COMMUNICATION

The rare *cis*-configured trisubstituted lactam products obtained by the Castagnoli–Cushman reaction in *N,N*-dimethylformamide†

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Unlike its *trans* counterpart, the *cis*-configured scaffold derived from the Castagnoli–Cushman reaction (CCR) is scarce and has not been explored in bioactive compound design. We found that conducting this reaction in DMF (in contrast to conventional toluene or xylene) led to a significantly higher proportion of *cis*-configured lactams in the diastereomeric product mixture. This allowed us, for the first time, to obtain and thoroughly characterize both stereoisomers of a significant number of lead-like CCR lactams. Simple rules for ^{1}H NMR-based stereochemical assignment have been devised and correlated with the single-crystal X-ray structures obtained for pure *cis*- and *trans*-configured lactams.

Discovered in 1969,[1] the Castagnoli–Cushman reaction (CCR) of imines **1** (formed *in situ* or in a separate step), succinic (**2**) or glutaric (**3**) anhydrides provides convenient access to the medicinally important[2] polysubstituted lactams **4**–**5** in a convenient, three-component format (Scheme 1).

   CCR has recently emerged[3] as an important synthetic tool for lead-oriented synthesis (LOS).[4] Considering the challenges of inventing new LOS methods[5] and our recent interest in

developing lead-like compound libraries,[6] particularly those employing the CCR,[7] we thought it important to try and overcome certain limitations of the CCR, which were evident from the literature. Besides limitations of scope which we discuss elsewhere,[8] several drawbacks associated with CCR are noteworthy. Firstly, in a vast majority of cases reported in the literature, the reaction involving simple anhydride inputs (such as **2**–**3**) is conducted in low polarity aromatic hydrocarbon solvent (toluene or xylene) and requires rather forcing conditions (reflux). These two aspects introduce solubility and structural tolerability limitations, respectively.[3] Secondly, almost universally the reaction was reported as proceeding with high diastereoselectivity (up to 95 : 5[2]) and only the major, *trans*-isomer was isolated and characterized (with the exception of the pioneering reports by Castagnoli[1] the minor, *cis*-isomer was isolated in <1% yield by fractional crystallization). Indirect synthesis of the *cis* counterpart of **4** (compound **6**) *via* desulfurization (with reversal of configuration) of tetrasubstituted lactams **7** (obtainable, in turn, *via* four-component reaction of maleic anhydride) was reported by Shaw (Scheme 2).[9] However, the *cis*-configured stereoisomer of **5** remain virtually unavailable. Multistep sequences leading to the *cis*-isomer of related δ-lactams have been reported by Stille[10] and others.[11] However, these strategies lack the practicality and flexibility offered by the multicomponent approach. From medicinal chemistry prospective, *cis*- and *trans*-versions of either **4** or **5** represent distinct scaffolds[12] that ensure different spatial projection of the molecular periphery and, therefore, are likely to have vastly different complementarities to a protein target. The fact that the *cis*-isomer is always formed in impractical minority severely curbs the stereochemical diversity[13] attainable by the CCR and represents a significant limitation of this chemistry.

   In this work, we sought to find a solution to the above-mentioned limitations by drastically changing the solvent in which the CCR would be conducted. While toluene and xylene indeed appear to be solvents of choice (from the literature review), we ventured to investigate the CCR of more
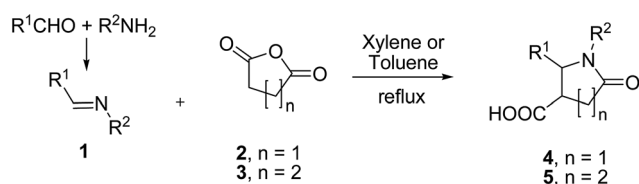
Scheme 1 Castagnoli–Cushman reaction of succinic and glutaric anhydrides.

