Tetrahedron Letters 51 (2010) 3807–3810

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed regioselective oxidative amination of alkenes: an efficient route to the synthesis of pyrrolocoumarin and pyrroloquinolone derivatives

K. C. Majumdar *, Srikanta Samanta, Raj Kumar Nandi, Buddhadeb Chattopadhyay

Department of Chemistry, University of Kalyani, Kalyani 741 235, WB, India

ARTICLE INFO

Article history:
Received 13 March 2010
Revised 10 May 2010
Accepted 17 May 2010

Keywords:
Palladium catalyst
Oxidative amination
IBX (2-iodoxybenzoic acid)
Pyrrolocoumarin
Pyrroloquinolone

ABSTRACT

Palladium-catalyzed IBX-induced intramolecular oxidative amination of alkenes has been utilized for the synthesis of pyrrolocoumarin and pyrroloquinolone derivatives in excellent yields in a short reaction time.

The prominence of five-membered nitrogen-containing heterocycles in natural products and biologically active molecules[1] has evoked considerable interest toward their synthesis. Natural products possessing coumarin and quinolone sub-units show broad-spectrum biological activities.[2–6] Various pyrrolocoumarins possess anti bacterial, monoamine oxidase (MAO) inhibitory, and anthelmintic activities.[7] They have also been used as fluorogenic probes.[8] A number of synthetic methodologies[9a–d] have been developed for the synthesis of coumarin- and quinolone-fused pyrroles by ring-closing reaction. The intramolecular addition of nitrogen functionality to an alkyne or an alkene is an important strategy. This often needs harsh reaction conditions if the carbon–carbon multiple bond is not sufficiently polarized.[10] Intramolecular oxidative amination[11,12] of olefins represents a powerful synthetic strategy for the synthesis of nitrogen heterocycles. Among the various metal-catalyzed (Ag, Cu) synthetic protocols developed, palladium is one of the widely used and accepted metal that is employed in different types of intramolecular oxidative amination of olefins. In principle, the reaction may be initiated by palladium–amine interaction followed by simultaneous transfer to the alkene, which may also be considered as alkene insertion into the amine–palladium bond (Fig. 1).[13]

Stahl and co-workers reported the palladium-catalyzed intermolecular[14a] aerobic oxidative amination of alkenes to synthesize different terminal enimides and intramolecular[14b] oxidative amination of olefins to produce pyrrolidine and pyrroline heterocycles efficiently using molecular oxygen. Liu and co-workers reported[15] a Brønsted base-modulated regioselective Pd-catalyzed intramolecular aerobic oxidative amination of alkenes for the formation of seven-membered amides. Palladium-catalyzed intramolecular amination of olefins has been reported for the formation of 2-methyl-1-tosyl indole under different conditions[16] in only 21–28% yields in a complex mixture. But there is no such report on the synthesis of pyrrolo-fused heterocycles by Pd-catalyzed oxidative amination starting from unactivated olefinic amine precursors. This has prompted us to undertake a study on the synthesis of pyrrolocoumarins and pyrroloquinolones by the intramolecular oxidative amination.

The starting materials **1a–f**, **2(a,b)**, **3** for this study were prepared according to our earlier published procedure.[17,18] We had earlier demonstrated[9b] the gold (III)-catalyzed amination of alkynes to synthesize pyrrolo-pyridine derivatives. Therefore, initially we have attempted Au(III) catalyst for the alkene–amine coupling. However, when 5-allyl-6-(ethylamino)-1-methylquinolone **1a** was subjected to react with $AuCl_3$ in acetonitrile, the desired cyclization to give pyrroloquinolone derivative did not occur even after refluxing for 14 h. The catalyst system was changed and $Pd(OAc)_2$ was tried in anhydrous DMF in the presence of Na_2CO_3 as base at 100 °C for 10 h. Pleasantly the cyclized product pyrrolo[3,2-*f*]quinolinone was obtained in good yield (71%) (Scheme 1).

