



Cite this: *RSC Adv.*, 2015, 5, 96720

Received 9th October 2015  
Accepted 3rd November 2015

DOI: 10.1039/c5ra20930g

www.rsc.org/advances

# Microwave-assisted telescoped cross metathesis-ring closing aza-Michael reaction sequence: step-economical access to nicotine–lobeline hybrid analogues†

E. Drège, J. Oko, P.-E. Venot, N. Gigant and D. Joseph\*

A series of 2,5-disubstituted pyrrolidines was synthesized through an efficient telescoped cross-metathesis/cyclizing aza-Michael addition involving N-heteroaromatic olefinic derivatives. This synthetic route was applied to the preparation of original nicotine–lobeline, nicotine–pelleterine and lobeline–nicotine–epibatidine hybrids.

## Introduction

Nicotinic acetylcholine receptors (nAChRs) belong to the family of pentameric ligand-gated channels. As they play a significant role in cognitive and sensory gating processes, nAChRs comprise potentially therapeutic targets in manifold brain disorders.<sup>1</sup> One of the major challenges in drug discovery targeting nAChRs, is to develop compounds that can selectively bind one receptor subtype. If fragment-based approach to find out selective receptor ligands is nowadays widely established in drug discovery and chemical biology, the application of this concept on nAChRs is delayed due to the lack of readily available structural information and sensitive biophysical screening methods. Only one fundamental example of a fragment merging optimization of ligand has been described for the acetylcholine binding protein, a model protein for the extracellular  $\alpha 7$  nAChR-subtype domain.<sup>2</sup> Therefore, the concept of molecular hybridization continues to be an alternative answer to find out new nAChRs ligands. More potent and selective ligands have been developed by combining the pharmacophores of natural alkaloids that exhibit a pronounced nAChR pharmacological activity such as nicotine (1), epibatidine (2), anatoxine (3) and lobeline (4) (Fig. 1).<sup>3</sup>

A part of our research program aims at shaping new step-economical synthetic processes of new *Lobelia* alkaloids

analogues as ligands of nAChR-subtypes.<sup>4</sup> In the context of targeting  $\alpha 4\beta 2$ -subtype, the synthesis of hybrid molecules appeared to us as an interesting challenge and we decided to investigate the preparation of original lobeline–natural nAChR ligands chimeric analogues 5 by connecting relevant pharmacophores (Fig. 1).

A key advantage of the concept of molecular hybridization is its capacity to create highly chemically diverse molecules with a high degree of congenital resemblance, an essential criterion for relevant structure–activity relationship studies. We thus made an effort at designing a diastereoselective synthetic pathway that could rapidly reach structural and functional diversity. The shortness and the flexibility of this synthetic strategy will be insured by a cross metathesis-ring closing aza-Michael (CM-RCAM) sequence (Scheme 1).

One of the challenges of our approach lies in the cross-metathesis of tethering N-heteroaromatic-containing olefinic substrates 6 with sensitive electron-poor olefinic coupling partners 7. Retrosynthetic analysis suggests that the transformation of the hydroxyl group of 8 into an amine function could easily lead to the formation of the key CM-RCAM precursors 6. It was further expected that the synthesis of the alcohol 8 would be secured by the condensation and 3-butenylmagnesium bromide with 2-substituted-5-carboxaldehydes 10.

