High-yielding synthesis of Nefopam analogues (functionalized benzoxazocines) by sequential one-pot cascade operations†

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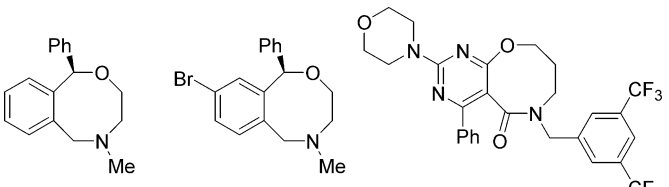
An efficient amine-/ruthenium-catalyzed three-step process for the synthesis of Nefopam analogues was achieved through combinations of cascade enamine amination/iso-aromatization/allylation and diene or enyne metathesis as key steps starting from functionalized Hagemann's esters. In this communication, we discovered the application of ruthenium-catalysis on olefins containing free amines without *in situ* formation of salts.

Drug-like highly substituted heterocycles are of considerable importance in a variety of industries. As such, the development of new and more general green methods for their preparation is of significant interest.[1] Especially, oxygen- and nitrogen-containing heterocycles have attracted considerable attention as a result of their biological activity and their presence in a variety of natural and unnatural products.[1] Thus, the diversity-oriented synthesis of oxygen- and nitrogen-containing heterocycles represents an important task because of the widespread occurrence of such structural motifs and their use as building blocks. For example, functionalized benzoxazocines and pharmaceutically acceptable salts thereof, may be useful as analgesic agents and for the treatment of emesis, depression, posttraumatic stress disorders, attention deficit disorders, obsessive compulsive disorders, sexual dysfunction and centrally acting skeletal muscle relaxants (see eqn (1)).[1g-o] Herein, we report for the first time the organocatalytic approach to the high yielding synthesis of functionalized benzoxazocines from a three-step sequence *via* "combination of amine-/ruthenium-catalysis".



(-)-Nefopam Nefopam analogue NK1 Antagonist

(1)

Recently olefin metathesis of hetero-dienes and enynes catalyzed by Grubbs' catalysts provided a general route to a variety of heterocycles in good yields.[2] The advent of olefin metathesis technology triggered a burst of activity in the synthesis of a huge variety of differently substituted heterocycles. In a similar manner, reactions were performed *via* a combination of multi-component and multi-catalysis approaches in one pot, generating desired targets efficiently in a single reaction vessel without the need to purify at each step.[3] A particularly attractive green cascade process occurs when two or more sequential reactions are mediated by a catalytic amount of a simple amine. The catalytic ability of a secondary amine (**3a**) to function as a catalyst for cascade enamine amination/iso-aromatization (EA/IA) reactions has led to several examples where combinations of these transformations provide efficient new entries into useful *o*-hydroxydiarylamine **4** products (Scheme 1).[3f]

During our studies on amine-catalyzed cascade EA/IA reactions,[3f] we noted that functionalized *o*-hydroxydiarylamines **4** can serve as suitable starting materials for the generation of Nefopam analogues *via O*-allylation, *N*-allylation and ring closing metathesis (RCM) as key processes (Scheme 1). Unfortunately, olefin metathesis, however, is known to be incompatible with free amines due to catalyst inhibition by the basic nitrogen, although the ammonium salts have been shown to undergo metathesis.[4] Furthermore, there have been reports of ring-closing metathesis of secondary and tertiary free amines protonated *in situ* to form six-membered heterocycles, as well as a report of RCM of a tertiary free amine to form a seven-membered ring under acidic conditions, but they required a higher catalyst loading (20 mol%).[5]

Herein, we discovered a novel and green technology for the three-step synthesis of highly substituted benzoxazocines using amine/potassium carbonate/sodium hydride/ruthenium-catalysis through cascade enamine amination/iso-aromatization/*O*-allylation (EA/IA/A), *N*-allylation, and diene or enyne metathesis as key steps starting from commercially available Hagemann's esters **1**, nitrosobenzenes **2**, allyl bromide, secondary amine **3a** and Grubbs 1st and 2nd generated ruthenium catalysts **3b**/**3c**, an approach we call "multi-catalysis approach to heterocycles" (Scheme 1). In this communication, we present for the first time the RCM reaction of olefins containing free amines without *in situ* salt formation.

We initiated our studies on the combination of a cascade EA/IA reaction, *O*-and *N*-allylations and diene metathesis as key steps for the synthesis of highly substituted 5,6-dihydro-2*H*-benzo[*b*][1,4]oxazocine **7aa** starting from Hagemann's ester **1a** and nitrosobenzene **2a** as shown in Table 1. Piperidine/K_2CO_3-catalyzed cascade EA/IA/A reaction of **1a**, **2a** and allyl bromide furnished the monoene amine **5aa** in 93% yield. But the same reaction under pyrrolidine/K_2CO_3-catalysis furnished the monoene amine **5aa** in 75% yield (result not shown in Table 1).