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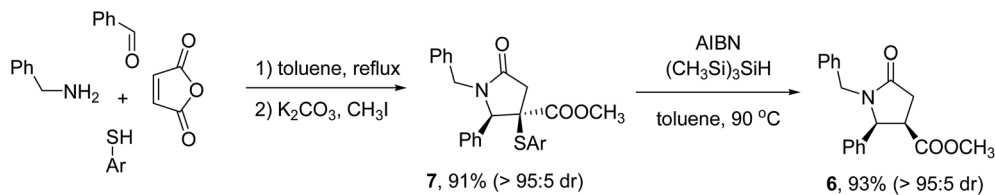
Scheme 2 Preparation of *cis*-configured γ-lactams reported by Shaw.[9]
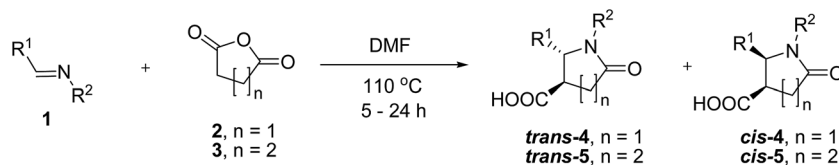
Scheme 3 The new CCR protocol developed in this work.

than two dozen three-component reactions in *N,N*-dimethylformamide (DMF).[14] The choice of high-boiling DMF as a reaction medium *in lieu* of toluene or xylene was dictated by its higher polarity and ability to dissolve a wider range of reactants. In this Communication, we report the results of these studies.

Table 1 γ- and δ-lactams **4** and **5** prepared in this work *via* the CCR in DMF
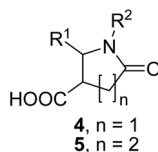
Compound	R^1	R^2	n	Isolated yield (%)	Reaction time	dr (*cis* : *trans*)
4a	4-MeOC$_6$H$_4$	Bn	1	74	5 h	1 : 3.5
4b	4-MeOC$_6$H$_4$	i-Pr	1	75	5 h	1 : 1.8
4c	4-MeOC$_6$H$_4$	*t*-Bu	1	69	5 h	1 : 1.7
4d	4-FC$_6$H$_4$	*n*-Pr	1	46	5 h	1 : 2.5
4e	4-MeC$_6$H$_4$	Et	1	70	5 h	1 : 2
4f	4-BrC$_6$H$_4$	Bn	1	48	24 h	1 : 3
4g	4-O$_2$NC$_6$H$_4$	*n*-Bu	1	28	24 h	1 : 4.5
4h	3-Py	*n*-Pr	1	62	6 h	1 : 2
4i	3-O$_2$NC$_6$H$_4$	Me	1	48	6 h	1 : 1.8
4j	4-Me$_2$NC$_6$H$_4$	Allyl	1	84	6 h	1 : 2
4k	1-Naphthyl	*n*-Pr	1	59	6 h	1 : 2.1
5a	4-MeOC$_6$H$_4$	Bn	2	66	24 h	1 : 2
5b	4-MeOC$_6$H$_4$	i-Pr	2	64	6 h	1 : 1.8
5c	4-MeOC$_6$H$_4$	*t*-Bu	2	59	6 h	1 : 1.4
5d	4-FC$_6$H$_4$	*n*-Pr	2	51	6 h	1 : 2
5e	2-Thienyl	*cyclo*-Pr	2	35	7 days	1 : 2.3
5f	4-MeC$_6$H$_4$	Et	2	53	6 h	1 : 2.2
5g	3,4-(MeO)$_2$C$_6$H$_3$	*n*-Bu	2	62	6 h	1 : 2
5h	4-O$_2$NC$_6$H$_4$	*n*-Bu	2	16	24 h	1 : 2.2
5i	2-MeOC$_6$H$_4$	Bn	2	52	24 h	1 : 1.7
5j	1-Naphthyl	*n*-Pr	2	58	24 h	1 : 3.6
5k	4-AcNHC$_6$H$_4$	*cyclo*-Pr	2	54	48 h	1 : 2.3
5l	3-Py	*n*-Pr	2	61	24 h	1 : 2.5
5m	Ph	Ph	2	39	22 h[a]	1 : 5
5n	4-MeC$_6$H$_4$	4-MeOC$_6$H$_4$	2	47	22 h[a]	1 : 4.2
5o	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	2	53	22 h[a]	1 : 4.1

[a] Reaction temperature was raised to 125 °C in order to ensure maximum conversion.

