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Palladium-catalyzed benzo[*d*]isoxazole synthesis by C–H activation/[4 + 1] annulation†

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We report a palladium-catalyzed intermolecular [4 + 1] annulation pathway for *N*-phenoxyacetamides with aldehydes to form 1,2-benzisoxazoles. By activating the C–H bonds *ortho* to phenol-derived O–N bonds, the method enables the simultaneous construction of C–C and C=N bonds in 1,2-benzisoxazoles with the O–N bonds intact. The method has been successfully applied to the synthesis of active pharmaceutical intermediates, such as risperidone.

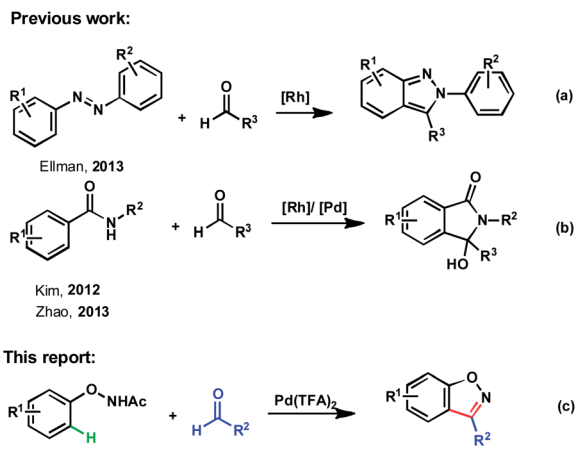
Introduction

Transition metal-catalyzed C–H activation–annulation reactions have become some of the most important and powerful methods in organic synthesis.[1] The direct insertion of unsaturated molecules *via* C–H bond transformation offers many efficient syntheses in an atom-economic fashion. Thanks to their commercial availability and low cost, aldehydes are widely used as coupling partners in metal-catalyzed C–H functionalizations.[2] Several recent reports have utilized aldehydes in directed transition metal-catalyzed annulations (Scheme 1), which enabled the simultaneous formation of C–C and C–heteroatom bonds.[3] Specifically, there are three reports highlighting a [4 + 1] annulation strategy involving aldehydes. Ellman *et al.* demonstrated a highly efficient Rh(III)-catalyzed reaction between azobenzenes and aldehydes to yield substituted *N*-aryl-2*H*-indazoles (Scheme 1a).[3a] Kim *et al.* reported the synthesis of 3-hydroxyisoindolin-1-ones *via* a Rh(III)-catalyzed cascade reaction.[3b] Zhao and co-workers recently reported improved Pd(II)-catalyzed reaction conditions (Scheme 1b).[3c]

Many natural products and pharmaceuticals, such as risperidone and zonisamide, contain 1,2-benzisoxazoles as a key fragment.[4] We hypothesized that *N*-phenoxyacetamides[5] might react with aldehydes to form 1,2-benzisoxazoles using a catalytic [4 + 1] annulation strategy (Scheme 1c). Herein we report the first example that introduces a Pd(II)-catalyzed intermolecular C–H activation route for the simultaneous construction of C–C and C=N bonds in 1,2-benzisoxazoles.

Results and discussion

The initial reaction of *N*-phenoxyacetamide (**1a**) and *p*-tolualdehyde (**2a**) was carried out in the presence of 10 mol% $Pd(TFA)_2$ and 4 equiv. *tert*-butyl hydroperoxide (TBHP) at 80 °C in THF under N_2 atmosphere, affording the desired product **3aa** in 31% yield (Table 1, entry 1). The crystal structure of product **3aa** is shown in Table 2.[6] Other oxidants such as Ag salts, $K_2S_2O_8$ and $Cu(OAc)_2$ did not promote the desired reaction (see Table S1†). We also examined different additives and found that acids and bases did not improve the reaction yield (see Table S1†). A variety of solvents were screened. DMSO improved the yield to 59% (entry 3) and *t*-AmOH was proved to be the most effective solvent, affording the product in 75% yield (entry 5), indicating that the solvent



Scheme 1 Heterocycle formation through [4 + 1] annulation.