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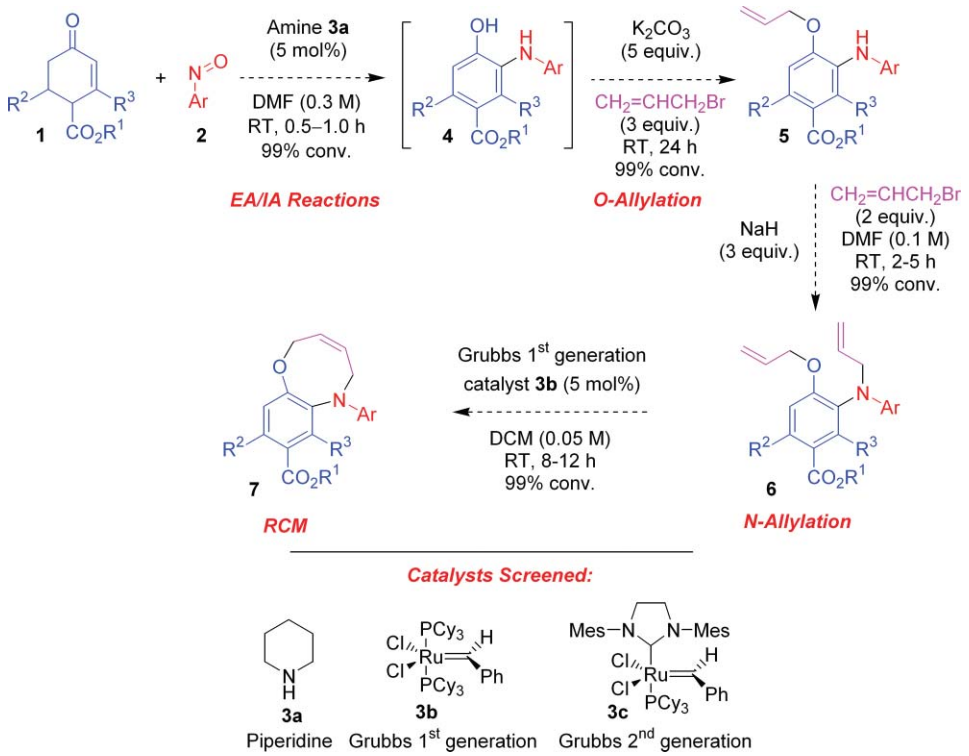
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds. CCDC reference numbers 637091 and 637092. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b910397j



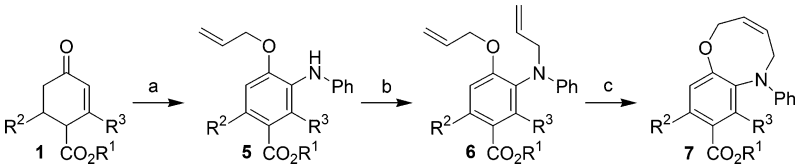
Scheme 1 Synthesis of Nefopam analogues *via* a three-step sequence.

In a similar manner, cascade EA/IA/A reaction of **1a**, **2a** and allyl bromide under the combination of other amines like glycine, proline, morpholine or benzylamine with K_2CO_3 is not superior compared to piperidine/K_2CO_3-catalysis (results not shown in Table 1). Further NaH-promoted *N*-allylation of cascade EA/IA/A product **5aa** furnished the diene amine **6aa** in 85% yield. Interestingly, RCM reaction of free diene amine **6aa** using Grubbs' 1st generation catalyst **3b** in CH_2Cl_2 at 25 °C for 8 h furnished the highly functionalized 5,6-dihydro-2*H*-benzo[*b*][1,4]oxazocine **7aa** in 85% yield; but the same reaction with Grubbs' 2nd generation catalyst **3c** furnished the **7aa** in 75% yield (Table 1). The technical advantage of these reactions is that the ruthenium-catalysis is performed on free diene amines without the need for *in situ* salt formation. With the optimized reaction conditions in hand, the scope of the three-step synthesis of **7** was investigated with various Hagemann's esters **1a–o** and nitrosobenzene **2a**. As summarized in Table 1, a series of Hagemann's esters **1a–o** were transferred into highly substituted 5,6-dihydro-2*H*-benzo[*b*][1,4]oxazocines **7aa–oa** in 33 to 67% overall yields *via* piperidine-/ruthenium-catalysis from a three-step sequence. Unfortunately, we were not able to recycle the ruthenium-catalyst **3b** in these reactions, because the reaction mixture was completely homogenous in dichloromethane solution.

Interestingly, monoene amines **5** can be synthesized directly from two equivalents of ethyl acetoacetate and aldehyde under piperidine-catalysis followed by *in situ* reaction with nitrosobenzene **2a** and allyl bromide to furnish **5** with moderate to good yields. So, for the synthesis of Hagemann's ester **1a–p** library, we utilized piperidine-catalyzed condensation of ethyl acetoacetate with different aldehydes in EtOH at 80 °C for 5–8 h through cascade Knoevenagel/Michael/aldol condensation/decarboxylation reactions.[31] For example, monoene amine **5ka** furnished with moderate yield (61%) from ethyl acetoacetate, 4-chlorobenzaldehyde, nitrosobenzene **2a**, and allyl bromide under piperidine- and K_2CO_3-catalysis through cascade Knoevenagel/Michael/aldol condensation/decarboxylation and cascade enamine amination/isoaromatization/*O*-allylation reactions in one pot (see Table 1). Further we were interested in investigating the RCM reaction on triene amine **6pa** to test the regioselectivity. Compound **6pa** was prepared from a Claisen rearrangement of **5ka** in DMF at 180 °C for 18 h followed by *O*- and *N*-allylation with allyl bromide under NaH-catalysis in one pot to furnish the triene amine **6pa** in good yield, which on further RCM reaction under **3b**-catalysis furnished the benzo[*b*]oxepine **7′pa** with 60% yield[6] and benzoxazocine **7pa** with 40% yield as shown in Table 1. The structure and regiochemistry of oxazocines **7aa–pa** was confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on **7ha** (Fig. 1).[7] Functionalized oxazocines **7** have shown many pharmaceutical applications like noradrenaline, serotonin reuptake inhibitors for treatment of pain and emesis, neurokinin receptor antagonists, anti-inflammatory activity and anti-depressive activity.[1g–o] This three-step synthetic strategy will have a great impact on the synthesis of a diversity-oriented library of substituted oxazocines to find suitable drug molecules.