* Corresponding author. Tel.: +91 33 2582 7521; fax: +91 33 2582 8282.
E-mail address: kcm_ku@yahoo.co.in (K.C. Majumdar).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.068

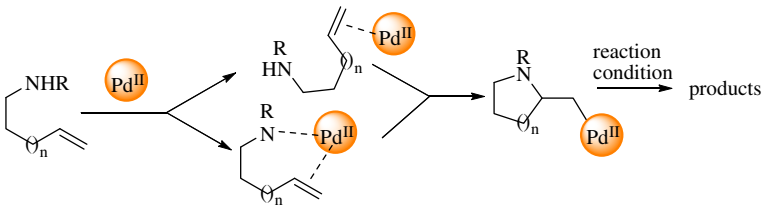
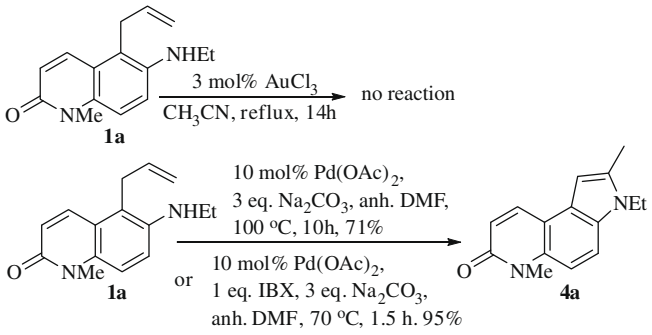


Figure 1. Mechanistic background of aminopalladation for heterocycle synthesis.



Scheme 1.

In order to improve the yield of the reaction we have then used IBX as an oxidant in the reaction. In the presence of IBX (2-iodoxybenzoic acid) surprisingly the yield of the product, pyrroloquinolone **4a**[19], was increased to 95% at 70 °C in only 1.5 h. We have carried out a series of experiments by sequential changes of catalyst, solvent, base, and oxidant. The results are summarized in Table 1.

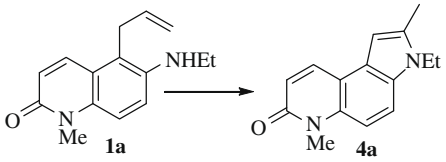
From Table 1 it is clear that $Pd(OAc)_2$ is much more efficient than $Pd(PPh_3)_4$ and $Cu(OAc)_2$. In the absence of any catalyst the reaction did not proceed at all (entry 8). Among the different solvents tried, DMF is the best choice compared to CH_3CN and DMA. In aqueous medium the reaction was sluggish (yield 15%, entry 13). IBX is preferable to iodobenzenediacetate (IBD) and benzoquinone (BQ) as a reoxidant. When the reaction was carried out at 70 °C for 1.5 h without IBX the product obtained was just 28% (entry 4) and on increasing the reaction time up to a stage that the reaction hardly proceeded anymore, the yield was 69% (entry 5). So the optimized reaction conditions are 10 mol % $Pd(OAc)_2$/1 equiv IBX/3 equiv Na_2CO_3/DMF/70 °C. All the other starting materials **1(b–f)**, **2(a,b)**, and **3** were treated under the optimized reaction conditions to afford the corresponding cyclized products **4(b–f)**, **5(a,b)**, and **6** in 85–97% yields. The results are given in Table 2.

We have been particularly interested in the oxidative amination reactions, and a simplified catalytic cycle for a representative reaction is shown in Scheme 2: aminopalladation of the alkene, followed by β-hydride elimination, generates the heterocyclic product **4a′**, which subsequently isomerizes to form the desired product **4a** and the reduced Pd catalyst (step IV, Scheme 2). The reduced catalyst then gets reoxidized directly by the oxidant IBX to regenerate the catalyst Pd^{II} (step V).