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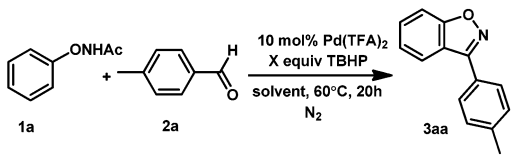
Table 1 Optimization of reaction conditions[a,b]



Entry	Solvent	*X*	Yield [%]
1[c]	THF	4	31
2[c]	1,4-Dioxane	4	46
3[c]	DMSO	4	59
4[c]	*t*-BuOH	4	46
5[c]	*t*-AmOH	4	75
6	*t*-AmOH	4	85
7[d]	*t*-AmOH	4	73
8	*t*-AmOH	3	80
9	*t*-AmOH	2.5	88
10	*t*-AmOH	—	N.R.

[a] Determined by GC analysis using mesitylene as an internal standard. [b] All reactions were kept in a dark place. [c] Reaction at 80 °C. [d] 5 mol% $Pd(TFA)_2$.

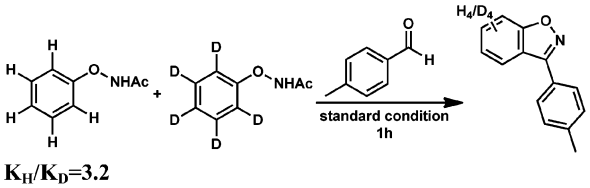
plays a key role in the reaction. Gratifyingly, by lowering the reaction temperature to 60 °C, the yield was improved to 85% (entry 6). When the catalyst loading was lowered from 10 mol% to 5 mol%, the yield was obviously reduced from 85% to 73% (entry 7). Using 2.5 equiv. TBHP in place of 4 equiv. TBHP (entry 9) had no obvious impact on the yield. In the absence of TBHP, no product was observed (entry 10). Eventually we set the standard reaction conditions to be $Pd(TFA)_2$ (10 mol%) and TBHP (2.5 equiv.) in *t*-AmOH under nitrogen at 60 °C.

Next, we explored the substrate scope for aldehydes (Table 2). The reaction went well for diverse substrates including aromatic, heterocyclic, and aliphatic aldehydes. When benzaldehyde derivatives were used as the starting materials, electron-donating substitution groups such as methyl (**2a**, **2b**, **2c**) and methoxyl (**2e**, **2f**, **2g**) afforded the corresponding products in moderate to high yields ranging from 56% to 90%, while electron-withdrawing groups such as ester (**2i**), trifluoromethyl (**2k**) and naphthyl (**2n**) gave products in yields ranging from 64% to 76%. With the same substitution group, the yield was typically highest when the *para*-position of the phenyl ring was occupied, and lowest for the *ortho*-substituted benzaldehyde (**3aa** > **3ab** > **3ac**, **3ae** > **3af** > **3ag**). This trend held true for different substitution groups of the same electron-withdrawing category on the phenyl ring (**3ai**, **3aj** > **3ak** > **3al**), indicating that steric hindrance might play a key role in the reaction. This transformation tolerated dual-substitution, such that 3,5-dimethoxybenzaldehyde (**2h**) and 3,5-dichlorobenzaldehyde (**2m**) proceeded smoothly to afford products in 53% and 48% yield, respectively. Heterocyclic aldehydes such as furfural (**2o**) and 2-thiophenecarboxaldehyde (**2p**) proceeded smoothly in moderate yields. Various aliphatic aldehydes could also form the desired products under standard conditions. Simple aliphatic aldehydes, such as butyraldehyde (**2q**), offered the desired product in 63% yield and branched isobutyraldehyde (**2r**) gave the corresponding product in 40% yield. The cycloalkane carboxaldehydes such as cyclohexanecarboxaldehyde (**2s**) and cyclopentanecarboxaldehyde (**2t**) participated in the coupling reaction to furnish products in 41% and 64% yield, respectively. The coupling reaction was facile enough that the cyclopropyl ring was kept intact when cyclopropanecarboxaldehyde (**2u**) reacted with *N*-phenoxyacetamide to afford the 3-cyclopropyl-1,2-benzisoxazole in 51% yield.

