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Tetrahedron Letters 44 (2003) 7913–7919

TETRAHEDRON LETTERS

Effects of allylic and homoallylic substituents on the ring closing metathesis reaction used to synthesise simplified eleuthesides

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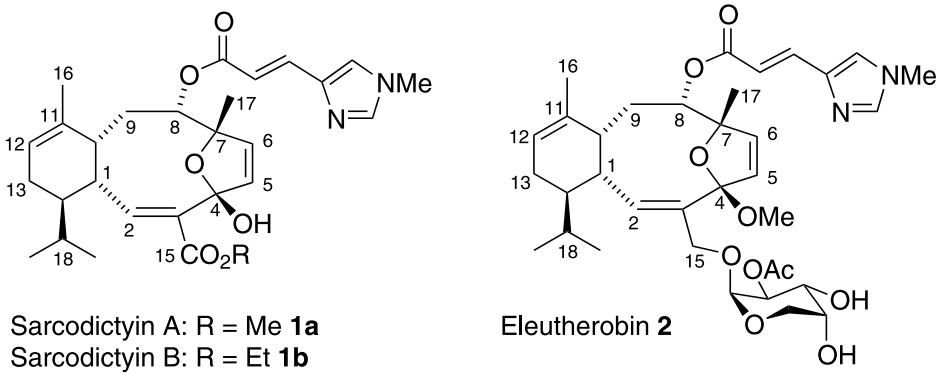
Received 10 July 2003; revised 24 August 2003; accepted 3 September 2003

Abstract—During the course of our synthetic studies towards simplified eleuthesides, we have found that *p*-methoxyphenyl (PMP) protected allylic alcohols are compatible with the RCM reaction and can give better yields than the corresponding free allylic alcohols.

Sarcodictyins A and B **1** and eleutherobin **2** (the 'eleutheside' family of microtubule-stabilising agents, Scheme 1) have been found to possess potent activities against paclitaxel-resistant tumour cell lines.[1–3] We have recently shown that simplified analogues of the natural products (lacking inter alia the C4/C7 ether bridge) retain potent microtubule-stabilising activity whilst being more easily accessible by total synthesis.[4]

The synthesis of these simplified analogues was achieved starting from commercially available (*R*)-carvone. Using standard chemistry already reported,[3a,g] the first key aldehyde intermediate **3** was generated on multigram scale. The diene cyclisation precursors were then synthesised using either Brown's isopinocampheylborane-mediated asymmetric allylation reactions[5] or, more recently, Hafner–Duthaler enantioselective allylti-



Scheme 1. Structures of sarcodictyins A, B and eleutherobin.

Keywords: ring closing metathesis; protective groups; *p*-methoxyphenyl (PMP); antitumour compounds.
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doi:10.1016/j.tetlet.2003.09.010

tanation chemistry.[6] The key-step of the syntheses is the formation of the 6–10 fused bicyclic ring-system using ring closing metathesis (RCM)[7] (Schemes 2 and 3).

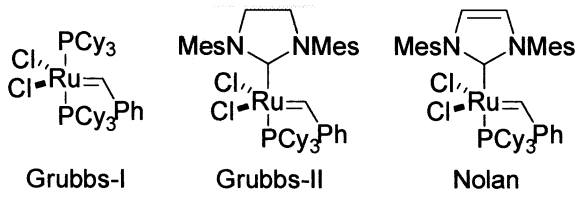
RCM has been used to great effect in the formation of many medium ring systems. The influence of concentration, temperature and catalyst structure has been the subject of much investigation, however the effects of the allylic and homoallylic substitution is still not completely understood.

The most simplified analogue, with only substitution at C3 and C8 (using the eleutheside numbering), could be obtained from the diene precursor **4** using the robust second generation 'Grubbs-II' RCM catalyst[9] in an excellent 88% isolated yield, solely as the *Z* stereoisomer (Scheme 4).[4,10] This stereochemical course, which was found to be common to all the substrates reported in the present letter (vide infra), is likely to reflect thermodynamic control.[11] No reaction was observed with the first generation 'Grubbs-I' catalyst.