With the success of a three-step synthesis of highly functionalized 5,6-dihydro-2*H*-benzo[*b*][1,4]oxazocines **7**, we continued our investigation of the generation of 3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,4]oxazocines **8** *via* sequential Pd/C-mediated hydrogenation of **7** through a one-pot synthesis due to a structural similarity with Nefopam. The results in Scheme 2 demonstrate the broad scope of this novel methodology covering a sequential

Table 1 Three-step synthesis of Nefopam analogues *via* combination of amine-/potassium carbonate-/sodium hydride-/ruthenium-catalysis[a]



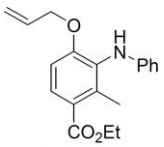
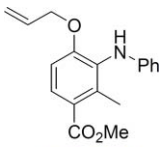
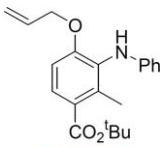
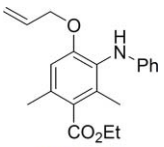
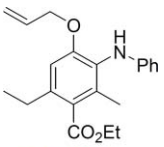
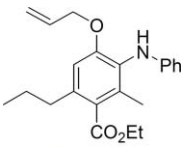
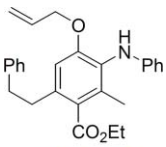
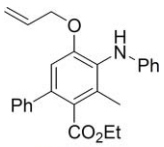
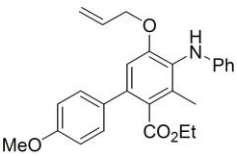
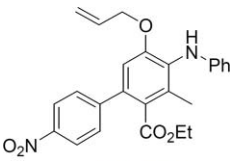
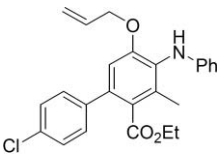
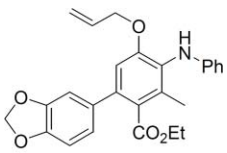
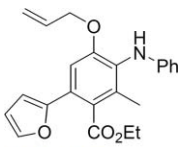
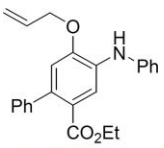
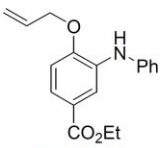
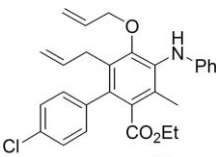
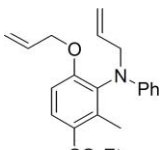
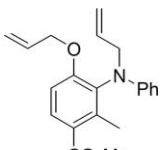
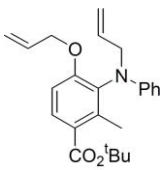
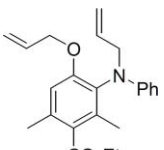
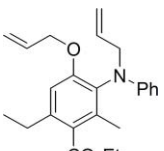
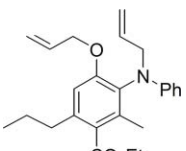
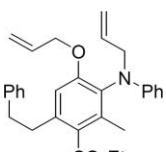
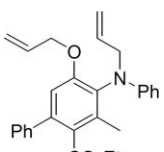
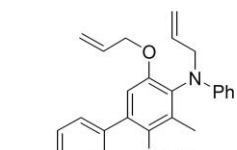
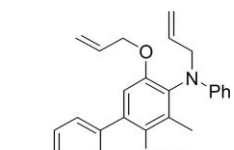