The past few years have seen an explosive growth in the demonstration and use of IBX as a selective reagent for unique oxidative transformations[20] including oxidation of benzylic carbons, oxidation of amines, dehydrogenation of carbonyl to the corresponding α,β-unsaturated analogues, dehydrogenation of *N*-heterocycles to heteroaromatics, and oxidative cleavage of dithioacetals and dithioketals. But its use as a reoxidant [Pd(0) to Pd(II)] is perhaps the first report.

It is relevant to mention that we failed to get the corresponding pyrroloquinolone and pyrrolocoumarin derivatives by the radical cyclization.[17c] It is interesting to note that here we have succeeded in developing a more generalized approach which overcomes the

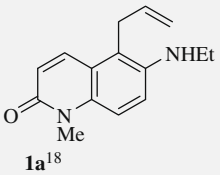
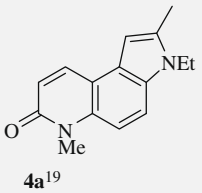
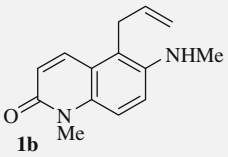
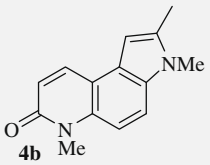
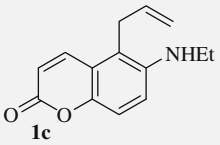
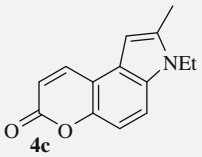
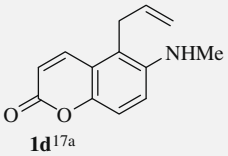
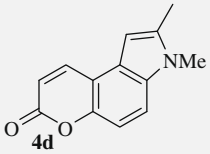
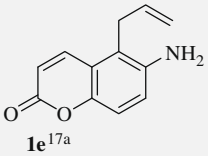
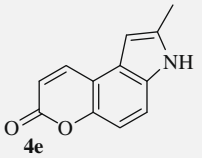
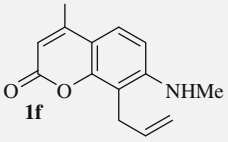
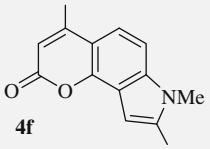
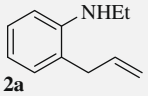
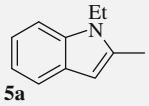
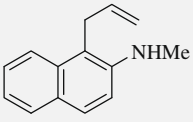
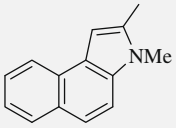
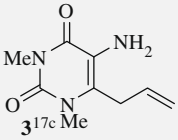
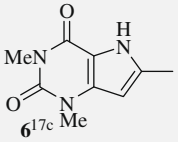
Table 1
Study under different conditions



Entries	Catalyst[a]	Solvent	Base[b]	Oxidant[c]	Temp (°C)	Time (h)	Yield[d] (%)
1	$Pd(OAc)_2$	DMF	Na_2CO_3	—	100	10	71
2	$Pd(OAc)_2$	DMF	Na_2CO_3	—	100	15	48
3[e]	**$Pd(OAc)_2$**	**DMF**	**Na_2CO_3**	**IBX**	**70**	**1.5**	**95**
4	**$Pd(OAc)_2$**	**DMF**	**Na_2CO_3**	—	**70**	**1.5**	**28**
5	$Pd(OAc)_2$	DMF	Na_2CO_3	—	70	16	69
6	$Pd(OAc)_2$	DMF	Na_2CO_3	IBD[f]	70	1.5	79
7	$Cu(OAc)_2$	DMF	KOAc	IBX	90	5	70
8	—	DMF	Na_2CO_3	IBX	100	12	NR[g]
9	$Pd(OAc)_2$	DMA	KOAc	IBX	100	12	15
10	$Pd(OAc)_2$	CH_3CN	Na_2CO_3	IBX	80	4	73
11	$Pd(OAc)_2$	DMF	Na_2CO_3	IBX	80	5	90
12	$Pd(OAc)_2$	DMF	Na_2CO_3	BQ[h]	80	2.5	80
13	$Pd(OAc)_2$	H_2O	Na_2CO_3	IBX	70	1.5	15
14	$Pd(PPh_3)_4$	DMF	Na_2CO_3	IBX	80	5	77