A brief screening of various temperature regimens for the reactions leading to **4a** and **5a** (R^1 = 4-MeOC$_6$H$_4$, R^2 = Bn) revealed that changing the solvent medium from toluene to DMF offered little advantage in terms of lowering the reaction temperature. However, it was immediately evident that the formation of the *cis*-isomer was significantly more favored in DMF compared to toluene (Table S1 in ESI†). Particularly encouraging were the dr values obtained with glutaric anhydride at 110 °C (*cis* : *trans* = 1 : 2.5), considering the fact that, apart from the initial reports by Castagnoli and Cushman (*vide supra*),[1] *cis*-configured δ-lactams **5** were practically unattainable by the CCR. It should be noted that, occasionally, other solvents (such as DMSO) also favored the formation of the *cis*-configured products (see ESI†). However, this can more reliably achieved with DMF as a solvent of choice.

Encouraged by these results, we extended the new reaction protocol to a range of Schiff bases (pre-formed by reaction of a primary amine with an aldehyde in presence of MgSO$_4$ or molecular sieves) which underwent CCR with succinic (**1**) and glutaric (**2**) anhydrides at 110 °C in DMF over 5–24 h period (Scheme 3).

The reaction times shown were required for the reactions to proceed to completion. The dr values were determined by the relative integration of characteristic signals in the ^{1}H NMR spectrum of the crude reaction mixture. The isolated yields were calculated for the analytically pure mixture of *cis*- and *trans*-**4**(**5**) in which the ratio of diastereomers remained practically unchanged compared to that in the crude reaction mixture (Table 1).

Some general observations can be made based on the results of the substrate survey. The outcome of the reaction seems to be independent of the steric bulk of around the imine nitrogen (R^2), which gives rise to the lactam nitrogen in the reaction product (*cf.* isolated yields of **5c** and **5d**, **4a** and **4c**). However, the reaction appears to be rather sensitive to the substituent effects – with electron-deficient groups drastically reducing the product yields (**4g** and **5h**), which is consistent with the earlier observations by Cushman.[15] Imines derived from anilines (such as those used in preparation of **5m–o**) were expectedly less reactive compared to their counterparts carrying an aliphatic amine portion (which may explain the scarcity of the respective CCR products reported in the literature).[16] For these bis-aryl

Table 2 Comparative summary of the ^{1}H NMR spectral characteristics of *cis*- and *trans*-isomers for compounds **4** and **5**

trans-4, n = 1
trans-5, n = 2
cis-4, n = 1
cis-5, n = 2

Compound	^3J (C^2–H), Hz		δ (C^2–H), ppm (multiplicity)		δ (C^3–H), ppm (multiplicity)		Δ [δ(C^3–H)] cis/trans, ppm
	cis	trans	cis	trans	cis	trans	
4a	9.0	5.8	4.64 (d)	4.50 (d)	3.54 (dt)	3.06 (ddd)	0.48
4b	9.1^a	4.4^a	4.97 (d)	4.79 (d)	3.61 (dt)	2.89 (ddd)	0.72
4c	8.6^a	1.0	5.13 (d)	5.09 (d)	3.53 (dt)	2.62 (ddd)	0.91
4d	9.2^a	5.6^a	5.00 (d)	4.81 (d)	3.66 (dt)	3.02 (ddd)	0.64
4e	9.3^a	5.9	4.99 (d)	4.76 (d)	3.63 (dt)	3.00 (ddd)	0.63
4f	9.3	5.5	4.72 (d)	4.55 (d)	3.66 (dt)	3.07 (ddd)	0.59
4g	9.2	5.4	5.17 (d)	4.99 (d)	3.72 (dt)	3.06 (ddd)	0.66
4h	9.3	5.7	5.06 (d)	4.85 (d)	3.73 (dt)	3.11 (ddd)	0.62
4i	9.3	6.2	5.13 (d)	4.94 (d)	3.71 (dt)	3.11 (ddd)	0.60
4j	9.0	5.7	4.77 (d)	4.62 (d)	3.64 (dt)	3.01 (ddd)	0.63
5a	5.0	5.6	4.71 (d)	4.70 (d)	3.11 (ddd)	2.78 (m)	0.33
5b	4.6^a	2.8	4.93 (d)	4.98 (d)	3.00 (dt)	2.72 (m)	0.29
5c	4.1^a	2.1	5.22 (d)	5.38 (d)	3.01 (dt)	2.79 (dt)	0.30
5d	5.1	4.1	4.95 (d)	4.97 (d)	3.18 (m)	2.82 (dt)	0.36
5e	4.7	3.6	5.17 (d)	5.19 (d)	3.25 (m)	2.95 (m)	0.18
5f	4.5^a	4.2	4.91 (d)	4.90 (d)	3.12 (m)	2.79 (dt)	0.33
5g	4.6	4.1	4.88 (d)	4.89 (d)	3.10 (m)	2.85 (dt)	0.25
5h	5.2	3.7	5.18 (d)	5.15 (d)	3.16 (m)	2.88 (m)	0.27
5i	4.9	4.0	5.10 (d)	5.17 (d)	3.04 (ddd)	2.81 (dt)	0.23
5j	5.4	2.3	5.91 (d)	5.85 (br s)	3.33 (m)	2.98 (dt)	0.35
5k	4.9	4.3	4.84 (d)	4.87 (d)	3.08 (m)	2.78 (dt)	0.30
5l	5.2	4.2	5.20 (d)	5.04 (d)	3.26 (ddd)	2.89 (dt)	0.37
5m	5.0	4.2	5.29 (d)	5.39 (d)	3.49 (ddd)	2.98 (dt)	0.51
5n	4.9^a	4.2	5.17 (d)	5.26 (d)	3.45 (ddd)	2.91 (dt)	0.54
5o	5.1	4.5	5.16 (d)	5.23 (d)	3.44 (ddd)	2.91 (dt)	0.53