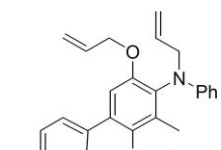
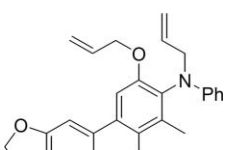
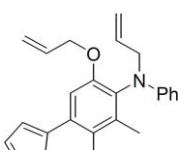
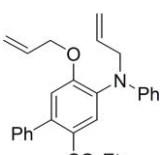
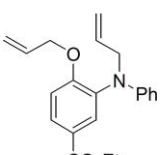
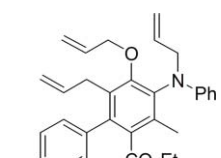
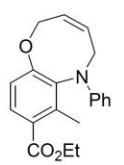
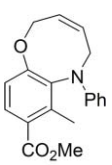
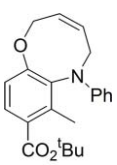
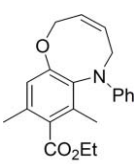
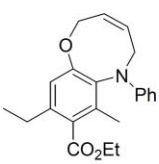
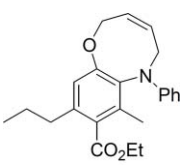
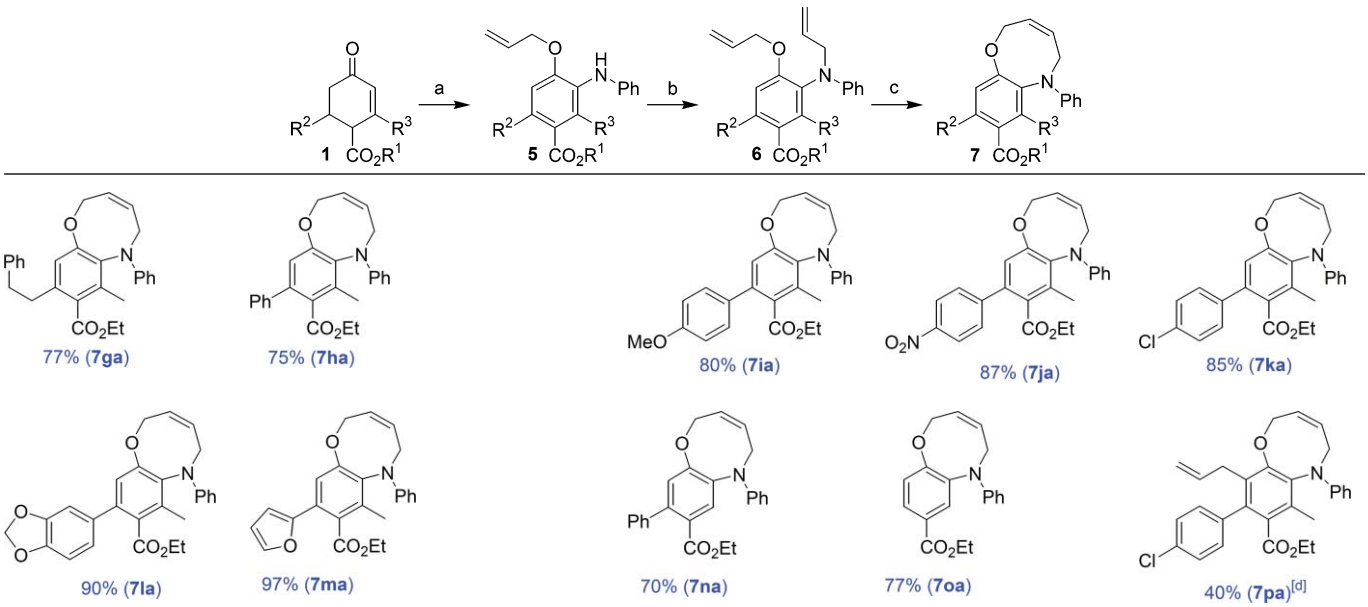
 93% (**5aa**)	 95% (**5ba**)	 73% (**5ca**)	 85% (**5da**)	 70% (**5ea**)	 70% (**5fa**)
 71% (**5ga**)	 88% (**5ha**)		 86% (**5ia**)	 75% (**5ja**)	 61% (**5ka**)
 80% (**5la**)	 90% (**5ma**)		 90% (**5na**)	 61% (**5oa**)	 65% (**5pa**)[b]
 85% (**6aa**)	 77% (**6ba**)	 85% (**6ca**)	 85% (**6da**)	 72% (**6ea**)	 87% (**6fa**)
 61% (**6ga**)	 80% (**6ha**)		 72% (**6ia**)	 90% (**6ja**)	 71% (**6ka**)
 80% (**6la**)	 70% (**6ma**)		 80% (**6na**)	 80% (**6oa**)	 65% (**6pa**)[b]
 85%, 75%[c] (**7aa**)	 73% (**7ba**)	 86% (**7ca**)	 85% (**7da**)	 83% (**7ea**)	 75% (**7fa**)

Table 1 (*Contd.*)



[a] *Reagents and conditions:* (a) Ph–N=O (0.5 equiv.), **3a** (5 mol%), DMF (0.3 M), 25 °C, 1 h; K_2CO_3 (5 equiv.), $H_2C{=}CHCH_2Br$ (3 equiv.), 25 °C, 24 h; (b) NaH (3 equiv.), $H_2C{=}CHCH_2Br$ (2 equiv.), DMF (0.1 M), 25 °C, 2–5 h; (c) CH_2Cl_2 (0.05 M), **3b** (5 mol%), 25 °C, 8–12 h; [b]Yield representing from **5ka** *via* two steps; [c]CH_2Cl_2 (0.05 M), **3c** (5 mol%), 25 °C, 4 h; [d]Highly substituted benzo[*b*]oxepine **7′pa** furnished as a byproduct in 60% yield (see ref. 6).