a = catalyst used 10 mol %, b = base used 3 equiv, c = oxidant used 1 equiv; d = isolated yield; e = optimized reaction condition; f = iodobenzenediacetate; g = no reaction; h = benzoquinone.

Table 2
Intramolecular oxidative amination of olefinic substrates

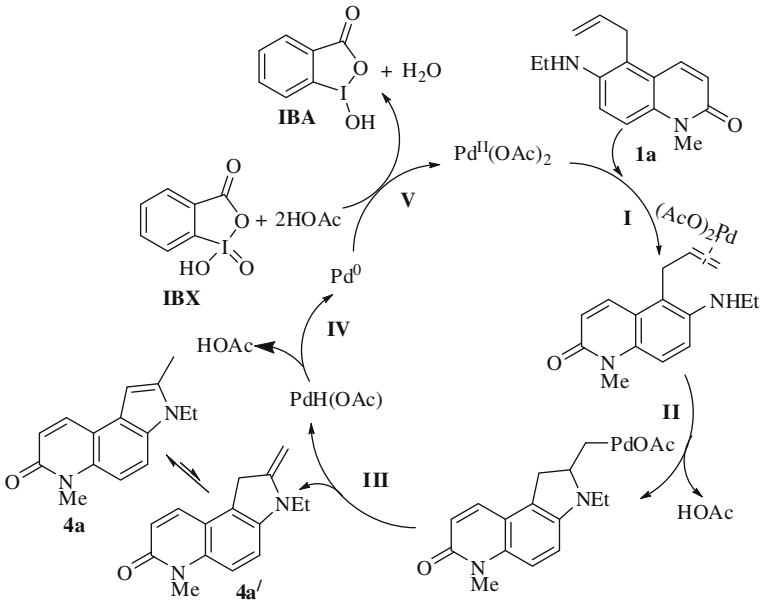
Entries	Starting	Product	Time (h)	Yield[a] (%)
1	 **1a**[18]	 **4a**[19]	1.5	95
2	 **1b**	 **4b**	2	91
3	 **1c**	 **4c**	1.5	97
4	 **1d**[17a]	 **4d**	1.5	95
5	 **1e**[17a]	 **4e**	2	96
6	 **1f**	 **4f**	2.5	89
7	 **2a**	 **5a**	3	91
8	 **2b**	 **5b**	3	85
9	 **3**[17c]	 **6**[17c]	1.5	96

a = isolated yield.

earlier drawbacks and limitations. The protocol has also been utilized for the transformation of **2** and **3** to **5** and **6**, respectively.

It has been mentioned earlier that intramolecular oxidative amination was also achieved by aerobic oxidation.[14b,15] The reactions when carried out in air is very slow giving a lower yield of the product. However, the yield of the reaction can be improved by passing molecular oxygen into the reaction mixture giving a 60% yield of the *N*-tosylindole in 16 h[14b] and in some cases mixtures of *exo*-methylene and internal olefin products were obtained. It is remarkable that we could achieve 85–97% yield of the internal olefin products regioselectively by simply using $Pd(OAc)_2$ with IBX as additives within a much shorter reaction time.

In conclusion, we have developed a novel protocol catalyzed by palladium (II) under mild conditions using IBX as a reoxidant. By the successful implementation of this protocol, a variety of pyrrolo-fused heterocycles and carbocycles have been prepared in excellent yields from the unactivated olefins. The starting materials for these reactions can readily be obtained via aza-Claisen rearrange-



Scheme 2. Probable mechanistic pathway of the oxidative cyclization.

ment in excellent yields. Therefore, we provide a concise, high yielding, atom-economic methodology for the synthesis of pyrrolo-fused carbocycle and heterocycles.