We present herein a short and efficient access to nicotine–natural nAChR ligand hybrids for which each synthesis step

Université Paris-Sud, BioCIS, Equipe de Chimie des Substances Naturelles, Université Paris-Saclay 5, rue Jean-Baptiste Clément, F-92296 Châtenay-Malabry, France. E-mail: delphine.joseph@u-psud.fr

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c5ra20930g

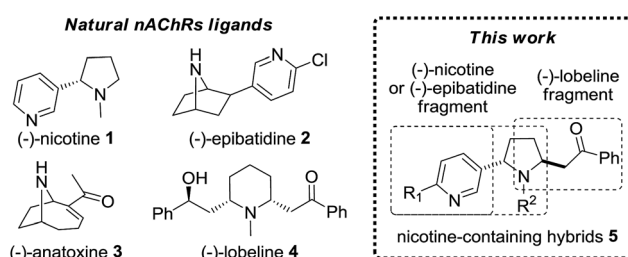
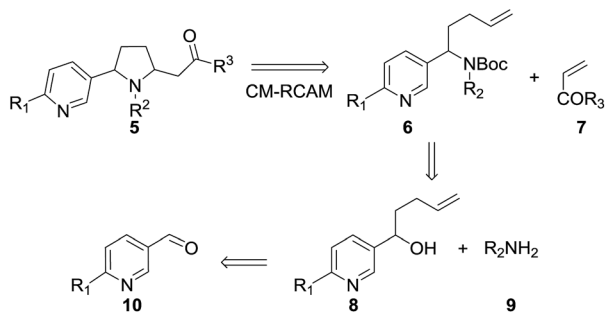


Fig. 1 Naturally occurring nAChR ligands and nicotine–lobeline hybrid analogues 5.



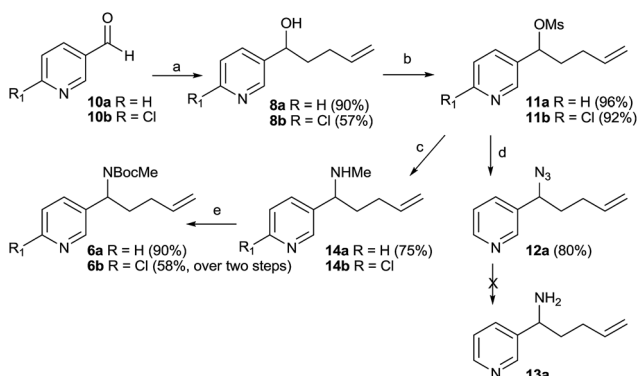


Scheme 1 Retrosynthetic strategy for the preparation of hybrids 5.

offers both diversity and flexibility with three distinct sites of modulation ( $R_1$ ,  $R_2$  and  $R_3$ ) and involves simple and commercially available precursors (7, 9 and 10).

## Results & discussion

Our synthetic efforts are depicted in Scheme 2 and started with the efficient preparation of the pent-4-en-1-ol **8a** and **8b**. The olefinic Grignard reagent was easily prepared starting from 4-bromo-1-butene in the presence of magnesium before reacting with the commercially available pyridine-3-carboxaldehyde **10a** or 6-chloropyridine-3-carboxaldehyde **10b**.<sup>5</sup> The hydroxyl function of the pyridinic pentenols **8** was then efficiently transformed in a leaving group by mesylation under standard conditions. The mesylates **11a** and **11b** were isolated without further purification in 96% and 92% yields, respectively. Our initial attempts to synthesize the required amine moiety were envisaged *via* a two-step sequence including the introduction of an azido group followed by its reduction into primary amine. Treatment of the mesylated derivative **11a** with sodium azide led to the desired azide **12a** in a 80% yield. Unfortunately, the Staudinger reduction of **12a** under usual conditions failed, giving a complex mixture of products. In the same way, other methods for converting an azido group into an amine function using propane-1,3-dithiol,<sup>6</sup> or indium metal and ammonium chloride<sup>7</sup> gave a mixture of inseparable polar products.



Scheme 2 Reagents and conditions for the synthesis of 4-penten-1-amines **6a** and **6b**: (a)  $\text{CH}_2=\text{CHCH}_2\text{CH}_2\text{MgBr}$ , THF,  $-20^\circ\text{C}$  to rt; (b)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ ; (c)  $\text{MeNH}_2$ , DMF,  $\text{H}_2\text{O}$ , or  $\text{MeNH}_2$  (2 M, in THF)  $50^\circ\text{C}$ ; (d)  $\text{NaN}_3$ , DMF; (e)  $\text{Boc}_2\text{O}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ .