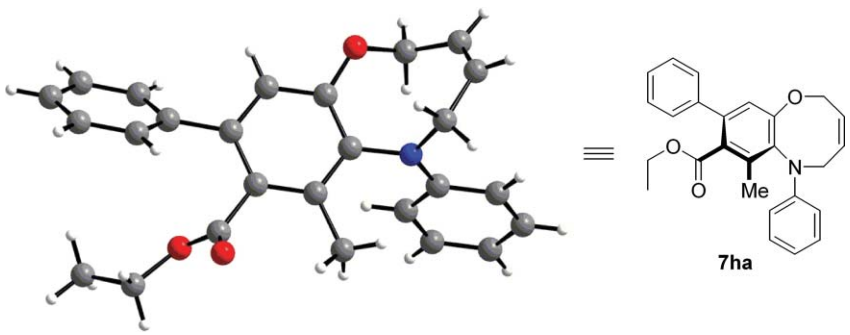
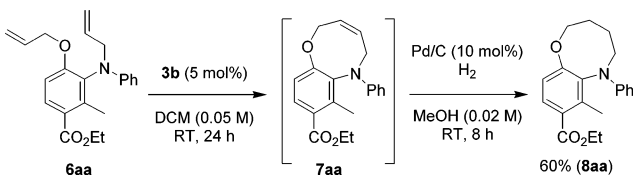


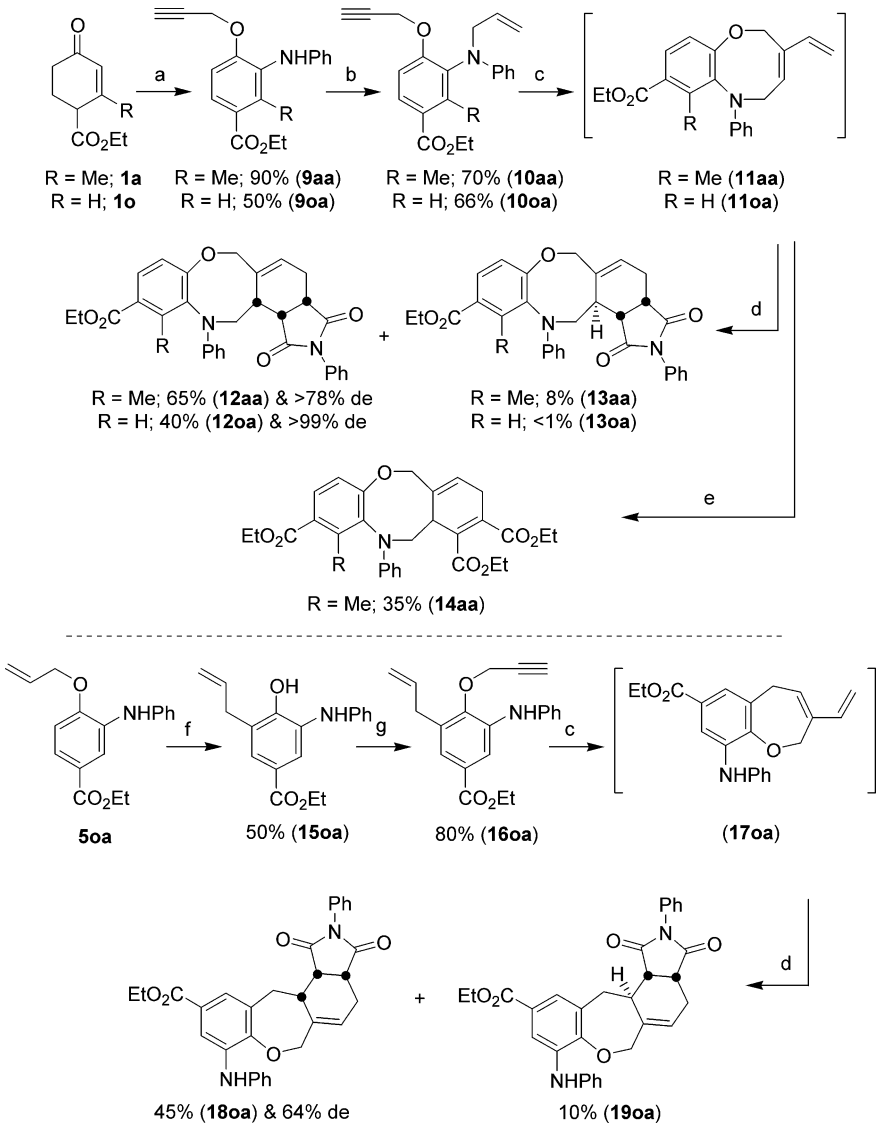
Fig. 1 X-Ray crystal structure of **7ha**.



