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# Gold(I) and platinum(II) switch: a post-Ugi intramolecular hydroarylation to pyrrolopyridinones and pyrroloazepinones†

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**A regioselective approach for the synthesis of pyrrolopyridinones and pyrroloazepinones is reported employing an Ugi reaction followed by a gold(I) or platinum(II) catalyzed intramolecular hydroarylation.**

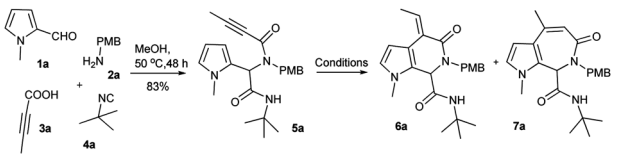
Transition metal-catalyzed carbocyclizations and heteroannulations of aromatic and heteroaromatic compounds with alkynes have attracted much attention in the last couple of decades.[1] In the vast literature about intramolecular alkyne cyclizations for the synthesis of biologically interesting carbo- and hetero-cycles, gold- and platinum-catalyses[2,3] have been on the front seat. Recently Beller and co-workers have reported a mechanistically interesting platinum-catalyzed intramolecular cyclization of alkynes on the pyrrole and the indole core.[4] Many elegant approaches involving gold-catalyzed alkyne cyclizations are also reported for the generation of various fused heterocycles.[5] Intermolecular gold-catalyzed reactions of pyrroles usually lack selectivity[6] and a less pronounced selectivity switch was observed in the related furan cyclizations with gold- and platinum-catalysis.[7] We have recently reported a post-Ugi gold(I)-catalyzed intramolecular hydroarylation approach to the synthesis of indoloazocines[8] and spiroindolines.[9] Inspired by this work and as a result of our interest in the application of transition metal-catalysis[10] and multicomponent reactions[11] for the synthesis of diversely substituted heterocycles, we here report a post-Ugi intramolecular hydroarylation to pyrrolopyridinones and pyrroloazepinones.[12]

Ugi 4-CR[13] of 2-formyl-*N*-methylpyrrole (**1a**), *p*-methoxybenzylamine (**2a**), 2-butynoic acid (**3a**) and *t*-Bu isonitrile (**4a**) in methanol at 50 °C furnishes the corresponding Ugi-adduct **5a** in 83% yield. This was further used for investigating the intramolecular hydroarylation.

The application of 5 mol% of AuCl or $AuCl_3$ as catalyst in $CDCl_3$ produced only pyrroloazepinone **7a** in 25% and 35% conversion respectively, while no reaction was observed with $Au(PPh_3)Cl$ (Table 1, entries 1–3). Use of cationic gold $Au(PPh_3)OTf$ (5 mol%) at rt furnished 47% of pyrrolopyridinone **6a**, while heating at 50 °C it gave 100% conversion, with an isolated yield of 93% (Table 1, entries 4 and 5). The switch of selectivity for the formation of **6a** or **7a** depending on the use of cationic gold(I) (Table 1, entry 5) or a $AuCl/AuCl_3$-catalyst (Table 1, entries 1 and 2) encouraged us to further optimize the conditions.

The application of $Au(PPh_3)SbF_6$ (5 mol%) at rt produced only 30% of **6a**, while employing solely AgOTf (5 mol%) at rt