The scope of the substituents on *N*-phenoxyacetamide was also investigated (Table 3). *N*-Phenoxyacetamides with either electron-rich or electron-deficient substituents proceeded smoothly. A variety of functionalities including methoxyl, fluoro, chloro and bromo groups were tolerable. The *meta*-substituted *N*-phenoxyacetamides were annulated only at the less hindered *ortho* positions. The complete regiospecificity suggested again that the steric effect is important (**3ca**, **3ea–3ha**). When the substitutions on the *N*-phenoxyacetamides were *para* (**3ga**, **3ha**) to the newly formed carbon–carbon bond, the yields were higher than when the substitutions were in *meta* positions (**3ia**, **3ja**). This might be attributed to the competing inductive effect and resonance stabilization, which could also explain the tendency of the yield, **3ha** > **3ga** > **3fa**.

Mechanism

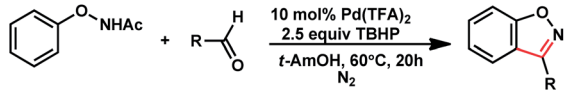
A kinetic isotope effect experiment was carried out between equimolar amounts of deuterio-**1a** and *N*-phenoxyacetamide **1a** with aldehyde **2a** under standard conditions for one hour. It gave a K_H/K_D ratio of 3.2, indicating that C–H bond cleavage was involved in the product determining step (eqn (1)).[7]

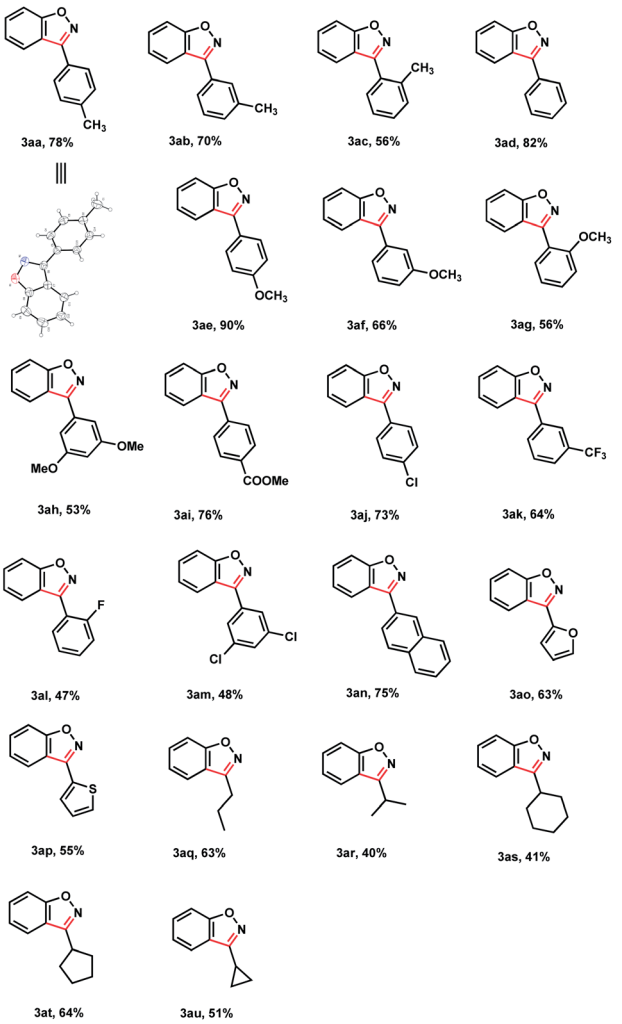


K_H/K_D=3.2 (1)

To probe the catalytic mechanism, we carried out a model reaction with 10 mol% $Pd(TFA)_2$ or 1 equiv. $Pd(TFA)_2$ in the absence of TBHP. No desired product was detected, suggesting that the mechanism is a Pd(II)–Pd(IV)–Pd(II) catalytic cycle instead of a Pd(II)–Pd(0)–Pd(II) cycle. When we added a radical scavenger to the reaction, such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO),[8] the reaction rate was suppressed in a dose-dependent manner from GC analysis. Thus radical intermediates might be involved in the mechanism. When the substrate (**1k**) was treated with 10 mol% $Pd(TFA)_2$ in *t*-AmOH at 60 °C under N_2, it was exclusively converted to the corresponding product **3ad**, indicating that **1k** was likely to be the intermediate