Scheme 2 Sequential combination of Ru- and Pd-catalysis in one pot for the synthesis of 3,4,5,6-tetrahydro-2*H*-benzo[*b*][1,4]oxazocines **8**.

combination of Ru- and Pd-catalysis to take place in one pot with a good yield.[8]

After successful demonstration of a high yielding three-step synthesis for the benzo[*b*][1,4]oxazocines **7** and **8**, we further extended the three-step synthesis into the construction of more functionalized molecules *via* a combination of cascade enamine amination/iso-aromatization/*O*-propargylation (EA/IA/P), *N*-allylation, cascade RCM/DA reactions (see Scheme 3). Hagemann's ester **1a** was converted into highly functionalized tetracyclic *endo*-product **12aa** with >78% de in a stereoselective manner with 46% overall yield through a sequence of amine/K_2CO_3-catalyzed cascade EA/IA/P, NaH-promoted *N*-allylation, ruthenium-promoted enyne RCM followed by heat-promoted Diels–Alder (DA) reaction with 1-phenyl-pyrrole-2,5-dione in one pot as shown in Scheme 3. Generality of the amine-/K_2CO_3-/NaH-/Ru-catalyzed stereoselective sequential one-pot cascade EA/IA/P, A and RCM/DA reactions was further confirmed by two more examples using a different Hagemann's ester **1o** and dienophile to furnish the expected highly functionalized compound **12oa** in 13.2% overall yield with >99% de and compound **14aa** in 22% overall yield, respectively, as shown in Scheme 3. The structure and stereochemistry of oxazocines **12–14**



Scheme 3 General application of three-step chemistry in the synthesis of heterocycles. *Reagents and conditions:* (a) Ph–N=O (0.5 equiv.), **3a** (5 mol%), DMF (0.5 M), 25 °C, 1 h; K_2CO_3 (3 equiv.), HC≡CCH_2Br (2 equiv.), 25 °C, 24 h; (b) NaH (3 equiv.), H_2C=$CHCH_2Br$ (2 equiv.), DMF (0.5 M), 0 °C → 25 °C, 3–6 h; (c) CH_2Cl_2 (0.05 M), **3b** (5 mol%), 25 °C, 12 h; (d) *N*-phenylmaleimide (1.2 equiv.), $C_6H_5CH_3$ (0.16 M), 110–120 °C, 21 h; (e) diethyl acetylenedicarboxylate (1.2 equiv), $C_6H_5CH_3$ (0.16 M), 120–140 °C, 21 h; (f) DMF (1.0 M), 190 °C, 6–8 h; (g) K_2CO_3 (2 equiv.), HC≡CCH_2Br (1.5 equiv.), DMF (0.5 M), 25 °C, 24 h.

was confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on **12aa** (Fig. 2).[7] For the pharmaceutical applications, a diversity-oriented library of tetra-cyclic compounds **12** could be generated by using our three-step sequence reactions.

With the success of a sequential three-step synthesis of highly functionalized heterocycles **12–14** based on the benzo[*b*]-[1,4]oxazocines **7** platform, we continued our investigation into the generation of highly functionalized heterocycles **18oa** and **19oa** based on 3-vinyl-2,5-dihydro-benzo[*b*]oxepines **17oa** through a combination of cascade EA/IA/A, Claisen rearrangement, *O*-propargylation, enyne RCM followed by DA reaction. The results in Scheme 3 demonstrate the broad scope of this novel methodology covering a structurally diverse group of Hagemann's esters **1** and nitrosobenzene **2a**.

Claisen rearrangement of **5oa** in DMF at 190 °C for 6–8 h furnished the expected phenol **15oa** in 50% yield, which on *O*-propargylation with propargyl bromide and K_2CO_3 furnished the enyne amine **16oa** in 80% yield. Direct treatment of enyne amine **16oa** with Grubbs' 1st generation catalyst **3b** generated the expected highly functionalized 3-vinyl-2,5-dihydro-benzo[*b*]oxepine **17oa** in good conversion as shown in Scheme 3, which on *in situ* treatment with 1-phenyl-pyrrole-2,5-dione in toluene at 110–120 °C for 21 h furnished the highly functionalized tetra-cyclic *endo*-product **18oa** with 64% de in a stereoselective manner with 22% overall yield.

In summary, we have developed three-step sequential multi-catalysis chemistry for the synthesis of highly substituted drug-like heterocycles **7**, **8**, **12**, **13**, **14**, **18** and **19** from simple starting materials *via* EA/IA/A, EA/IA/P, *C*,*N*,*O*-allylations, Claisen

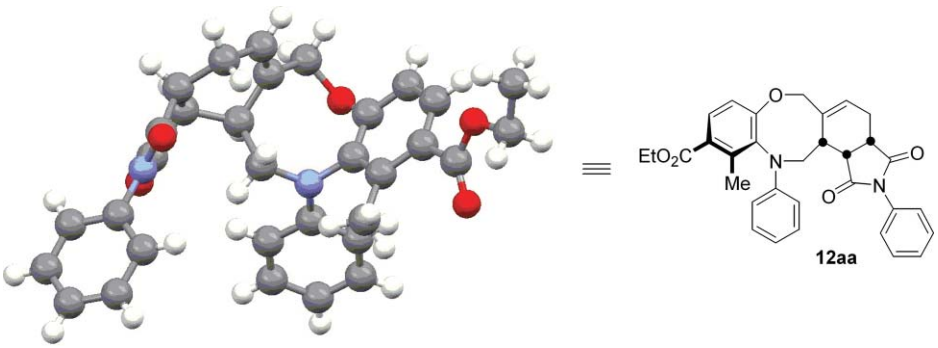


Fig. 2 X-Ray crystal structure of **12aa**.

rearrangement, diene RCM, enyne RCM and Diels–Alder reactions. The multi-catalysis strategy proceeds in good yields with high selectivity using piperidine/K_2CO_3/NaH/ruthenium-complex as the catalysts. Further work is in progress to utilize novel multi-catalysis reactions in synthetic chemistry.