**Table 1** Optimization of the intramolecular hydroarylation[a]




| Entry | Catalyst (mol%) | Solvent | Time (h) | Temp (°C) | Conversion[b] (%) (**6a**/**7a**) |
|---|---|---|---|---|---|
| 1 | AuCl (5) | $CDCl_3$ | 24 | 50 | 25 (0/25) |
| 2 | $AuCl_3$ (5) | $CDCl_3$ | 24 | 50 | 35 (0/35) |
| 3 | $Au(PPh_3)Cl$ (5) | $CDCl_3$ | 24 | 50 | 0 (0/0) |
| 4 | $Au(PPh_3)OTf$ (5) | $CDCl_3$ | 24 | rt | 47 (47/0) |
| **5** | **$Au(PPh_3)OTf$ (5)** | **$CDCl_3$** | **3** | **50** | **100 (93/0)[c]** |
| 6 | $Au(PPh_3)SbF_6$ (5) | $CDCl_3$ | 24 | rt | 30 (30/0) |
| 7 | AgOTf (5) | $CDCl_3$ | 24 | rt | 0 (0/0) |
| 8 | AgOTf (5) | $CDCl_3$ | 24 | 50 | 50 (0/50) |
| 9 | $PtCl_2$ (5) | $CDCl_3$ | 24 | rt | 0 (0/0) |
| **10** | **$PtCl_2$ (5)** | **$CDCl_3$** | **14** | **50** | **100 (10/82)[c]** |
| 11 | $PtCl_2$ (5) | $CDCl_3$ | 24 | 35 | 10 (0/10) |
| 12 | $PtCl_2$ (5) | $CDCl_3$ | 6 | 80 | 100 (25/75) |
| 13 | $PtCl_2$ (5) | $CDCl_3$ | 4 | 120 | 100 (35/75) |
| 14 | $H_2PtCl_6{\cdot}6H_2O$ (5) | $CDCl_3$ | 24 | rt | 0 (0/0) |
| 15 | $H_2PtCl_6{\cdot}6H_2O$ (5) | $CDCl_3$ | 24 | 50 | Traces (0/traces) |
| 16 | $Au(PPh_3)OTf$ (5) | ACN-$d_3$ | 24 | 50 | 100 (60/0)[c,d] |
| 17 | $Au(PPh_3)OTf$ (5) | THF-$d_8$ | 24 | 50 | 100 (45/0)[c,d] |
| 18 | $Au(PPh_3)OTf$ (5) | Toluene-$d_8$ | 24 | 50 | 47 (47/0) |
| 19 | $PtCl_2$ (5) | ACN-$d_3$ | 24 | 50 | 0 (0/0) |
| 20 | $PtCl_2$ (5) | THF-$d_8$ | 24 | 50 | 5 (0/5) |
| 21 | $PtCl_2$ (5) | Toluene-$d_8$ | 24 | 50 | 15 (0/15) |
| 22 | $Au(PPh_3)OTf$ (2) | $CDCl_3$ | 24 | 50 | 40 (40/0) |
| 23 | $PtCl_2$ (2) | $CDCl_3$ | 48 | 50 | 50 (10/40) |

[a] All reactions were run on a 0.1 mmol scale of **5a** in a screw capped vial. [b] Conversion and ratio based on $^1H$ NMR analysis. [c] Isolated yields. [d] Unidentified byproducts formed. PMB = *p*-methoxybenzyl.

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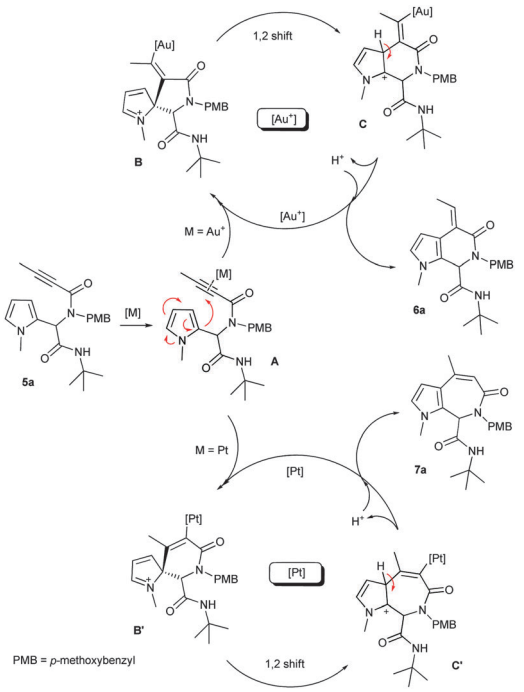