Acknowledgments

We thank the CSIR (New Delhi) and the DST (New Delhi) for financial assistance and two of us (S.S. and R.K.N.) are grateful to the CSIR (New Delhi) for their fellowships. We also thank the DST (New Delhi) for providing Brucker NMR (400 Mz) and Perkin–Elmer CHN analyzer.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.068.

References and notes

1. See for example, O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446.
2. Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Carroll, J. G.; Mackerracher, D.; Malone, J. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3397–3405.
3. Bar, G.; Parsons, A. F.; Thomas, C. B. *Tetrahedron* **2001**, *57*, 4719–4728.
4. Lee, Y. R.; Kim, B. S.; Kweon, H. I. *Tetrahedron* **2000**, *56*, 3867–3874.
5. Pirrung, M. C.; Blume, F. J. *J. Org. Chem.* **1999**, *64*, 3642–3649.
6. Dickinson, J. M. *Nat. Prod. Rep.* **1993**, *10*, 71–98.
7. Hiremath, S. P.; Badiger, G. R.; Jivanagi, A. S.; Purohit, M. G. *Indian J. Chem.* **1992**, *31B*, 583–589.
8. Chen, G.; Yee, D. J.; Gubernator, N. G.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4544–4545.
9. (a) Majumdar, K. C.; Mondal, S. *Tetrahedron Lett.* **2008**, *49*, 2418–2420; (b) Majumdar, K. C.; Samanta, S.; Chattopadhyay, B. *Tetrahedron Lett.* **2008**, *49*, 7213–7216; (c) Majumdar, K. C.; Chattopadhyay, B.; Samanta, S. *Synthesis* **2009**, 311–317; (d) Majumdar, K. C.; Chakravorty, S.; Shyam, P. K.; Taher, A. *Synthesis* **2009**, 403–408.
10. (a) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703; (b) Beller, M.; Riermeier, T. H.. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 1998; Vol. 1, pp 184–193; (c) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415–1418; (d) Kukharev, B. F.; Stankevich, V. K.; Klimenko, G. R. *Russ. J. Org. Chem.* **1993**, *29*, 2005–2012; (e) Taube, R.. In *Applied Homogenous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: New York, 1996; Vol. 1, pp 507–520.
11. (a) Hegedus, L. S.; Allen, G. F.; Waterman, E. L. *J. Am. Chem. Soc.* **1976**, *98*, 2674–2676; (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807; (c) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583–3587; (d) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444–2451; (e) Hegedus, L. S.; Akermark, B.; Zetterberg, K.; Olsson, L. F. *J. Am. Chem. Soc.* **1984**, *106*, 7122–7126; (f) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335–4338.
12. (a) Pugin, B.; Venanzi, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 6877–6881; (b) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994–4002; (c) Tamaru, Y.; Tanigawa, H.; Itoh, S.; Kimura, M.; Tanaka, S.; Fugami, K.; Sekiyama, T.; Yoshida, Z. *Tetrahedron Lett.* **1992**, *33*, 631–634.
13. Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142–1152.
14. (a) Rogers, M. M.; Kotov, V.; Chatwichien, J.; Stahl, S. S. *Org. Lett.* **2007**, *9*, 4331–4334; (b) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem.* **2002**, *114*, 172–174.