^{a} Stereochemical assignment confirmed by single-crystal X-ray analysis.
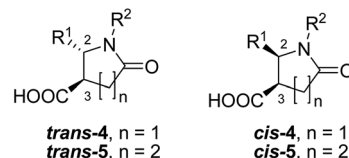
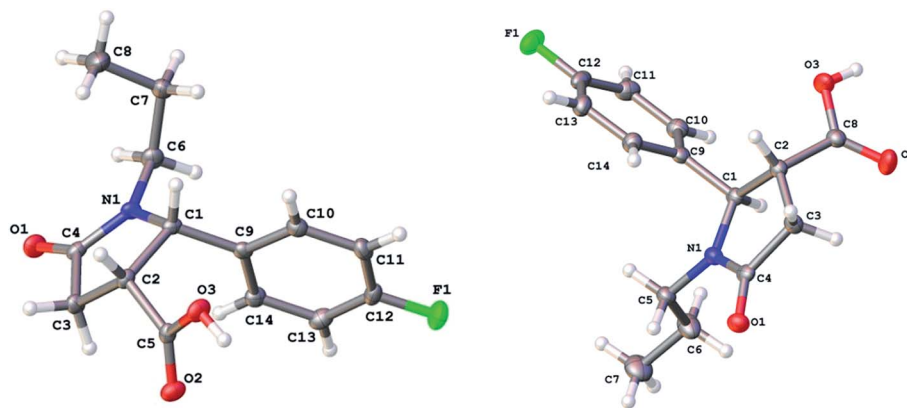**Fig. 1** Single-crystal X-ray structures of *cis*- and *trans*-isomers (left and right, respectively) of compound **4d**.

substrates, the reaction temperature was raised to 125 °C and the reaction time extended to 22–24 h, in order to reach maximum conversion. This, in turn, was associated with lower proportion of the *cis*-configured δ-lactam in the product mixture.

Considering the latter observation, we were curious to see if prolonged reaction times can could cause a 'drift' in the observed dr values, *via* a gradual isomerization of the *cis*-isomer into the thermodynamically more stable *trans*-isomer (a transformation certainly achievable with good yield on treatment with a strong base, such as potassium *tert*-butoxide).[9] To verify that, diastereomeric mixtures of **4a** (*cis/trans* = 1 : 3.5) and **5a** (*cis/trans* = 1 : 2) were heated in DMF at 110 °C for a period of up to 10 days with periodic monitoring of the dr. As the result, the dr of **4a** changed drastically to 1 : 13.8 while **5a** was somewhat more resistant to thermal isomerization: its dr only changed to 1 : 3.9. This, however, clearly indicates that, in order to maximize the formation of the *cis*-isomer, the CCR should be closely monitored and the reactions should be stopped as soon as the maximum conversion is reached (the data reported in Table 1 was obtained in this manner).