Attempts to generate 'trisubstituted' analogues were made using the dienes **5** and **6** (Scheme 4). These RCM precursors were prepared from successive asymmetric allylation and methoxyallylation reactions using Brown's methodology. Treatment with the Grubbs-II or Nolan catalysts,[9] however, gave only decomposition in the case of **5** and possible dimerisation with **6**. Changing catalyst loading and reaction times still gave no observable product. Similarly, attempted RCM reaction of the tetrasubstituted diene **7**, obtained from two successive Brown methoxyallylations, also gave none of the desired cyclised tetrasubstituted framework (Scheme 4).

A similar lack of reactivity in the RCM reaction was observed with the tetrasubstituted dienes **8** possessing two MOM protected allylic alcohols (Scheme 5). Deprotection of the allylic O-MOM groups to reveal free allylic alcohols (**9**) did not aid reactivity in the RCM reaction. Using a silyl bridge (**10**) to add a conformational constraint also failed to improve reactivity.

The allylic alcohols **11** and **12** were prepared in a similar fashion (Brown's allylation and MOM-oxyallylation followed by O-MOM deprotection) and subjected to the RCM reaction.[4] The precursors were smoothly

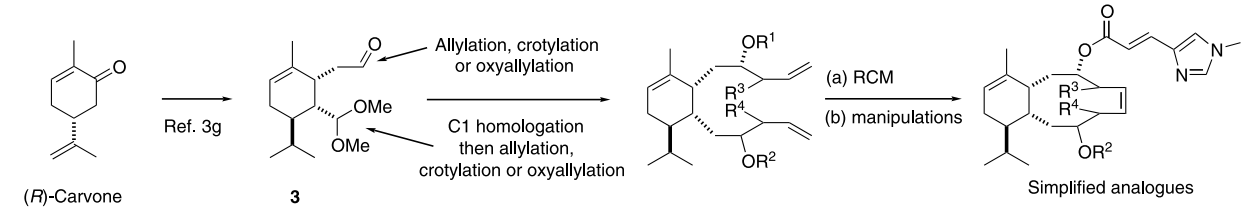


Scheme 3. RCM catalyst structures and terms used.[8]

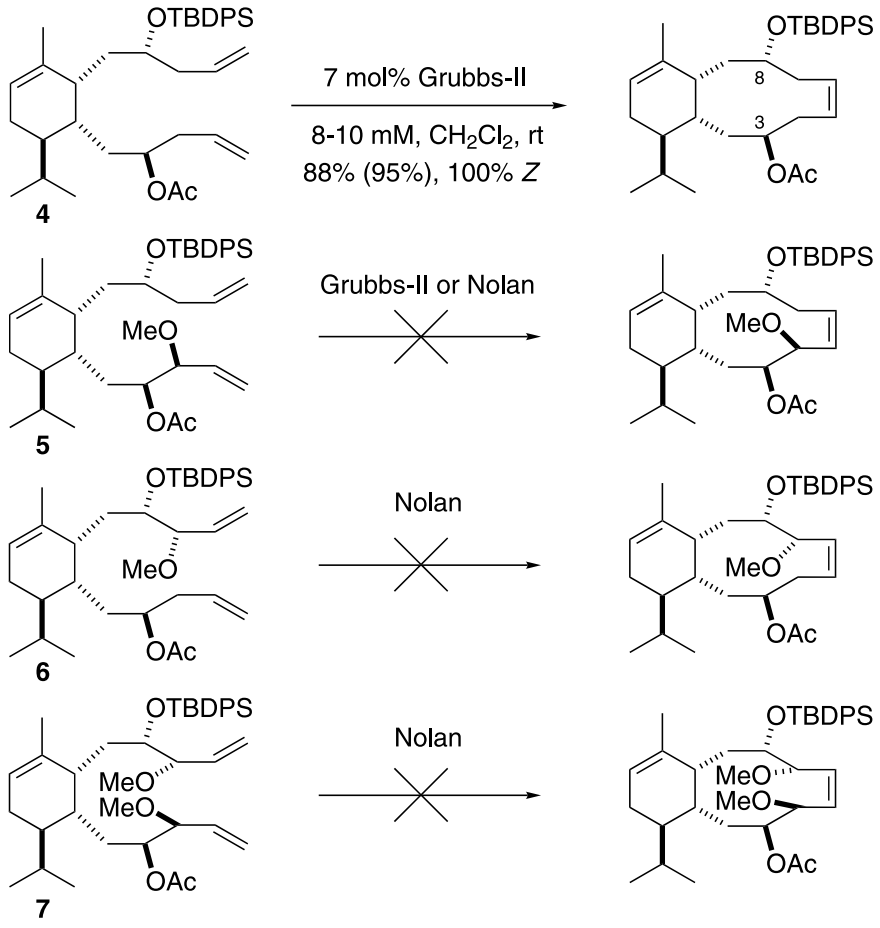
cyclised, compared to the allylic methyl ether **5**, to afford the corresponding 'south trisubstituted' 6–10 fused bicyclic framework in good yields (Scheme 6).[4] These results are in accordance with the observations of Hoye and others: allylic ethers were found to retard the RCM reaction while a rate acceleration was associated with allylic alcohols.[12,13] The lack of reactivity of the allylic diol **9** could be attributed to the dense functionality at the reaction site.