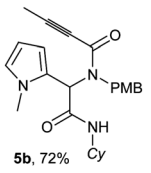
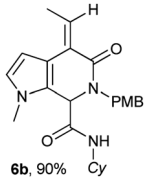
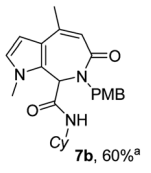
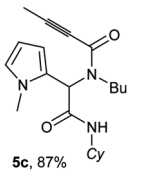
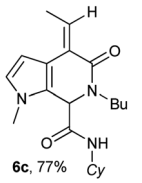
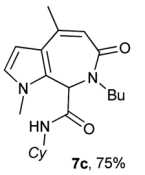
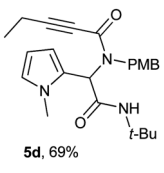
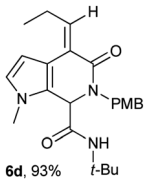
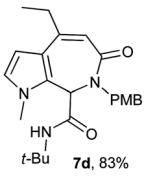
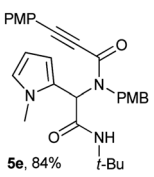
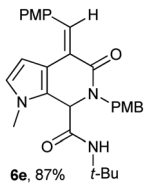
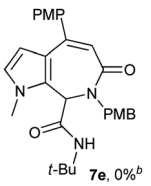
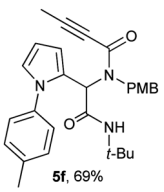
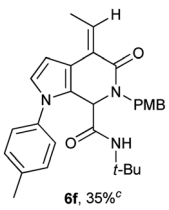
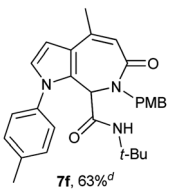
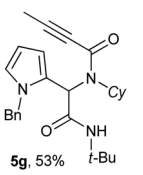
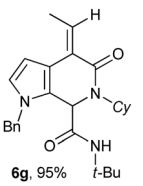
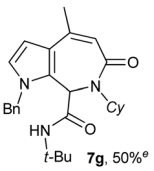
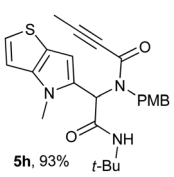
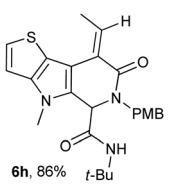
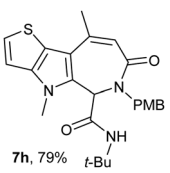
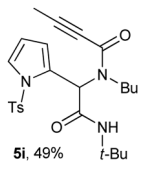
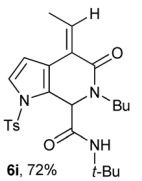
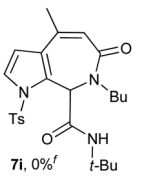

**Scheme 1** Plausible mechanism for the intramolecular regioselective hydroarylation.

did not give any conversion. Interestingly upon heating at 50 °C AgOTf gave 50% of **7a** as the sole product in 24 h (Table 1, entries 6–8). $PtCl_2$ (5 mol%) did not show any conversion at rt, while upon heating at 50 °C 100% conversion was obtained in 14 h with **7a** being the major product in 82% isolated yield (Table 1, entries 9 and 10). To check the influence of the temperature on the selectivity, the reactions were carried out at 35 °C, 80 °C and 120 °C with $PtCl_2$, but no amelioration was observed (Table 1, entries 11–13). No conversion could be obtained when $H_2PtCl_6{\cdot}6H_2O$ (5 mol%) was used at rt or under heating (Table 1, entries 14 and 15). In the case of cationic gold catalysis, a change of the solvent decreased the yield while for the platinum catalyst the conversion was strongly reduced (Table 1, entries 16–21). Diminishing the catalyst loading to 2 mol% resulted in a decreased conversion in both cases (Table 1, entries 22 and 23).

A plausible mechanism[2,8,9] is depicted in Scheme 1. Coordination of the metal with the alkyne in **5a** generates intermediate **A**. In the case of cationic gold the nucleophilic attack of the pyrrole on the activated alkyne occurs in an *exo*-dig fashion generating intermediate **B**. This is followed by a 1,2-shift to furnish intermediate **C**, which upon deprotonation and protodeauration forms pyrrolopyridinone **6a**. When platinum is used, the nucleophilic attack of the pyrrole on the activated alkyne occurs in an *endo*-dig fashion generating intermediate **B′**. After 1,2-shift, deprotonation and protodeplatination pyrroloazepinone **7a** is formed.

