Tetrahedron 67 (2011) 4327–4332

Contents lists available at ScienceDirect

Tetrahedron

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

Direct annulation and alkylation of indoles with 2-aminobenzyl alcohols catalyzed by TFA

Forest J. Robertson, Bradshaw D. Kenimer, Jimmy Wu *

Dartmouth College, Department of Chemistry, Hanover, NH 03755, USA

ARTICLE INFO

Article history:
Received 17 January 2011
Received in revised form 18 February 2011
Accepted 22 February 2011
Available online 1 March 2011

Keywords:
Annulation
Alkylation
Indole
Communesin
Alcohol

ABSTRACT

An efficient method for the annulation of indoles with 2-aminobenzyl alcohols, catalyzed by TFA, to furnish 5,6-fused indoline aminals is reported. This method can be extended to the alkylation of indoles at C3. 2-Aminobenzyl alcohols are used directly without recourse to protection of the aniline nitrogen or activation of the alcohol.

1. Introduction

For several years, our group has been interested in developing new methodologies for the utilization of free alcohols as electrophiles without the need for pre-activation. Achieving this goal for a broad range of carbon-bond forming reactions is difficult for several reasons. First, the acidic nature of alcohols is often incompatible with strongly basic nucleophiles. Second, alcohols are inherently poor leaving groups—hence the requirement for pre-activation (e.g., conversion to the corresponding sulfonate ester). Overcoming these obstacles could potentially be very rewarding since the only significant by-product generated in these reactions is water. To this end, our group has reported several studies, which directly utilize alcohols without the need for pre-activation. These include the one-pot synthesis of thioethers from alcohols and phosphorothioate esters,[1] and the UV-promoted[2] or $Ga(OTf)_3$-catalyzed[3] displacement of alcohols with sulfur nucleophiles.

In the present study, we reveal that TFA is an effective catalyst for the reaction between 2-aminobenzyl alcohols and 3-substituted indoles to furnish 5,6-fused indoline aminals (Eq. 1). This ring system is highly unusual and is present in only a handful of natural products. Included among these is the communesin family of indoline alkaloids (Fig. 1).[4] These compounds exhibit a range of cytotoxic and insecticidal properties.[5] The combination of broad bioactivity as well as their unique and densely functionalized structure has engendered numerous studies toward their syntheses.[6] Presently, there have been three completed total syntheses reported.[7]

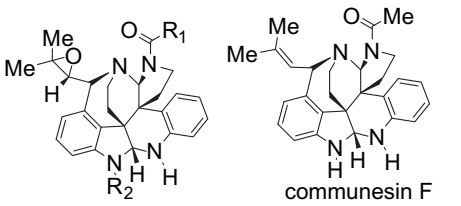
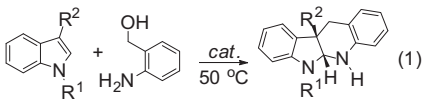


Fig. 1. Communesin indoline alkaloids.



* Corresponding author. Tel.: +1 603 646 6481; fax: +1 603 646 3946; e-mail address: jimmy.wu@dartmouth.edu (J. Wu).

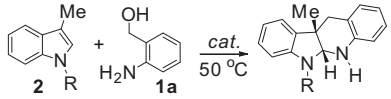
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.02.067

Other groups have adopted analogous cyclization strategies with 3-substituted indoles to furnish 5,6-fused indoline aminals. However, consistent amongst each of these protocols is the requirement for protection of the aniline nitrogen and conversion of the alcohol to a superior leaving group, such as sulfonate,[8] halide,[6b,c] carbonate,[6a] aziridine,[6d] or carbamate.[6e] This strategy was first articulated by Corey and is believed to proceed via a highly reactive aza *ortho*-quinone methide intermediate.[9] With the exception of a thermally-promoted reaction (160 °C),[6a] these methods proceed under basic conditions. There have been examples of either Lewis[10] or Brønsted[11] acid promoted activation of free alcohols in C–C bond-forming reactions; however, to the best of our knowledge, these methods have never been applied to the preparation of 5,6-fused indoline aminals. Cozzi has also reported the substitution of alcohols 'on-water'.[12]

2. Results

Herein, we report that TFA can catalyze the reaction depicted in Eq. (1) with only mild heating (50 °C). We elected to first examine $Ga(OTf)_3$ as a catalyst because of our ongoing interest in this reagent.[3] $Ga(OTf)_3$ is an inexpensive, air- and water-tolerant Lewis acid.[13] Initial optimization studies reveal that 10% $Ga(OTf)_3$ effectively promotes the reaction between *N*-methylskatole (**2a**) and **1a** (Table 1, entry 1). The use of acylated or silyl-protected indoles yielded no reaction (entries 2 and 3). The use of *N*–H starting material **2e** (entry 5) resulted in significant amounts of a rearranged by-product (vide infra).