Following the above rationale, diene **13a** was chosen as the cyclisation precursor since a free allylic alcohol, together with pivaloyl- and TBDPS-protected homoallylic alcohols, were shown to be compatible with the RCM reaction (for comparison see Scheme 6 and the failed cyclisation of the allylic methyl ether **6** in Scheme 4). Formation of the diene **13a** was accomplished using Brown's chemistry, which established the *syn* relationship at C7–C8. Submission of the allylic alcohol **13a** to the RCM reaction conditions, however, failed to afford any of the cyclised material. Protection of the C8 alcohol as the acetate (**13b**) or oxidation to the ketone (**13c**) did not aid cyclisation. Attempts to cyclise the acetonide diene **14** also failed.[14] Interconversion of the C3 and C8 protective groups of the diene **13a** gave the allylic alcohol **15** which did undergo cyclisation, albeit in a disappointing 24% yield (Scheme 7).

The rationale for this interconversion was that although the substitution pattern in compound **13a** is the same as that shown by the successful cyclisation precursors **11** and **12** (allylic alcohol, homoallylic OPiv and OTBDPS, Scheme 6), it is not the same with respect to the relationship *between* the groups [OH adjacent to OTBDPS (**13a**) versus OH adjacent to OPiv (**11** and **12**)]. Again this observation demonstrates the importance of fine tuning the allylic and homoallylic alcohol protective groups for a successful RCM reaction.



Scheme 2. General synthetic strategy to the simplified eleutheside analogues.



Scheme 4. Attempted RCM reactions with various allylic and homoallylic substituents.[8]

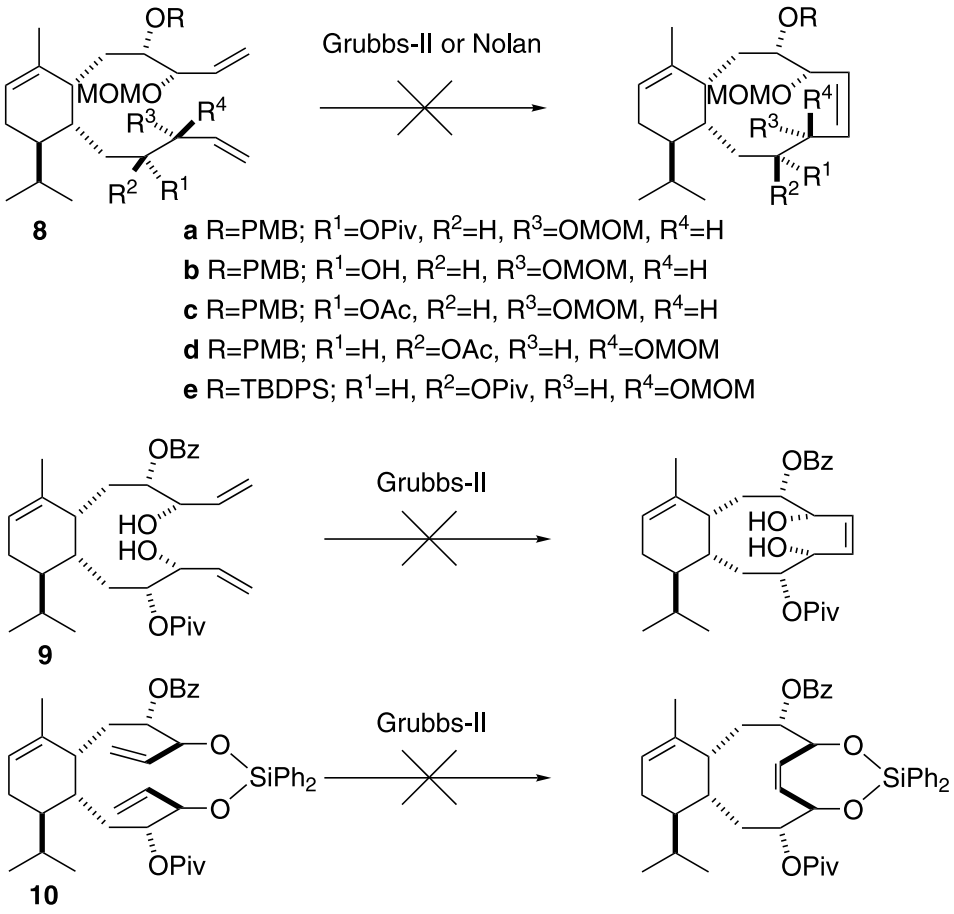
The formation of the 'north trisubstituted' diene **16** with C7–C8 *anti* stereochemistry was accomplished using a stereoselective oxyallyltitanation reaction.[6] Using PMPOallyl as the reagent, the product obtained was the PMP protected allylic alcohol (PMP = *p*-methoxyphenyl). Using Brown's allylation chemistry,[5] the second olefin fragment was stereoselectively inserted in the south chain to give diene **18**. Protective group manipulations transformed diene **18** into the desired cyclisation precursor **16** which had the same substitution pattern as shown in diene **15**. Reaction with Grubbs-II catalyst gave a mixture of compounds, from which the desired product could be isolated in a similarly poor yield (21%, Scheme 8). No significant difference was observed in the reactivity of the two diastereomers (**15** and **16**) in the RCM reaction.[15]