Having optimized the conditions for this intramolecular hydroarylation, diversely substituted Ugi-adducts **5b–i** were synthesized and subjected to the protocol. Mostly the *exo*-dig cyclization proceeds smoothly when cationic gold was used giving pyrrolopyridinones **6b–i** in good yields. Various substituents on the isonitrile, the amine, the alkyne and the pyrrole are well tolerated (Table 2). A bulky substituent like a *p*-methoxyphenyl on

**Table 2** Scope of the regioselective hydroarylation process

| Entry | Ugi adduct **5** | Pyrrolopyridinone **6** | Pyrroloazepinone **7** |
|---|---|---|---|
| 1 |  **5b**, 72% |  **6b**, 90% |  **7b**, 60%[a] |
| 2 |  **5c**, 87% |  **6c**, 77% |  **7c**, 75% |
| 3 |  **5d**, 69% |  **6d**, 93% |  **7d**, 83% |
| 4 |  **5e**, 84% |  **6e**, 87% |  **7e**, 0%[b] |
| 5 |  **5f**, 69% |  **6f**, 35%[c] |  **7f**, 63%[d] |
| 6 |  **5g**, 53% |  **6g**, 95% |  **7g**, 50%[e] |
| 7 |  **5h**, 93% |  **6h**, 86% |  **7h**, 79% |
| 8 |  **5i**, 49% |  **6i**, 72% |  **7i**, 0%[f] |

[a] 25% of **6b** was formed. [b] 30% of **6e** was formed after 24 h and rest of the starting **5e** was recovered. [c] Unidentified byproducts were formed. [d] 20% of **6f** was formed. [e] 46% of **6g** was formed. [f] No product was formed even after 48 h; only starting **5i** was recovered.

the alkyne or a thiophene fused with the pyrrole ring is also well tolerated delivering **6e** and **6h** respectively. However, when *N*-*p*-tolyl pyrrole was subjected to reaction conditions, the corresponding pyrrolopyridinone **6f** was obtained in a moderate yield of 35%, probably due to steric factors. Surprisingly application of a tosyl protected pyrrole did not affect the nucleophilicity of the ring and **6i** was obtained in 72% yield.

The same Ugi-adducts **5b–i** were subjected to *endo*-dig cyclization by reaction with catalytic $PtCl_2$. Gratifyingly, most of the reactions proceed well and the corresponding pyrroloazepinones **7** were isolated in good yields (Table 2). Upon using *p*-methoxyphenyl substituted alkyne, only 30% of *exo*-dig cyclized product **6e** could be observed after 24 h and no *endo*-dig cyclized product formed. This could be rationalized by the fact that *exo*-dig cyclization is sterically unaffected by the *p*-methoxyphenyl group, while the *endo*-dig cyclization is strongly hampered and hence no **7e** could be formed. When the thiophene fused pyrrole was used the corresponding tricyclic-azepinone **7h** was formed in 79% yield. Surprisingly, in contrast to the *exo*-dig cyclization (**6i**) a tosyl protected pyrrole did not undergo *endo*-dig cyclization.

In summary, we have developed a diversity-oriented regioselective intramolecular hydroarylation for the synthesis of pyrrolopyridinones and pyrroloazepinones employing gold(I)- and platinum(II)-catalysis respectively. The method allows the selective formation of 6 and 7 membered pyrrole fused heterocycles from easily available starting materials employing mild reaction conditions. The use of this strategy for different heterocycles is under current investigation.

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## Notes and references

1 (*a*) I. Ojima, M. Tzamarioudaki, Z. Li and R. J. Donovan, *Chem. Rev.*, 1996, **96**, 635; (*b*) N. T. Patil and Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395.

