**3k**), 1405393 (**4a**), and 1436545 (**4h**) contain supplementary crystallographic data for this paper.These data can be obtained free of charge from The Cambridge CrystallographicData Centre via www.ccdc.cam.ac.uk/data_request/cif

4 J. Luo, Z. Xie, J. W. Y. Lam, L. Cheng, B. Z. Tang, H. Chen, C. Qiu, H. S. Kwok, X. Zhan, Y. Liu and D. Zhu, *Chem. Commun.* **2001**,1740.

5 J. Mei, Y. Hong, J. W. Y. Lam, A. Qin, Y. Tang and B. Z. Tang, *Adv. Mater.* **2014**, *26*, 5429.

6 (a) Z. Wang, H. Shao, J. Ye, L. Tang and P. Lu, *J. Phys. Chem. B* **2005**, *109*, 19627; (b) H. Shao, X. Chen, Z. Wang and P. Lu, *J. Phys. Chem. B* **2007**, *111*, 10386.

7 H. Tong, Y. Hong, Y. Dong, M. Häußler, J. W. Y. Lam, Z. Li, Z. Guo, Z. Guo and B. Z. Tang, *Chem. Commun.* **2006**, 3705.

8 H. Tong, Y. Dong, Y. Hong, M. Häussler, J. W. Y. Lam, H. H. Y. Sung, X. Yu, J. Sun, I. D. Williams, H. S. Kwok and B. Z. Tang, *J. Phys. Chem. C* **2007**, *111*, 2287.

9 B. Yu, Y. Chen, M. Hong, P. Duan, S. Gan, H. Chao, Z. Zhao and J. Zhao, *Chem. Commun.* **2015**, *51*, 14365.

10 (a) D. Xiao, W. Yang, J. Yao, L. Xi, X. Yang and Z. Shuai, *J. Am. Chem. Soc.* **2004**, *126*, 15439; (b) R. Kuroda and S. F. Mason, *J. Chem. Soc., Perkin Trans. 2* **1981**, 167.

11 J. Chen, C. C. W. Law, J. W. Y. Lam, Y. Dong, S. M. F. Lo, I. D. Williams, D. Zhu and B. Z. Tang, *Chem. Mater.* **2003**, *15*, 1535.

12 (a) A. Pucci, F. Di Cuia, F. Signori and G. Ruggeri, *J. Mater. Chem.* **2007**, *17*, 783; (b) Y. Dong, J. W. Y. Lam, A. Qin, J. Liu, Z. Li, B. Z. Tang, J. Sun and H. S. Kwok, *Appl. Phys. Lett.* **2007**, *91*, 11111; (c) Z. Ning, Z. Chen, Q. Zhang, Y. Yan, S. Qian, Y. Cao and H. Tian, *Adv. Funct. Mater.* **2007**, *17*, 3799; (d) B. R. Crenshaw, M. Burnworth, D. Khariwala, A. Hiltner, P. T. Mather, R. Simha and C. Weder, *Macromolecules* **2007**, *40*, 2400; (e) M. Kinami, B. R. Crenshaw and C. Weder, *Chem. Mater.* **2006**, *18*, 946; (f) S. J. Toal, K. A. Jones, D. Magde and W. C. Trogler, *J. Am. Chem. Soc.* **2005**, *127*, 11661.

13 A. Kishimura, T. Yamashita, K. Yamaguchi and T. Aida, *Nat. Mater.* **2005**, *4*, 546.

14 (a) S. Hirata and T. Watanabe, *Adv. Mater.* **2006**, *18*, 2725; (b) S. Lim, B. An, S. D. Jung, M. Chung and S. Y. Park, *Angew. Chem., Int. Ed.* **2004**, *43*, 6346.