As the transformation of the azide function appeared to be quite problematic, an alternative synthetic pathway was investigated. In this way, we evidenced that the mesylate **11a** easily underwent nucleophilic substitution ( $\text{S}_{\text{N}}2$ ) in the presence of aqueous methylamine in DMF at  $60^\circ\text{C}$ , affording the pentenamine **14a** in a satisfying 60% yield. The yield was increased to 75% by using a 2 M THF solution of methylamine rendering the purification step simpler as well. These amination conditions were also successfully applied to **11b** delivering **14b** in a good 70% yield. Nonetheless, a longer reaction time was necessary to reach full conversion: four days were needed for **14b** instead of twelve hours in the case of **14a** suggesting a deactivating effect of the chlorine atom on the nucleophilic substitution. Interestingly, it must be pointed out that these *N*-methyl-pent-4-en-1-amines **14** did not require any further purification, before being engaged in the following step, highlighting the synthetic process cleanliness. At this stage of our synthesis, the protection of the methylamine group of **14** by an electron-withdrawing group was envisaged to avoid potential deactivating coordination between the amine function by the ruthenium-based catalyst during the olefin cross-metathesis (CM). *N*-Methylamines **14** were thus treated with  $\text{Boc}_2\text{O}$  providing the advanced key intermediates **6a** and **6b** in high yields (90% and 75%, respectively).

Only few examples of tandem CM/aza-Michael process have already been reported in the literature.<sup>4c,8</sup> The bibliography becomes particularly poor for substrates bearing a strong Lewis base such as a free amine or a pyridine that may dramatically deactivate the catalyst.<sup>9</sup> To the best of our knowledge, the reactivity of these potentially metal-coordinating substrates has never been described in the presence of electronically biased olefins, such as  $\alpha,\beta$ -unsaturated ketones. Following our recent results in this field,<sup>4c</sup> we decided to screen the efficiency of five commercially available Ru complexes (Fig. 2). These pre-catalysts were selected based on their catalytic features: three standard metathesis complexes such as the Grubbs 2nd generation **I** (G-II),<sup>10a</sup> the Grubbs-Hoveyda 2nd generation **II** (GH-II)<sup>10b</sup> and the indenylidene-based complex **III** ( $\text{M}_2$ ),<sup>10c</sup> and two well-defined fast-initiation Hoveyda-type complexes bearing either a  $\text{SiMe}_3$  (**IV**) or a  $\text{SiPr}$  (**V**) NHC unit.<sup>11</sup>

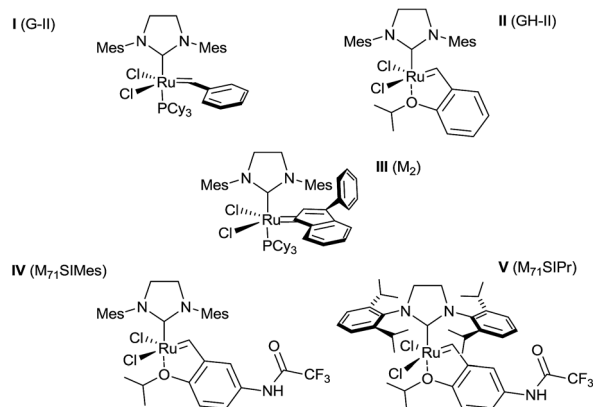


Fig. 2 Screened ruthenium-based metathesis complexes.