2 For reviews on gold- and platinum-catalysis, see (*a*) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410; (*b*) A. Fürstner, *Chem. Soc. Rev.*, 2009, **38**, 3208; (*c*) A. S. K. Hashmi and M. Rudolph, *Chem. Soc. Rev.*, 2008, **37**, 1766; (*d*) M. Rudolph and A. S. K. Hashmi, *Chem. Commun.*, 2011, **47**, 6536; (*e*) M. Rudolph and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2012, **41**, 2448; (*f*) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Commun.*, 2007, 333; (*g*) A. M. Echavarren, *Nat. Chem.*, 2009, **1**, 431; (*h*) A. S. K. Hashmi, W. Yang and F. Rominger, *Angew. Chem., Int. Ed.*, 2011, **50**, 5762; (*i*) A. Arcadi, *Chem. Rev.*, 2008, **108**, 3266; (*j*) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180; (*k*) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239; (*l*) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev.*, 2008, **108**, 3351; (*m*) M. Bandini, *Chem. Soc. Rev.*, 2011, **40**, 1358; (*n*) H. C. Shen, *Tetrahedron*, 2008, **64**, 3885; (*o*) H. C. Shen, *Tetrahedron*, 2008, **64**, 7847.

3 For gold-catalyzed tandem approaches leading to polycyclic indoles, see (*a*) C. C. J. Loh, J. Badorrek, G. Raabe and D. Enders, *Chem.–Eur. J.*, 2011, **17**, 13409; (*b*) Y. Lu, X. Du, X. Jia and Y. Liu, *Adv. Synth. Catal.*, 2009, **351**, 1517; (*c*) X. Xie, X. Du, Y. Chen and Y. Liu, *J. Org. Chem.*, 2011, **76**, 9175; (*d*) L. Zhang, *J. Am. Chem. Soc.*, 2005, **127**, 16804; for gold-catalyzed approaches towards tetracyclic indolines, see; (*e*) G. Cera, P. Crispino, M. Monari and M. Bandini, *Chem. Commun.*, 2011, **47**, 7803; (*f*) Y. Liu, W. Xu and W. Wang, *Org. Lett.*, 2010, **12**, 1448; for platinum catalysis, see; (*g*) A. Fürstner and P. W. Davies, *J. Am. Chem. Soc.*, 2005, **127**, 15024; (*h*) G. Zhang, V. J. Catalano and L. Zhang, *J. Am. Chem. Soc.*, 2007, **129**, 11358; (*i*) G. B. Bajracharya, N. K. Pahadi, I. D. Gridnev and Y. Yamamoto, *J. Org. Chem.*, 2006, **71**, 6204.

4 (*a*) M. Gruit, D. Michalik, A. Tillack and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 7212; (*b*) M. Gruit, A. Pews-Davtyan and M. Beller, *Org. Biomol. Chem.*, 2011, **9**, 1148.

5 For gold catalysis, see (*a*) C. Ferrer and A. M. Echavarren, *Angew. Chem., Int. Ed.*, 2006, **45**, 1105; (*b*) C. Ferrer, C. H. M. Amijs and A. M. Echavarren, *Chem.–Eur. J.*, 2007, **13**, 1358; (*c*) D. B. England and A. Padwa, *Org. Lett.*, 2008, **10**, 3631; (*d*) C. Ferrer, A. Escribano-Cuesta and A. M. Echavarren, *Tetrahedron*, 2009, **65**, 9015; (*e*) A. S. K. Hashmi, A. M. Schuster and F. Rominger, *Angew. Chem., Int. Ed.*, 2009, **48**, 8247; (*f*) A. S. K. Hashmi, W. Yang and F. Rominger, *Angew. Chem., Int. Ed.*, 2011, **50**, 5762; (*g*) A. S. K. Hashmi, W. Yang and F. Rominger, *Chem.–Eur. J.*, 2012, **18**, 6576; (*h*) W. Chaładaj, M. Corbet and A. Fürstner, *Angew. Chem., Int. Ed.*, 2012, **51**, 6929; (*i*) A. S. K. Hashmi, P. Haufe, C. Schmid, A. R. Nass and W. Frey, *Chem.–Eur. J.*, 2006, **12**, 5376.