It was noted, however, that if the RCM reaction was performed with the precursor PMP-protected allylic alcohol (**17**), higher yields could be obtained under similar reaction conditions. This is, for the first time, a result in disagreement with the 'free allylic alcohol' effect.[12,13] Given the success of the diene **17** in the reaction, attempts were made to cyclise the precursor **18**. Reaction of the diene **18** with a free homoallylic alcohol and a PMP-protected allylic alcohol with the Grubbs-II catalyst gave the desired 6–10 fused bicycle in 80% yield (Scheme 8).

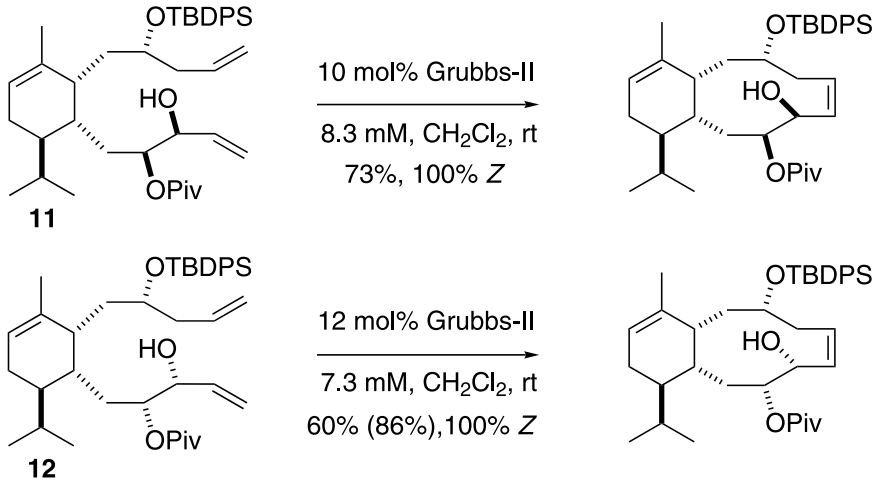
At present, the reasons why the allylic OPMP group facilitates the RCM reaction are not completely understood. Sterically, the PMP can be considered relatively small, even smaller than a Me group (effective Van der Waals radius of Ph = 1.62 Å compared to Me = 1.80 Å).[16]

The C8 methyl substituted dienes **19** and **20** with C7-C8 *anti* stereochemistry were prepared by stereoselective crotyltitanation.[6] Treatment with the Grubbs-II catalyst in toluene at 80°C gave the desired cyclised products in good yields. These results demonstrate that the RCM reaction is compatible with both the allylic methyl and homoallylic MOM-protected alcohol functionalities. Again the stereochemistry at C3 appears not to have a dramatic effect on the reaction, as similar yields were achieved (Scheme 9).