We first evaluated the feasibility of this reaction by submitting the pyridinic olefinic derivatives **14** and **6** with methyl acrylate **7a** or ethyl acrylate **7b**. As earlier described by the group of Cossy on pyridinic homoallylic alcohols,<sup>9a</sup> the CM involving the pyridinic olefinic amine **14a** in the presence of the Grubbs catalysts **I** or **II** (10 mol%) in refluxing dichloromethane for 24 h only permitted the recovery of the starting material. These results were in coherence with the known poisonous character of both the amine and the pyridine substituents which deactivate the ruthenium catalyst by coordinating the metal centre.<sup>9b</sup> The study was thus pursued using the pyridines **6a** and **6b** and our results are summarized in Table 1. In this way, starting from the *N*-Boc protected derivative **6a**, the desired cross-coupled product **15aa** was formed in an encouraging 55% yield in the presence of the 2nd generation Grubbs catalyst **I** under the same aforementioned reaction conditions (Table 1, entry 1). The use of GH-II catalyst (**II**) provided the CM product **15aa** in an enhanced 60% yield even with a lower 5 mol% catalyst loading (Table 1, entries 2 and 3). Moreover, the reaction time was dramatically reduced from 24 h to 45 min or 60 min when microwave heating was employed (Table 1, entries 1–3). Interestingly, yields were improved up to 70% by using more hindered catalysts such as **IV** or **V** with ethyl acrylate **7b** as olefinic partner (Table 1, entries 4–6).

Encouraged by these successful results with alkyl acrylates, we next examined the less studied cross-metathesis coupling with several vinyl ketones. Starting from methyl vinyl ketone **7c**, the desired enone **15ac** was isolated in a good 70% yield by combining the GH-II catalyst **II** with microwave irradiation (Table 1, entry 7).

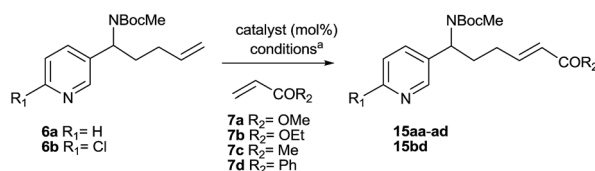
Phenyl vinyl ketone<sup>12</sup> **7d** was next submitted to cross-metathesis with the terminal alkene **6a** (Table 1, entries 8–11). The reaction was particularly reluctant under conventional

heating conditions and did not work whatever the catalyst used. Contrastingly, the coupling product **15ad** was easily obtained in a modest 50% yield, in only 3 hours combining microwave irradiation with GH-II catalyst **II** (Table 1, entry 8). Remarkably, following fully optimized conditions (*i.e.* 7.5 mol% of the pre-catalyst **IV**, 1 h of microwave irradiation), the expected product **15ad** was produced in a 70% yield (Table 1, entry 10). This protocol was finally extended to the more reactive chloropyridine scaffold **6b**, and very satisfyingly, the highly functionalized Michael acceptor **15bd** was isolated with a complete *E* selectivity in a 90% yield (Table 1, entry 11). This result was in accordance with the demonstrated favourable effect of a chlorine electron-withdrawing C-2 substituent that reduces the Lewis basicity of the pyridinic nitrogen atom.<sup>9a</sup>

With the precursors **15** in hands, we focused on the cyclising aza-Michael step. Even though amino-enone **15ab** underwent Boc-deprotection in the presence of a catalytic amount of HCl in *i*-PrOH at 60 °C, the RCAM did not occur. Pleasingly, microwave heating (100 °C, 200 W) efficiently reached the whole cascade in only 45 min, yielding the targeted pyrrolidines **5ab** and **5ac** in 50% to 65% yields (Scheme 3, eqn (1)). In addition, the best conditions for the tandem deprotection-cyclization sequence applied to **15ad** were reached under ultrasound exposure for 3 hours and to **15bd** by using conventional heating at 80 °C for 2 hours.