Table 1
Optimization studies[a]



Entry	R	**2** (equiv)	Catalyst	Yield	Product
1	Me (**2a**)	2.0	10% $Ga(OTf)_3$	75%	**3**
2	TIPS (**2b**)	2.0	10% $Ga(OTf)_3$	—[b]	**4**
3	Ac (**2c**)	2.0	10% $Ga(OTf)_3$	—[b]	**5**
4	Bn (**2d**)	2.0	10% $Ga(OTf)_3$	48%	**6**
5	H (**2e**)	2.0	10% $Ga(OTf)_3$	46%[c]	**7**
6	Me (**2a**)	1.2	30% TfOH	56%	**3**
7	Me (**2a**)	1.2	30% *p*-TSA	67%	**3**
8	Me (**2a**)	1.2	30 mol % TFA	74%	**3**
9	Me (**2a**)	2.0	30 mol % TFA	86%	**3**
10	Bn (**2d**)	2.0	30 mol % TFA	65%	**6**

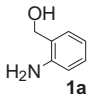
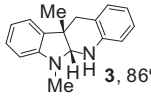
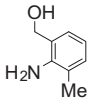
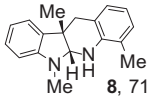
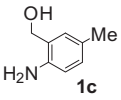
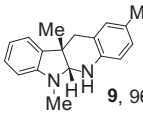
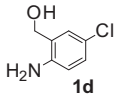
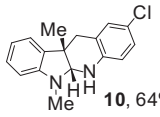
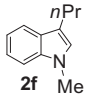
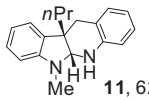
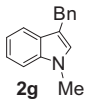
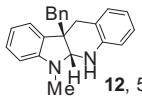
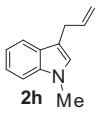
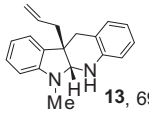
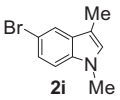
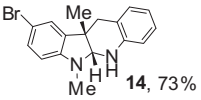
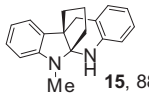
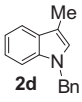
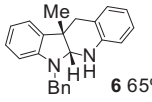
[a] Conducted at 50 °C in dichloroethane.
[b] No reaction.
[c] Lower yield is due to formation of rearranged side-products.

We also discovered that various Brønsted acids are effective, with TFA furnishing the highest yield (entries 6–10). It should be noted that these results do not necessarily imply that the active catalyst in the $Ga(OTf)_3$-promoted reactions (entries 1–5) is TfOH, especially since $Ga(OTf)_3$ is known to be hydrolytically stable.[13]

With these optimized conditions in hand, we examined the scope of the TFA-catalyzed cyclization reaction (Table 2). This process is amenable to several substrates possessing an assortment of substitution patterns. Notably, halides (entries 4 and 8) as well as cyclic indoles (entry 9) furnished the desired products in good to excellent yields. Unfortunately, other heterocyclic nucleophiles, such as pyrroles, imidazoles, benzimidazoles, thiophenes, and furans with various permutations of methylation in the 1- ,2-, and 5-positions yielded only decomposition products. Similar results were obtained when aminobenzyl alcohols possessing a 2° alcohol were examined.

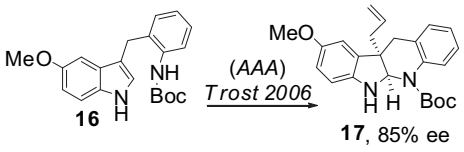
In 2006, Trost and co-workers demonstrated that substrates, such as **16** can undergo Pd-catalyzed asymmetric allylic alkylation

Table 2
Scope of reaction[a]

Entry	Indole	Alcohol	Product
1	**2a**	 **1a**	 **3**, 86%
2	**2a**	 **1b**	 **8**, 71%
3	**2a**	 **1c**	 **9**, 96%
4	**2a**	 **1d**	 **10**, 64%
5	 **2f**	**1a**	 **11**, 62%
6	 **2g**	**1a**	 **12**, 50%
7	 **2h**	**1a**	 **13**, 69%
8	 **2i**	**1a**	 **14**, 73%
9	 **2j**	**1a**	 **15**, 88%
10	 **2d**	**1a**	 **6** 65%

[a] Reaction conducted with 30 mol % TFA in DCE at 50 C.

(AAA) to furnish enantioenriched 5,6-fused indoline aminals (Scheme 1).[14] However, their synthesis of **16** required high temperatures (170 °C) and proceeded in moderate yield (59%). Inspired by the utility of their methodology, we decided to improve the synthesis of **16**, and its derivatives, by implementing the protocol described in this report.