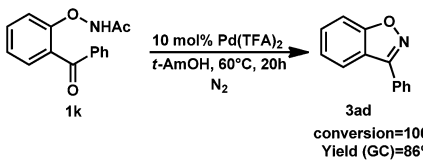
Table 2 Scope of aldehydes[a,b]





[a] *Reaction conditions*: **1a** (0.2 mmol), **2** (0.4 mmol), *t*-AmOH (1 ml). [b] Isolated yields.

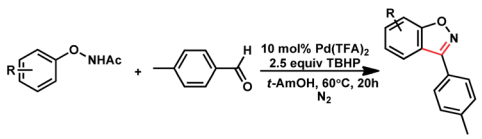
in the process of the reaction (eqn (2)) (see the ESI† for the mechanism study in detail).

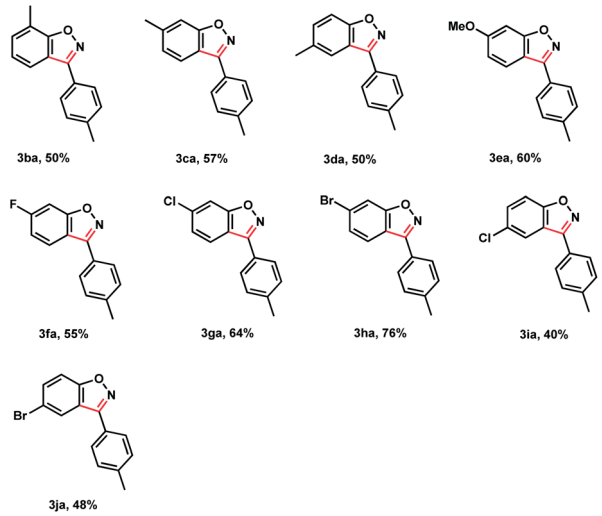


(2)

On the basis of these observations, a possible mechanism was proposed, as shown in Scheme 2. Density functional theory (DFT) studies were conducted to further elucidate the mechanism (Scheme 3). The catalyst $Pd(TFA)_2$ and substrate *N*-phenoxyacetamides were taken as the reference points. The

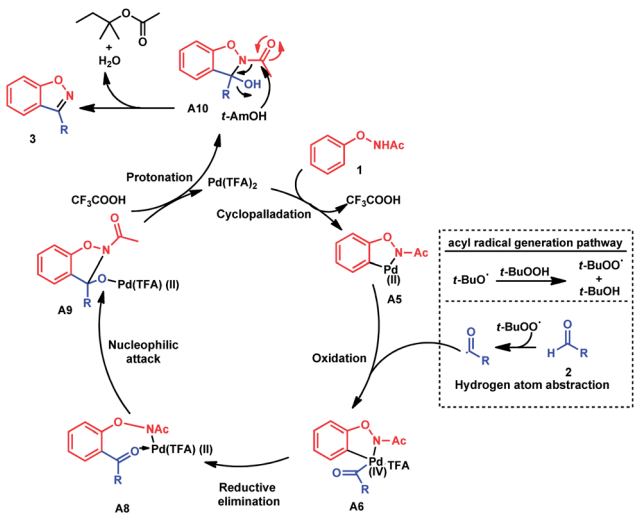
Table 3 Scope of *N*-phenoxyacetamides[a,b]