In our continuing interest for developing economically favorable synthetic procedure, we surmised that the sequential CM/RCAM process could be telescoped. Indeed, Fustero and co-workers reported diastereoselective domino cross-metathesis/aza-Michael reaction catalyzed by ruthenium complexes with Lewis acid as co-catalyst for the synthesis of piperidine, pyrrolidine and lactam derivatives.<sup>8c,e,f</sup> Directly applied to our pyridinic olefins, the cascade process using either Ti(OiPr)<sub>4</sub> or

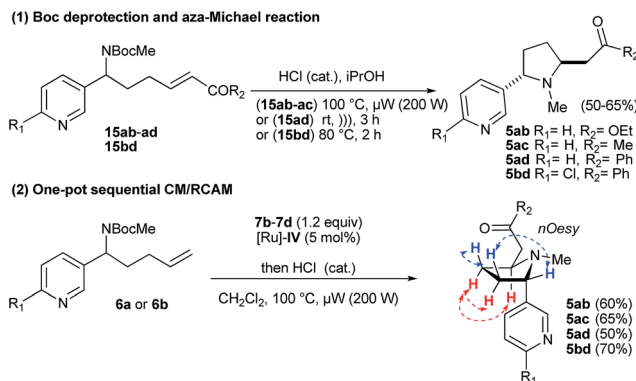
Table 1 Optimization of the cross-metathesis of pyridine derivatives with electron-poor olefinic partners<sup>a</sup>



Entry	R <sub>1</sub>	R <sub>2</sub>	Cat. (mol%)	Product	Thermal yield <sup>b</sup> (%)	μwaves yield <sup>b</sup> (%) (time)
1	H	OMe	<b>I</b> (10)	<b>15aa</b>	55	65 (1 h)
2	H	OMe	<b>II</b> (10)	<b>15aa</b>	60	70 (1 h)
3	H	OMe	<b>II</b> (5)	<b>15aa</b>	60	70 (45 min)
4 <sup>c</sup>	H	OEt	<b>III</b> (10)	<b>15ab</b>	—	30 (3 h)
5 <sup>c</sup>	H	OEt	<b>IV</b> (5)	<b>15ab</b>	—	70 (45 min)
6 <sup>c</sup>	H	OEt	<b>V</b> (5)	<b>15ab</b>	—	70 (45 min)
7	H	Me	<b>II</b> (5)	<b>15ac</b>	50	70 (1 h)
8	H	Ph	<b>II</b> (5)	<b>15ad</b>	SM <sup>d</sup>	50 (3 h)
9 <sup>c</sup>	H	Ph	<b>III</b> (5)	<b>15ad</b>	—	10 (3 h)
10	H	Ph	<b>IV</b> (7.5)	<b>15ad</b>	SM <sup>d</sup>	70 (1 h)
11 <sup>c</sup>	Cl	Ph	<b>IV</b> (5)	<b>15bd</b>	—	90 (1 h)

<sup>a</sup> Conditions: 1 equiv. **6a** or **6b**, 1.3 equiv. **7a–7d**, CH<sub>2</sub>Cl<sub>2</sub> (0.5 M), reflux, 24 h or, 100 °C μwaves (200 W). <sup>b</sup> Isolated yield. <sup>c</sup> The reactions were only performed under microwave irradiation. <sup>d</sup> Starting material.





Scheme 3 RCAM reaction and telescoped CM-RCAM reaction.

BF<sub>3</sub>·OEt<sub>2</sub> as Lewis acid co-catalyst failed, providing complete degradation of the starting materials. To our delight, under microwave irradiation, sequential addition of a catalytic amount of concentrated hydrochloric acid after the cross-metathesis completion (controlled by TLC), initiated the *N*-Boc cleavage and activated the subsequent aza-Michael induced ring closure.

Extension of these optimized conditions provided the isolation of the original pyrrolidines **5ab**, **5ac**, **5ad** and **5bd** in 50–70% yields over three steps (Scheme 3, eqn (2)). More in details, a mixture of both diastereomers was obtained. If the 2,5-*cis* diastereoisomer was kinetically favoured, it rapidly equilibrated in solution toward the thermodynamically more stable 2,5-*trans* epimer through a well-known auto-catalyzed retro-aza-Michael/aza-Michael cyclization process.<sup>4d</sup> The relative configuration of the major diastereoisomer was established by nOesy experiments and revealed a *trans* configuration between the both hydrogen atoms of the pyrrolidine C-2 and C-5 atoms (Scheme 3, eqn (2)).