6 A. S. K. Hashmi, R. Salathé and W. Frey, *Eur. J. Org. Chem.*, 2007, 1648.

7 A. S. K. Hashmi, E. Kurpejović, W. Frey and J. W. Bats, *Tetrahedron*, 2007, **63**, 5879.

8 S. G. Modha, D. D. Vachhani, J. Jacobs, L. Van Meervelt and E. V. Van der Eycken, *Chem. Commun.*, 2012, **48**, 6550.

9 S. G. Modha, A. Kumar, D. D. Vachhani, J. Jacobs, S. K. Sharma, V. S. Parmar, L. Van Meervelt and E. V. Van der Eycken, *Angew. Chem., Int. Ed.*, 2012, **51**, 9572.

10 (*a*) S. G. Modha, J. C. Trivedi, V. P. Mehta, D. S. Ermolat'ev and E. V. Van der Eycken, *J. Org. Chem.*, 2011, **76**, 846; (*b*) S. G. Modha, V. P. Mehta, D. Ermolat'ev, J. Balzarini, K. Van Hecke, L. Van Meervelt and E. V. Van der Eycken, *Mol. Diversity*, 2010, **14**, 767; (*c*) V. P. Mehta and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2011, **40**, 4925; (*d*) C. O. Kappe and E. Van der Eycken, *Chem. Soc. Rev.*, 2010, **39**, 1280; (*e*) P. A. Donets, K. Van Hecke, L. Van Meervelt and E. V. Van der Eycken, *Org. Lett.*, 2009, **11**, 3618; (*f*) V. A. Peshkov, S. Van Hove, P. A. Donets, O. P. Pereshivko, K. Van Hecke, L. Van Meervelt and E. V. Van der Eycken, *Eur. J. Org. Chem.*, 2011, 1837; (*g*) P. A. Donets and E. V. Van der Eycken, *Synthesis*, 2011, 2147.

11 (*a*) V. P. Mehta, S. G. Modha, E. Ruijter, K. Van Hecke, L. Van Meervelt, C. Pannecouque, J. Balzarini, R. V. A. Orru and E. V. Van der Eycken, *J. Org. Chem.*, 2011, **76**, 2828; (*b*) V. A. Peshkov, O. P. Pereshivko and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2012, **41**, 3790.

12 For details and synthesis of azepine and pyridine fused pyrrole and indole containing natural products, see (*a*) C. Schultz, A. Link, M. Leost, D. W. Zaharevitz, R. Gussio, E. A. Sausville, L. Meijer and C. Kunick, *J. Med. Chem.*, 1999, **42**, 2909; (*b*) C. Eder, P. Proksh, V. Wray, K. Steube, G. Bringmann, R. W. M. Van Soest, Sudersono, E. Ferdinandus, L. A. Pattisina, S. Wiryowidagdo and W. Moka, *J. Nat. Prod.*, 1999, **62**, 184; (*c*) R. G. Linington, D. E. Williams, A. Tahir, R. van Soest and R. J. Andersen, *Org. Lett.*, 2003, **5**, 2735; (*d*) Q. He, W. Chen and Y. Qin, *Tetrahedron Lett.*, 2007, **48**, 1899; (*e*) N. Mangu, H. M. Kaiser, A. Kar, A. Spannenberg, M. Beller and M. K. Tse, *Tetrahedron*, 2008, **64**, 7171; (*f*) J. R. F. Allen and B. R. Holmstedt, *Phytochemistry*, 1980, **19**, 1573; (*g*) A. Brossi, *The Alkaloids*, ed. G. A. Cordell, Academic Press, New York, 1993, vol. 43, pp. 119.

13 For isonitrile based multicomponent reactions, see (*a*) A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168; (*b*) A. Dömling, *Chem. Rev.*, 2006, **106**, 17; for asymmetric multicomponent reactions, see; (*c*) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602; for multicomponent reactions in general, see; (*d*) B. Ganem, *Acc. Chem. Res.*, 2009, **42**, 463; (*e*) L. El Kaïm and L. Grimaud, *Mol. Diversity*, 2010, **14**, 855; (*f*) E. Ruijter, R. Scheffelaar and R. V. A. Orru, *Angew. Chem., Int. Ed.*, 2011, **50**, 6234; (*g*) A. Dömling, W. Wang and K. Wang, *Chem. Rev.*, 2012, **112**, 3083.