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Notes and references

1 (*a*) H. J. Knolker and K. R. Reddy, *Chem. Rev.*, 2002, **102**, 4303–4427; (*b*) N. L. Snyder, H. M. Haines and M. W. Peczuh, *Tetrahedron*, 2006, **62**, 9301–9320; (*c*) J. B. Bremner, *Progress in Heterocyclic Chemistry*, 2004, **16**, 431–450; (*d*) J. B. Bremner, *Progress in Heterocyclic Chemistry*, 2003, **15**, 385–430; (*e*) J. O. Hoberg, *Tetrahedron*, 1998, **54**, 12631–12670; (*f*) S. Kato, I. Fujiwara and N. Yoshida, *Medicinal Research Reviews*, 1999, **19**, 25–73; (*g*) A. D. Baxter, PCT Int. Appl. 2006, 18pp. CODEN: PIXXD2 WO 2006095187 A1 20060914, CAN 145:336084; (*h*) A. D. Baxter, A. Walmsley and E. Lasterra, U.S. Pat. Appl. Publ. 2006, 56 pp. CODEN: USXXCO US 2006019940 A1 20060126, CAN 144:150402; (*i*) S. Seto, A. Tanioka, M. Ikeda and S. Izawa, *Bioorg. Med. Chem.*, 2005, **13**, 5717–5732; (*j*) S. Seto, A. Tanioka, M. Ikeda and S. Izawa, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1479–1484; (*k*) S. Seto, A. Tanioka, M. Ikeda and S. Izawa, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 1485–1488; (*l*) C. J. Ohnmacht, J. S. Albert, P. R. Bernstein, W. L. Rumsey, B. B. Masek, B. T. Dembofsky, G. M. Koether, D. W. Andisik and D. Aharony, *Bioorg. Med. Chem.*, 2004, **12**, 2653–2669; (*m*) P. Bernstein, PCT Int. Appl. 2002, 33 pp. CODEN: PIXXD2 WO 2002026724 A1 20020404, CAN 136:294860; (*n*) M. R. Stillings, S. Freeman, P. L. Myers, M. J. Readhead, A. P. Welbourn, M. J. Rance and D. C. Atkinson, *J. Med. Chem.*, 1985, **28**, 225–33; (*o*) S. Tanaka and K. Hashimoto, *Ger. Offen.*, 1971, 21 ppCODEN: GWXXBX DE 2044508 19710519, CAN 75:36173.

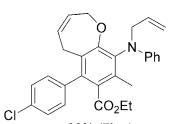
2 For review articles, see: (*a*) S. K. Chattopadhyay, S. Karmakar, T. Biswas, K. C. Majumdar, H. Rahman and B. Roy, *Tetrahedron*, 2007, **63**, 3919–3952; (*b*) A. Michaut and J. Rodriguez, *Angew. Chem. Int. Ed.*, 2006, **45**, 5740–5750; (*c*) A. Gradillas and J. Perez-Castells, *Angew. Chem. Int. Ed.*, 2006, **45**, 6086–6101; (*d*) A. Deiters and S. F. Martin, *Chem. Rev.*, 2004, **104**, 2199–2238; (*e*) M. D. McReynolds, J. M. Dougherty and P. R. Hanson, *Chem. Rev.*, 2004, **104**, 2239–2258; (*f*) A. Furstner, *Angew. Chem. Int. Ed.*, 2000, **39**, 3012–3043; (*g*) T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18–29.