## Conclusions

We shaped a synthetic pathway allowing a short and efficient access to a series of lobeline–nicotine, pelletierine–nicotine and lobeline–nicotine–epibatidine hybrids. More generally, we demonstrated that this approach based on a challenging monotope sequential microwave-mediated cross-metathesis/cyclizing aza-Michael reaction is expandable to the diastereoselective preparation of 2,5-*trans* disubstituted pyrrolidines. This synthetic strategy has the advantages of (i) involving simple starting reagents and available Ru-precatalysts, (ii) producing several purification-free synthetic intermediates and (iii) facilitating the introduction of molecular diversity. Moreover, the developed methodology enabled, under microwave irradiation, the telescoping of the cross-metathesis and the intramolecular aza-Michael reaction into a single efficient process, readily amenable to scale up. New applications of this strategy for the enantioselective synthesis of pyrrolidines as well as the nAChR-subtypes binding affinity and activity of selected nicotine–lobeline hybrid analogues are currently in progress and will be reported in due course.

## Acknowledgements

The authors are indebted to Oméga Cat System Company for the generous gifts of ruthenium catalysts. The authors are grateful to Claire Troufflard and Karine Leblanc for performing respectively NMR experiments and elemental analyses. The authors thank the University Paris-Sud for the grant of P.-E. V. The University Paris-Sud, the LabEx LERMIT, the French Ministry of Higher Education and Research and the CNRS are gratefully acknowledged for their financial support.

## Notes and references

- (a) A. Taly, P. J. Corring, D. Guedin, P. Lestage and J. P. Changeux, *Nat. Rev. Drug Discovery*, 2009, **8**, 733; (b) C. Gotti, F. Clementi, A. Fornari, A. A. Gaimarri, S. Guiducci, I. Manfredi, M. Moretti, P. Pedrazzi, L. Pucci and M. Zoli, *Biochem. Pharmacol.*, 2009, **78**, 703; (c) C. Gotti, L. Riganti, S. Vailati and F. Clementi, *Curr. Pharm. Des.*, 2006, **12**, 407; A. A. Jensen, B. Frolund, T. Liljefors and P. Krogsgaard-Larsen, *J. Med. Chem.*, 2005, **48**, 4705. (d) S. P. Arneric, M. Holladay and M. Williams, *Biochem. Pharmacol.*, 2007, **74**, 1092; (e) M. N. Romanelli, P. Gratteri, L. Guandalini, E. Martini, C. Bonaccini and F. Gualtieri, *ChemMedChem*, 2007, **2**, 746.
- E. Edink, P. Rucktooa, K. Retra, A. Akdemir, T. Nahar, O. Zuiderveld, R. van Elk, E. Janssen, P. van Nierop, J. van Muijlwijk-Koezen, A. B. Smit, T. K. Sixma, R. Leurs and I. J. P. de Esch, *J. Am. Chem. Soc.*, 2011, **133**, 5363.
- (a) A. Sutherland, T. Gallagher, C. G. V. Sharples and S. Wonnacott, *J. Org. Chem.*, 2003, **68**, 2475; (b) E. Wright, T. Gallagher, C. G. V. Sharples and S. Wonnacott, *Bioorg. Med. Chem. Lett.*, 1997, **7**, 2867; (c) N. Houllier, M.-C. Lasne, R. Bureau, P. Lestage and J. Rouden, *Tetrahedron*, 2010, **66**, 9231; (d) W. Hatton, F.-X. Felpin, M. Evain, M. Mathé-Allainmat and J. Lebreton, *Synlett*, 2010, 1631.
- (a) L. Cabral dos Santos, Z. Bahlaouan, K. El Kassimi, C. Troufflard, F. Hendra, S. Delarue-Cochin, M. Zahouily, C. Cavé and D. Joseph, *Heterocycles*, 2007, **73**, 751; (b) Z. Amara, E. Drège, C. Troufflard, P. Retailleau and D. Joseph, *Org. Biomol. Chem.*, 2012, **10**, 7148; (c) H. Boufroua, M. Mauduit, E. Drège and D. Joseph, *J. Org. Chem.*, 2013, **78**, 2346; (d) Z. Amara, G. Bernadat, P.-E. Venot, P. Retailleau, C. Troufflard, E. Drège, F. le Bideau and D. Joseph, *Org. Biomol. Chem.*, 2014, **12**, 9797; (e) E. Drège, P.-E. Venot, F. le Bideau, P. Retailleau and D. Joseph, *J. Org. Chem.*, 2015, **80**, 10119.
- The starting material was prepared on a 10 g scale and used without purification according to a known procedure, see: J. B. Summers, S. K. Davidsen, D. H. Steinman, J. G. Phillips, M. B. Martinand and D. E. Guinn, *US Pat.*, 5149704, 1992.
- (a) M. A. Peterson, B. L. Nilsson, S. Sarker, B. Doboszewski, W. Zhang and M. J. Robins, *J. Org. Chem.*, 1999, **64**, 8183; (b) Y. Pei and B. O. S. Wickham, *Tetrahedron Lett.*, 1993, **34**, 7509.