In conclusion, our observations demonstrate the importance of fine tuning the allylic and homoallylic alcohol

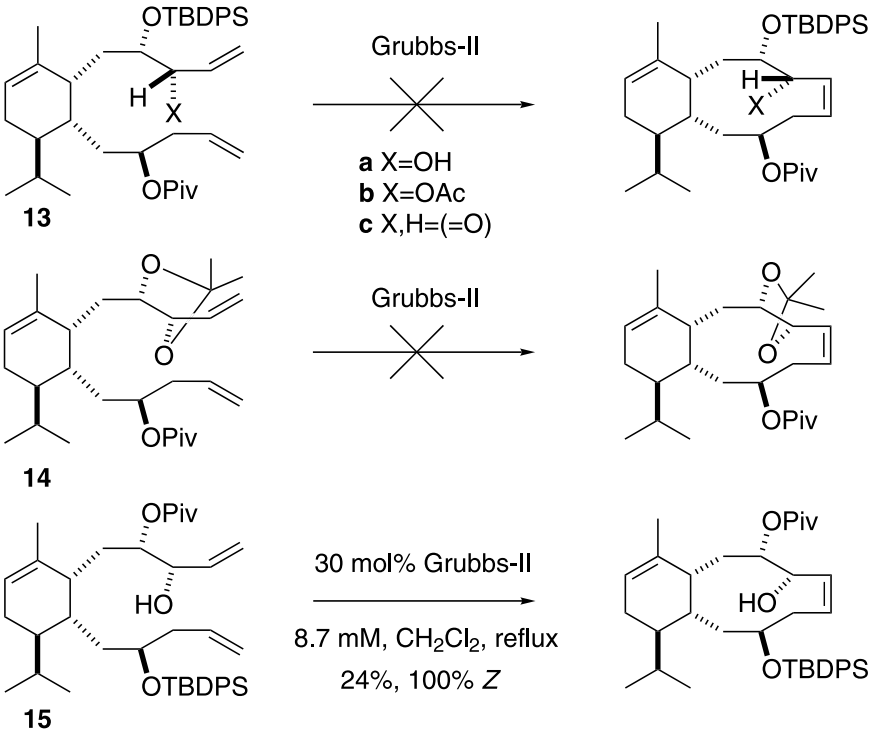


Scheme 5. Changes of allylic and homoallylic stereochemistry and protective groups.[8]