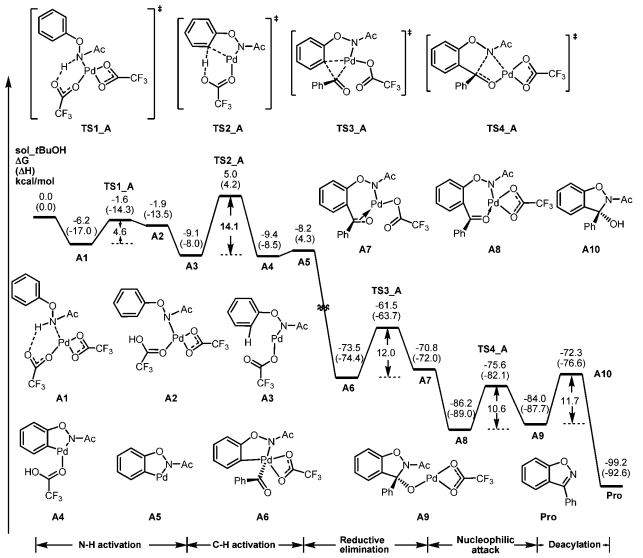


[a] *Reaction conditions*: **1** (0.2 mmol), **2a** (0.4 mmol), *t*-AmOH (1 ml). [b] Isolated yield.

catalytic cycle started from $Pd(TFA)_2$, which was first ligated to compound **1** with a concomitant loss of two molecules of trifluoroacetic acid. The N–H activation step *via* **TS1-A** had a very low barrier (4.6 kcal mol^{-1}), which contributed to the deprotonated *N*-phenoxyacetamide in the intermediate **A2**. Next, we proposed that intermediate **A4** was obtained *via* a C–H activation pathway through a concerted metalation–deprotonation (CMD) transition state (**TS2-A**). The CMD step had an activation energy of about 14.1 kcal mol^{-1}, which is the rate-determining



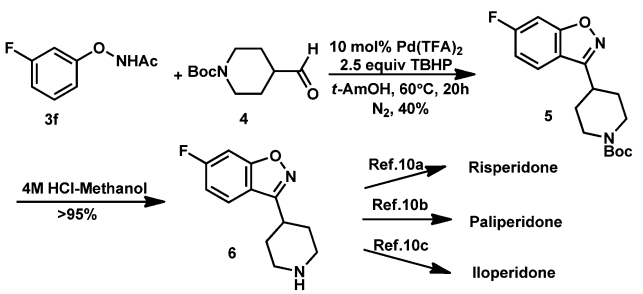
Scheme 2 Proposed mechanism of 1,2-benzisoxazole synthesis.



Scheme 3 The M06 free energy profile for the palladium-catalyzed benzo[*d*]isoxazole synthesis. Enthalpies are given in parentheses.

step. Subsequently, the trifluoroacetic acid ligand dissociates and produces a Pd(II) complex **A5**. The oxidative addition of the intermediate **A5** with an acyl radical, which was generated from the aldehyde *via* hydrogen atom abstraction by *t*-BuOO$^{\bullet}$ (ref. 9) from TBHP, would generate a Pd(IV) intermediate **A6**. This process was calculated to be very exergonic ($\Delta G = -65.3$ kcal mol^{-1}). Reductive elimination from intermediate **A6** *via* **TS3-A** ($\Delta G^{\ddagger} = 12.0$ kcal mo1^{-1}) allowed for the C–C bond formation and delivered intermediate **A8**. Intramolecular nucleophilic attack occurs *via* **TS4-A** to form a palladium alkoxide **A9**, which was protonated by trifluoroacetic acid to afford the corresponding organic intermediate **A10**. Finally, deacylation and dehydration yield the desired product **3** and regenerate the palladium catalyst. The other two possible mechanisms, an aldehyde insertion mechanism[2c] and a nitrogen radical initiation mechanism[3c] were also studied and found to be unfavorable (see ESI†).

The synthetic applicability of our methodology was further illustrated by the assembly of a 1,2-benzisoxazole compound **6** (Scheme 4). The desired product **5** was obtained conveniently in 40% yield in a single step under standard reaction conditions. Compound **5** was further deprotected in nearly quantitative yield (>95%). Compound **6** was the key intermediate in the synthesis of pharmaceuticals of risperidone, paliperidone and iloperidone.[10]



Scheme 4 The catalytic synthesis of key intermediate **6**.