- 7 G. V. Reddy, G. V. Rao and D. S. Iyengar, *Tetrahedron Lett.*, 1999, **40**, 3937.
- 8 (a) H. Liu, C. Zeng, J. Guo, M. Zhang and S. Yu, *RSC Adv.*, 2013, **3**, 1666; (b) S.-S. P. Chou and J.-L. Huang, *Tetrahedron Lett.*, 2012, **53**, 5552; (c) S. Fustero, C. Báez, M. Sánchez-Roselló, A. Asensio, J. Miro and C. del Pozo, *Synthesis*, 2012, **44**, 1863; (d) Q. Cai, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2010, **49**, 8666; (e) S. Fustero, S. Monteagudo, M. Sánchez-Roselló, S. Flores, P. Barrio and C. del Pozo, *Chem.-Eur. J.*, 2010, **16**, 9835; (f) S. Fustero, D. Jiménez, M. Sánchez-Roselló and C. del Pozo, *J. Am. Chem. Soc.*, 2007, **129**, 6700.
- 9 (a) K. Lafaye, L. Nicolas, A. Guérinot, S. Reymond and J. Cossy, *Org. Lett.*, 2014, **16**, 4972; (b) S. J. P'Pool and H.-J. Schanz, *J. Am. Chem. Soc.*, 2007, **129**, 14200.
- 10 (a) M. Scholl, S. Ding, C. W. Lee and R. H. Grubbs, *Org. Lett.*, 1999, **1**, 953; (b) S. B. Garber, J. S. Kingsbury, B. L. Gray and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2000, **122**, 8168; (c) H. Clavier, C. A. Urbina-Blanco and S. P. Nolan, *Organometallics*, 2009, **28**, 2848.
- 11 (a) H. Clavier, F. Caijo, E. Borre, D. Rix, F. Boeda, S. P. Nolan and M. Mauduit, *Eur. J. Org. Chem.*, 2009, 4254; (b) D. Rix, F. Caijo, I. Laurent, F. Boeda, H. Clavier, S. P. Nolan and M. Mauduit, *J. Org. Chem.*, 2008, **73**, 4225.
- 12 For the preparation of **7d**, see: F. Wu, H. Li, R. Hong and L. Deng, *Angew. Chem., Int. Ed.*, 2006, **45**, 947.