3 For multi-catalysis reactions, see: (*a*) D. B. Ramachary, M. Kishor and K. Ramakumar, *Tetrahedron Lett.*, 2006, **47**, 651–656; (*b*) D. B. Ramachary, M. Kishor and G. Babul Reddy, *Org. Biomol. Chem.*, 2006, **4**, 1641–1646; (*c*) D. B. Ramachary and G. Babul Reddy, *Org. Biomol. Chem.*, 2006, **4**, 4463–4468; (*d*) D. B. Ramachary and M. Kishor, *J. Org. Chem.*, 2007, **72**, 5056–5068; (*e*) D. B. Ramachary, G. Babul Reddy and M. Rumpa, *Tetrahedron Lett.*, 2007, **48**, 7618–7623; (*f*) D. B. Ramachary, K. Ramakumar and V. V. Narayana, *J. Org. Chem.*, 2007, **72**, 1458–1463; (*g*) D. B. Ramachary, M. Kishor and Y. V. Reddy, *Eur. J. Org. Chem.*, 2008, 975–998; (*h*) D. B. Ramachary, Y. V. Reddy and B. V. Prakash, *Org. Biomol. Chem.*, 2008, **6**, 719–726; (*i*) D. B. Ramachary and R. Sakthidevi, *Org. Biomol. Chem.*, 2008, **6**, 2488–2492; (*j*) D. B. Ramachary and M. Kishor, *Org. Biomol. Chem.*, 2008, **6**, 4176–4187; (*k*) D. B. Ramachary, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.*, 2008, **6**, 4188–4197; (*l*) D. B. Ramachary, V. V. Narayana and K. Ramakumar, *Eur. J. Org. Chem.*, 2008, 3907–3911; (*m*) D. B. Ramachary, K. Ramakumar and V. V. Narayana, *Chem. Eur. J.*, 2008, **14**, 9143–9147; (*n*) D. B. Ramachary and R. Sakthidevi, *Chem. Eur. J.*, 2009, **15**, 4516–4522; (*o*) D. B. Ramachary, C. Venkaiah, Y. V. Reddy and M. Kishor, *Org. Biomol. Chem.*, 2009, **7**, 2053–2062; For recent papers on organocatalytic cascade and multi-component reactions from other research groups, see: (*p*) T. Bui and C. F. Barbas III, *Tetrahedron Lett.*, 2000, **41**, 6951–6954; (*q*) S. -I. Watanabe, A. Cordova, F. Tanaka and C. F. Barbas III, *Org. Lett.*, 2002, **4**, 4519–4522; (*r*) N. S. Chowdari, D. B. Ramachary and C. F. Barbas III, *Org. Lett.*, 2003, **5**, 1685–1688; (*s*) D. B. Ramachary, N. S. Chowdari and C. F. Barbas III, *Angew. Chem. Int. Ed.*, 2003, **42**, 4233–4237; (*t*) D. B. Ramachary, K. Anebouselvy, N. S. Chowdari and C. F. Barbas III, *J. Org. Chem.*, 2004, **69**, 5838–5849; (*u*) D. B. Ramachary and C. F. Barbas III, *Chem. Eur. J.*, 2004, **10**, 5323–5331; (*v*) D. B. Ramachary and C. F. Barbas III, *Org. Lett.*, 2005, **7**, 1577–1580; (*w*) J. W. Yang, M. T. Hechavarria Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036–15037; (*x*) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051–15053; (*y*) M. Marigo, T. Schulte, J. Franzen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 15710–15711; (*z*) S. Brandau, E. Maerten and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2006, **128**, 14986–14991; (*aa*); D. Enders, M. R. M. Huettl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861–863; (*ab*); D. Enders, M. R. M. Huettl, J. Runsink, G. Raabe and B. Wendt, *Angew. Chem. Int. Ed.*, 2007, **46**, 467–469; (*ac*); G.-L. Zhao, W.-W. Liao and A. Cordova, *Tetrahedron Lett.*, 2006, **47**, 4929–4932; (*ad*); R. Rios, H. Sunden, I. Ibrahem, G.-L. Zhao, L. Eriksson and A. Cordova, *Tetrahedron Lett.*, 2006, **47**, 8547–8551; (*ae*); W. Wang, H. Li, J. Wang and L. Zu, *J. Am. Chem. Soc.*, 2006, **128**, 10354–10355.

4 G. C. Fu, S. B. T. Nguyen and R. H. Grubbs, *J. Am. Chem. Soc.*, 1993, **115**, 9856–9857.

5 (*a*) D. L. Wright, J. P. Schulte and M. A. Page, *Org. Lett.*, 2000, **2**, 1847–1850; (*b*) A. S. Edwards, R. A. J. Wybrow, C. Johnstone, H. Adams and J. P. A. Harrity, *Chem. Commun.*, 2002, 1542–1543; (*c*) S. H. L. Verhelst, B. P. Martinez, M. S. M. Timmer, G. Lodder, G. A. Van Der Marel, H. S. Overkleeft and J. H. van Boom, *J. Org. Chem.*, 2003, **68**, 9598–9603; (*d*) P. Wipf, S. R. Rector and H. Takahashi, *J. Am. Chem. Soc.*, 2002, **124**, 14848–14849; (*e*) C. Boga, C. Fiorelli and D. Savoia, *Synthesis*, 2006, 285–292; (*f*) W. H. Pearson, A. Aponick and A. L. Dietz, *J. Org. Chem.*, 2006, **71**, 3533–3539.

6 Structure of functionalized benzo[b]oxepine **7′pa**:.



60% (**7′pa**)

7 Crystal structure data for **7ha**: $C_{26}H_{25}NO_3$, M_r = 399.47, monoclinic, space group $P2_1/c$, a = 14.2321(13), b = 13.8619(13), c = 11.2976(11) Å,

$\alpha = 90$, $\beta = 105.460(2)$, $\gamma = 90°$, $V = 2148.2(4)$ Å^3, $T = 298(2)$ K, 22021 reflections collected. Crystal structure data for **12aa**: $C_{32}H_{30}N_2O_5$, $M_r = 522.58$, monoclinic, space group $P2_1/n$, $a = 12.9791(7)$, $b = 15.0018(8)$, $c = 13.9935(8)$ Å, $\alpha = 90$, $\beta = 91.827(1)$, $\gamma = 90°$, $V = 2723.3(3)$ Å^3, $T = 298(2)$ K, 19684 reflections collected. CCDC-637091 for **7ha** and CCDC-637092 for **12aa** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or mailto:deposit@ccdc.cam.ac.uk.

8 (*a*) B. M. Trost, M. R. Machacek and B. D. Faulk, *J. Am. Chem. Soc.*, 2006, **128**, 6745–6754; (*b*) S. Ko, B. Kang and S. Chang, *Angew. Chem. Int. Ed.*, 2005, **44**, 455–457.