Formation of a higher proportion of the *cis*-isomer of lactams **4** and **5** allowed, for the first time, separation, on preparative scale, and full characterization of *cis*- and *trans*-isomers of compounds presented in Table 1 (see ESI†). There has not been much progress in comparative characterization of diastereomeric CCR products since the pioneering work of Castagnoli and Cushman.[1] Therefore, in this work we also aimed to establish, using the wide range of compounds synthesized, a basis for assigning *cis*- or *trans*-configuration to the γ- and δ-

lactams obtainable by the CCR based on their NMR spectra and to correlate these findings with a single-crystal X-ray crystallography data.

As it is evident for the value of the coupling constants of the C^2–H protons provide a rather solid basis for stereochemical assignment of γ-lactams **4a–j**, as was also reported earlier.[1,3] However, the difference in the same coupling constants is not that pronounced for δ-lactams **5a–o** and varies from 0.5 to 2.0 Hz (though the value appears to be always larger for the *cis*-isomer compared to its *trans*-counterpart). In an attempt to look for more characteristic patterns that could additionally aid in the stereochemical assignment, we also looked at the chemical shifts of C^2–H and C^3–H protons. While the former displayed no characteristic pattern, the latter appear to be universally positioned downfield for the *cis*-isomer compared to the *trans*-isomer. This difference also appears to be more pronounced for of γ-lactams **4** compared to δ-lactams **5** (Table 2). In order to ultimately confirm our stereochemical assignment (which was initially based on the dr values observed and then confirmed by the ^{1}H NMR patterns displayed by the respective stereoisomers, as discussed above), we obtained a number of single-crystal X-ray structures of individual *cis*- and *trans*-isomers of the CCR lactams in both **4** and **5** series (see ESI,† a representative pair is shown in Fig. 1). To the best of our knowledge, until today, crystallographic information on the *cis*-isomers of the CCR lactams (whilom scarcely available) has been lacking in the literature.

The individual *cis*- and *trans*-isomers reported in this Communication were obtained by preparative reverse-phase HPLC separation of diastereomeric mixtures of carboxylic
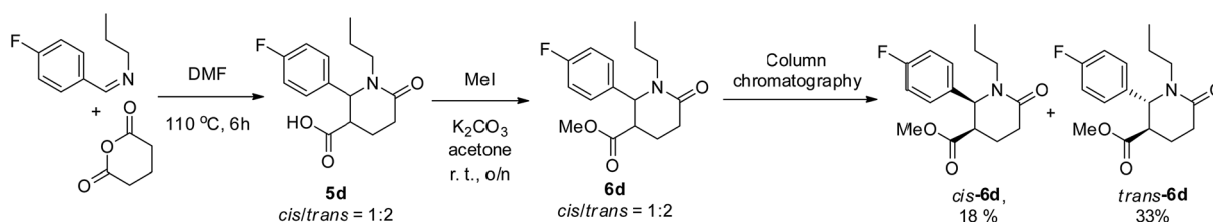
Scheme 4 Diastereomer separation of methyl esters obtained from compound **5d**.

acid lactams **4** and **5** (which are difficult to separate by conventional column chromatography). Alternatively, the carboxylic acids can be converted to the respective methyl esters, in order to facilitate chromatographic separation on silica gel.[9] This strategy was successfully realized for compound **5d** (Scheme 4).

In conclusion, we established that the Castagnoli–Cushman reaction in DMF leads to higher yields of the *cis*-configured γ- and δ-lactams. This enabled preparative isolation and characterization of this rare type of lead-like scaffolds in comparison with their well-described *trans*-configured counterparts. This, in turn, led to a more reliable basis for stereochemical assignment based on characteristic ^{1}H NMR patterns displayed by the two isomeric series, which was correlated with a number of X-ray structures. Efforts to unveil the medicinal chemistry potential of the *cis*-isomeric CCR lactams are underway in our laboratories. The results will be reported in due course.

Acknowledgements

Notes and references

1 (*a*) N. Castagnoli, *J. Org. Chem.*, 1969, **34**, 3187–3189; (*b*) M. Cushman and N. Castagnoli, *J. Org. Chem.*, 1973, **38**, 440–448; (*c*) M. Cushman and N. Castagnoli, *J. Org. Chem.*, 1974, **39**, 1546–1550.

2 M. González-López and J. T. Shaw, *Chem. Rev.*, 2009, **108**, 164–189.

3 S. V. Ryabukhin, D. M. Panov, D. S. Granat, E. N. Ostapchuk, D. V. Kryvoruchko and O. O. Grygorenko, *ACS Comb. Sci.*, 2014, **16**, 146–153.