Conclusions

Taken together, we have developed a novel Pd(II)-catalyzed intermolecular [4 + 1] annulation pathway for the synthesis of 1,2-benzisoxazoles, utilizing *N*-phenoxyacetamides and aldehydes as starting materials. Interestingly, Lu and co-workers recently reported Rh-catalyzed directed C–H bond activations on *N*-phenoxyacetamides. Their ingenious work suggested that the O–N functionality acted as an internal oxidant as well as a directing group.[5] In contrast, the O–N bonds were kept intact and became part of the 1,2-benzisoxazole products in our Pd-catalyzed system. DFT calculations on our Pd-catalyzed reaction supported a Pd(II)–Pd(IV)–Pd(II) catalytic cycle involving a concerted metalation–deprotonation process. Investigations on developing a wider scope of metal-catalyzed [4 + 1] annulation to furnish interesting heterocycles are underway and will be reported in due course.

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Notes and references

1 For recent general reviews on C-H functionalization for heterocycle synthesis, see: (*a*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960; (*b*) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (*c*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*d*) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094; (*e*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173.

2 For a review, see: (*a*) C. Pan, X. Jia and J. Cheng, *Synthesis*, 2012, **44**, 677; For Pd-catalyzed C-H activation with aldehydes, see: (*b*) X. Jia, S. Zhang, W. Wang, F. Luo and J. Cheng, *Org. Lett.*, 2009, **11**, 3120; (*c*) O. Baslé, J. Bidange, Q. Shuai and C.-J. Li, *Adv. Synth. Catal.*, 2010, **352**, 1145; (*d*) C.-W. Chan, Z. Zhou, A. S. C. Chan and W.-Y. Yu, *Org. Lett.*, 2010, **12**, 3926; (*e*) Q. Zhang, C. Li, F. Yang, J. Li and Y. Wu, *Tetrahedron*, 2013, **69**, 320; (*f*) A. Banerjee, S. K. Santra, S. Guin, S. K. Rout and B. K. Patel, *Eur. J. Org. Chem.*, 2013, 1367; (*g*) H. Li, P. Li and L. Wang, *Org. Lett.*, 2013, **15**, 620; (*h*) S. Sharma, J. Park, E. Park, A. Kim, M. Kim, J. H. Kwak, Y. H. Jung and I. S. Kim, *Adv. Synth.*

Catal., 2013, **355**, 332; (*i*) C.-W. Chan, Z. Zhou and W.-Y. Yu, *Adv. Synth. Catal.*, 2011, **353**, 2999; (*j*) C. Li, L. Wang, P. Li and W. Zhou, *Chem.–Eur. J.*, 2011, **17**, 10208; (*k*) Y. Wu, B. Li, F. Mao, X. Li and F. Y. Kwong, *Org. Lett.*, 2011, **13**, 3258; (*l*) Y. Wu, P. Y. Choy, F. Mao and F. Y. Kwong, *Chem. Commun.*, 2013, **49**, 689; (*m*) F. Szabó, J. Daru, D. Simkó, T. Z. Nagy, A. Stirling and Z. Novák, *Adv. Synth. Catal.*, 2013, **355**, 685; For Rh-catalyzed C-H activation with aldehydes, see: (*n*) Y. Yang, B. Zhou and Y. Li, *Adv. Synth. Catal.*, 2012, **354**, 2916; (*o*) J. Park, E. Park, A. Kim, Y. Lee, K.-W. Chi, J. H. Kwak, Y. H. Jung and I. S. Kim, *Org. Lett.*, 2011, **13**, 4390; (*p*) B. Zhou, Y. Yang and Y. Li, *Chem. Commun.*, 2012, **48**, 5163; (*q*) L. Yang, C. A. Correia and C.-J. Li, *Adv. Synth. Catal.*, 2011, **353**, 1269; (*r*) Y. Li, X.-S. Zhang, K. Chen, K.-H. He, F. Pan, B.-J. Li and Z.-J. Shi, *Org. Lett.*, 2012, **14**, 636; For other metal-catalyzed C-H activation with aldehydes, see: (*s*) Y. Fukumoto, K. Sawada, M. Hagihara, N. Chatani and S. Murai, *Angew. Chem., Int. Ed.*, 2002, **41**, 2779; (*t*) B.-J. Li and Z.-J. Shi, *Chem. Sci.*, 2011, **2**, 488; (*u*) Y. Kuninobu, Y. Fujii, T. Matsuki, Y. Nishina and K. Takai, *Org. Lett.*, 2009, **11**, 2711; (*v*) Y. Kuninobu, Y. Nishina, T. Takeuchi and K. Takai, *Angew. Chem., Int. Ed.*, 2007, **46**, 6518; (*w*) J. Wang, C. Liu, J. Yuan and A. Lei, *Angew. Chem., Int. Ed.*, 2013, **52**, 2256.