15. Wu, L.; Qiu, S.; Liu, G. *Org. Lett.* **2009**, *11*, 2707–2710.
16. Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chelmer, S. R. *Organometallics* **2004**, *23*, 5618–5621.
17. (a) Majumdar, K. C.; Samanta, S.; Chattopadhyay, B.; Nandi, R. K. *Synthesis* **2010**, 863–869; (b) Majumdar, K. C.; Nandi, R. K.; Samanta, S.; Chattopadhyay, B. *Synthesis* **2010**, 985–990; (c) Majumdar, K. C.; Mondal, S. *Tetrahedron* **2009**, *65*, 9604–9608.
18. *5-Allyl-6-(ethylamino)-1-methylquinolin-2(1H)-one* (**1a**): This substrate was prepared according to earlier published procedure.[17] Compound **1a** obtained as a solid; mp 102–104 °C; yield 85%. IR (KBr): 3358, 1648, 1304 cm^{-1}. ^1H NMR($CDCl_3$, 300 MHz): δ_H = 1.29 (t, 3H, *J* = 6.9 Hz, NCH_2CH_3), 3.21 (q, 2H, *J* = 6.9 Hz, NCH_2CH_3), 3.57 (d, 2H, *J* = 4.5 Hz, CH_2), 3.71 (s, 3H, NCH_3), 4.91 (d, 1H, *J* = 17.1 Hz, $=CH_aH_b$), 5.10 (d, 1H, *J* = 10.2 Hz, $=CH_aH_b$), 5.90–6.01 (m, 1H, =CH), 6.70 (d, 1H, *J* = 9.9 Hz, C_3-*H* of quinolone), 7.04 (d, 1H, *J* = 9.3 Hz, Ar*H*), 7.25 (d, 1H, *J* = 9.3 Hz, Ar*H*), 7.81 (d, 1H, *J* = 9.9 Hz, C_4-*H* of quinolone) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 15.0, 29.5, 30.1, 39.1, 113.5, 115.6, 116.4, 119.0, 120.0, 121.7, 133.1, 134.4, 134.8, 141.7, 161.3 ppm. HRMS (ESI): Calcd: 265.1317 $(M+Na)^+$. Found: 265.1317 $(M+Na)^+$.
19. *3-Ethyl-2,6-dimethyl-3H-pyrrolo[3,2-f]quinolin-7(6H)-one* (**4a**): *Typical procedure*: A mixture of **1a** (100 mg, 0.41 mmol), $Pd(OAc)_2$ (9.2 mg, 10 mol %), anhyd Na_2CO_3 (130.4 mg, 1.23 mmol), and IBX (115 mg, 0.41 mmol) was taken in dry *N*,*N*-dimethylformamide (DMF) (10 mL) and was stirred at 70 °C for 1.5 h. The reaction mixture was cooled, water (20 mL) was added, extracted with ethyl acetate (3 × 20 mL), and the ethylacetate extract was washed with water (4 × 10 mL), brine (10 mL), dried (Na_2SO_4), and the solvent was distilled off to furnish a viscous mass which was purified by column chromatography over silica gel. Elution of the column with 45% (ethyl acetate/pet) afforded the product **4a** as a solid; mp 126–128 °C, yield 95%. IR (KBr): 2922, 1643, 1360 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ_H = 1.37 (t, 3H, *J* = 7.2 Hz, NCH_2CH_3), 2.50 (s, 3H, CH_3), 3.81 (s, 3H, NCH_3), 4.19 (q, 2H, *J* = 7.2 Hz, NCH_2CH_3), 6.55 (s, 1H, =CH), 6.77 (d, 1H, *J* = 9.6 Hz, C_3-*H* of quinolone), 7.17 (d, 1H, *J* = 9 Hz, Ar*H*), 7.49 (d, 1H, *J* = 9 Hz, Ar*H*), 8.09 (d, 1H, *J* = 9.3 Hz, C_4-*H* of quinolone) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 12.7, 15.5, 30.1, 38.1, 98.0, 107.4, 112.4, 119.8, 125.2, 131.2, 134.9, 135.4, 137.7, 150.1, 162.5 ppm. HRMS (ESI): Calcd: 241.1335 $(M+H)^+$. Found: 241.1328 $(M+H)^+$.
20. (a) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258; (b) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192–5201.