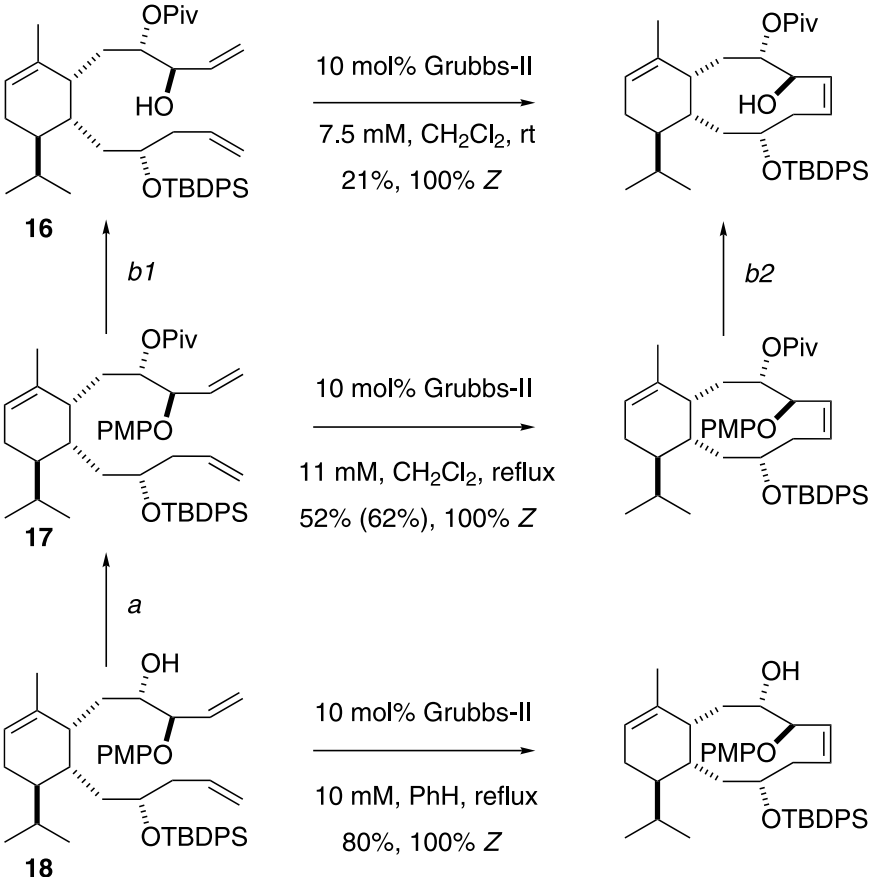


Scheme 6. RCM reactions with a free allylic alcohol.[8]

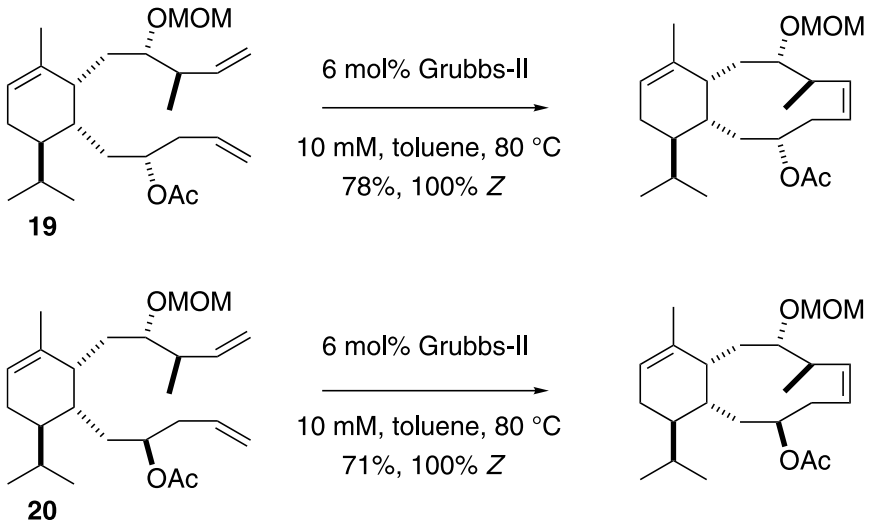
protective groups for a successful RCM reaction. For the first time a substrate possessing a PMP-protected allylic alcohol, the product of a stereoselective oxyallylation, was successfully cyclised. It is believed, on the evidence given above, that the allylic OPMP group is not only compatible in the RCM reaction, but may also aid cyclisation, giving better yields than the corresponding free allylic alcohol. As for the synthetic utility, the PMP group could be cleaved after cyclisation in good yield.



Scheme 7. Interplay of protective groups.[8]



Scheme 8. Successful RCM reactions with a PMP protected allylic alcohol. *Reagents and conditions:* (a) PivCl, DMAP, CH_2Cl_2, rt, 66%; (b) CAN, MeCN/H_2O 1:1, 0°C, (1) 55%, (2) 80%.[8]



Scheme 9. Allylic methyl substitution.[8]

Acknowledgements

We thank the European Commission for financial support (IHP Network grant 'Design and synthesis of microtubule stabilizing anticancer agents' HPRN-CT-2000-00018) and for postdoctoral fellowships to L. Caggiano and R. Beumer (HPRN-CT-2000-00018), P. Bayón ('Marie Curie' HPMF-CT-2000-00838) and J. Telser ('Marie Curie' HPMF-CT-1999-00001). We also like to thank Merck (Merck's Academic Development Program Award to C. Gennari, 2001-02), M.U.R.S.T. COFIN 2000 (MM03155477) for financial support, and the University of Milano for a graduate fellowship (to D. Castoldi). We wish to thank Dr Andrew Bell, Dr Simona Ceccarelli and Piergiuliano Bugada for preliminary experiments related to some entries.

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8. % Yields reported in brackets are calculated considering the recovered starting material. Cy = cyclohexyl; Mes = mesityl; TBDPS = *tert*-butyldiphenylsilyl; PMB = *p*-methoxybenzyl; Piv = *t*-BuCO; Bz = PhCO; MOM = methoxymethyl; DMAP = 4-dimethylaminopyridine; CAN = cerium(IV) ammonium nitrate; PMP = *p*-methoxyphenyl; rt = room temperature.
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