3 (*a*) Y. Lian, R. G. Bergman, L. D. Lavis and J. A. Ellman, *J. Am. Chem. Soc.*, 2013, **135**, 7122; (*b*) S. Sharma, E. Park, J. Park and I. S. Kim, *Org. Lett.*, 2012, **14**, 906; (*c*) Q. Yu, N. Zhang, J. Huang, S. Lu, Y. Zhu, X. Yu and K. Zhao, *Chem.–Eur. J.*, 2013, **19**, 11184; (*d*) Y. Lian, T. Huber, K. D. Hesp, R. G. Bergman and J. A. Ellman, *Angew. Chem., Int. Ed.*, 2013, **52**, 629; (*e*) Y. Lian, R. G. Bergman and J. A. Ellman, *Chem. Sci.*, 2012, **3**, 3088; (*f*) X. Shi and C.-J. Li, *Adv. Synth. Catal.*, 2012, **354**, 2933; (*g*) Y. Kuninobu, Y. Nishina, C. Nakagawa and K. Takai, *J. Am. Chem. Soc.*, 2006, **128**, 12376.

4 (*a*) E. D. Deeks, *Drugs*, 2010, **70**, 1001, and references cited therein; (*b*) Y. Chen, S. Wang, X. Xu, X. Liu, M. Yu, S. Zhao, S. Liu, Y. Qiu, T. Zhang, B.-F. Liu and G. Zhang, *J. Med. Chem.*, 2013, **56**, 4671; (*c*) S.-B. Andreas, *Expert Opin. Pharmacother.*, 2010, **11**, 115; (*d*) R. M. Vitale, C. Pedone, P. Amodeo, J. Antel, M. Wurl, A. Scozzafava, C. T. Supuran and G. D. Simone, *Bioorg. Med. Chem.*, 2007, **15**, 4152; (*e*) M. Kramer, G. Simpson, V. Maciulis, S. Kushner, U. Vijapurkar, P. Lim and M. Eerdekens, *J. Clin. Psychopharmacol.*, 2007, **27**, 6; (*f*) J. T. Strupczewski, K. J. Bordeau, Y. Chiang, E. J. Glamkowski, P. G. Conway, R. Corbett, H. B. Hartman, M. R. Szewczak, C. A. Wilmot and G. C. Helsley, *J. Med. Chem.*, 1995, **38**, 1119.

5 (*a*) G. Liu, Y. Shen, Z. Zhou and X. Lu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6033; (*b*) Y. Shen, G. Liu, Z. Zhou and X. Lu, *Org. Lett.*, 2013, **15**, 3366.

6 See ESI.†

7 E. M. Simmons and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2012, **51**, 3066.

8 (*a*) J. J. Warren and J. M. Mayer, *J. Am. Chem. Soc.*, 2010, **132**, 7784; (*b*) W. Liu, H. Cao, H. Zhang, H. Zhang, K. H. Chung, C. He, H. Wang, F. Y. Kwong and A. Lei, *J. Am. Chem. Soc.*, 2010, **132**, 16737.

9 (*a*) A. J. Catino, J. M. Nichols, H. Choi, S. Gottipamula and M. P. Doyle, *Org. Lett.*, 2005, **7**, 5167; (*b*) E. C. McLaughlin, H. Choi, K. Wang, G. Chiou and M. P. Doyle, *J. Org. Chem.*, 2009, **74**, 730.

10 (*a*) G. Zhang, Y. Zhu, C. Fan, M. Zhang and J. Wang, WO2009012721, 2009; (*b*) V. T. Mathad, B. S. Pandit, B. U. Sekhar and P. V. Solanki, WO2012035554A1, 2012; (*c*) S. D. Dwivedi, D. J. Patel and A. P. Shah, WO2012063269A2, 2012.