4 A. Nadin, C. Hattotuwagama and I. Churcher, *Angew. Chem., Int. Ed.*, 2012, **51**, 1114–1122.

5 R. Doveston, S. Marsden and A. Nelson, *Drug Discovery Today*, 2014, **19**, 813–819.

6 (*a*) A. Mishchuk, N. Shtil, M. Poberezhnyk, K. Nazarenko, T. Savchenko, A. Tolmachev and M. Krasavin, *Tetrahedron Lett.*, 2016, **57**, 1056–1059; (*b*) P. Mujumdar, P. Sarnpitak,

A. Shetnev, M. Dorogov and M. Krasavin, *Tetrahedron Lett.*, 2015, **56**, 2827–2831.

7 D. Dar'in, O. Bakulina, M. Chizhova and M. Krasavin, *Org. Lett.*, 2015, **17**, 3930–3933.

8 M. Krasavin and D. Dar'in, *Tetrahedron Lett.*, 2016, **57**, 1635–1640.

9 J. Wei and J. T. Shaw, *Org. Lett.*, 2007, **9**, 4077–4080.

10 (*a*) K. Paulvannan, J. B. Schwarz and J. R. Stille, *Tetrahedron Lett.*, 1993, **34**, 215–218; (*b*) K. Paulvannan and J. R. Stille, *Tetrahedron Lett.*, 1993, **34**, 8197–8200; (*c*) K. Paulvannan and J. R. Stille, *J. Org. Chem.*, 1994, **59**, 1613–1620; (*d*) G. R. Cook, L. G. Beholz and J. R. Stille, *J. Org. Chem.*, 1994, **59**, 3575–3584.

11 (*a*) A. Samarat, J. B. Kraïem, T. Ben Ayed and H. Amri, *Tetrahedron*, 2008, **64**, 9540–9543; (*b*) N. M. Garrido, M. R. Sanchez, D. Diez, F. Sanz and J. G. Urones, *Tetrahedron: Asymmetry*, 2011, **22**, 872–880.

12 C. Agami, L. Hamon, C. Kadouri-Puchot and V. Le Guen, *J. Org. Chem.*, 1996, **61**, 5736–5742.

13 P. Y. Ng, Y. Tang, W. M. Knosp, H. S. Stadler and J. T. Shaw, *Angew. Chem., Int. Ed.*, 2007, **46**, 5352–5355.

14 The CCR of homophthalic anhydride (but not of **2** or **3**) was investigated in different solvents (CHCl$_3$, MeOH and HCONH$_2$): M. Cushman and E. J. Madaj, *J. Org. Chem.*, 1987, **52**, 907–915.

15 M. Cushman and E. J. Madaj, *J. Org. Chem.*, 1987, **52**, 907–915.

16 According to SciFinder search performed in February 2016, only six examples of bis-aryl piperidones similar to **5m–o** have been reported: (*a*) T. Mani, D. Liu, D. Zhou, L. Li, W. E. Knabe, F. Wang, K. Oh and S. O. Meroueh, *ChemMedChem*, 2013, **8**, 1963–1977; (*b*) M. Tabcheh, M. Baroudi, F. Elomar, A. Elzant, M. Elkhatib and V. Rolland, *Asian J. Chem.*, 2006, **18**, 1771–1782; (*c*) J. Robert, A. Boucherle and C. Luu-Duc, *J. Pharm. Belg.*, 1989, **44**, 36–40. The same search identified less than one hundred γ-lactams related to **4**, many of which had been prepared using methods other than CCR: (*d*) Z. Li, Y. Feng, Z. Li and J. Lan, *Synlett*, 2014, **25**, 2899–2902; (*e*) M. Pohmakotr, N. Yotapan, P. Tuchinda, C. Kuhakarn and V. Reutrakul, *J. Org. Chem.*, 2007, **72**, 5016–5019; (*f*) M. Pohmakotr, N. Yotapan, P. Tuchinda, C. Kuhakarn and V. Reutrakul, *Tetrahedron*, 2007, **63**, 4328–4337; (*g*) X. Zhao, D. A. DiRocco and T. Rovis, *J. Am. Chem. Soc.*, 2011, **133**, 12466–12469; (*h*) M. Tang, D. Xing, H. Huang and W. Hu, *Chem. Commun.*, 2015, **51**, 10612–10615.