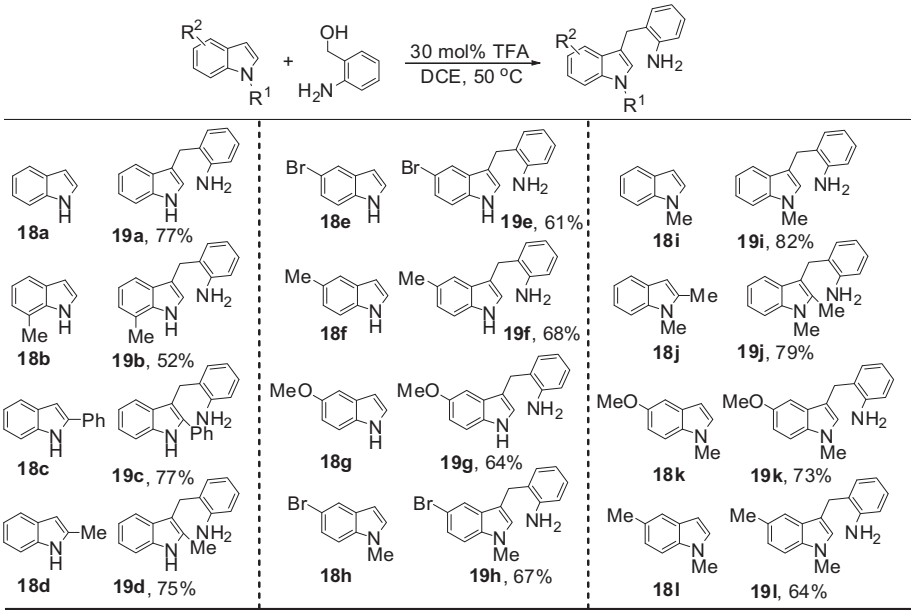


Scheme 1. Palladium-catalyzed asymmetric allylic alkylation (AAA) followed by cyclization.

Once again, the alkylation was efficient across numerous indole derivatives (Table 3). Electron donating and withdrawing substituents were well-tolerated for both *N*–H and *N*-methylated indole starting materials. An especially salient feature of this protocol is that it operates under considerably lower reaction temperatures as compared to what Trost and co-workers reported.[14] There have been previous reports of Brønsted acid-catalyzed alkylation of indoles at C3. However, these studies were restricted to the use of 3° alcohols,[15] doubly benzylic and allylic/propargylic alcohols,[11a,16] or the use of TFA as solvent.[17]

As mentioned already, for entry 5 in Table 1, significant amounts of a by-product resulting from rearrangement were isolated. The identity of this compound was confirmed via ^{1}H NMR and NOE studies to be **23** (Fig. 2). A plausible mechanism for the formation of **23** is alkylation at C3 followed by 1,2-alkyl shift (**2e**→**22**→**23**).[18] Importantly, this does not preclude a concerted pathway (path b) for the formation of **7**. In principle, each of the steps depicted in Fig. 2 is reversible. Protonation of **7** would lead to **24**, which is likely to be in equilibrium with iminium **22**. A 1,2-alkyl shift, as described previously, would lead to **23**.

Table 3
Scope of the alkylation with C3–(H) indole derivatives



3. Discussion

Consistent with what previous groups have proposed, we believe that the reactions illustrated in Tables 2 and 3 proceed via an aza *ortho*-quinone methide intermediate **21** (Fig. 2). This species can be generated through intramolecular hydrogen-bond activation of the alcohol by the adjacent protonated aniline nitrogen. Cyclization can occur either in a stepwise (path a) or concerted (path b) fashion. Attack on **21** by **2e**, followed by ring closure onto the resultant iminium **22** would lead to the desired product **7**. Alternatively, cycloaddition between **21** and indole **2e**, followed by proton transfer would lead directly to **7** via a concerted pathway (path b).

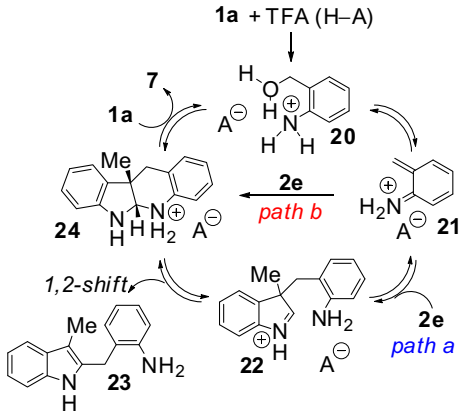


Fig. 2. Proposed mechanism.

Because the indole substrates in Table 3 are unsubstituted at C3, re-aromatization of the corresponding iminium via deprotonation can occur to furnish the observed products.

4. Conclusion

In summary, we have described an efficient method for the direct annulation or alkylation reactions between various indoles and 2-aminobenzyl alcohols. Protection of the aniline nitrogen or pre-activation of the alcohol is not necessary. These reactions proceed with only mild heating and the use of base is not required. Broad substrate compatibility has been demonstrated. We anticipate that this method will find utility in the synthesis of 5,6-fused indoline aminals, an unusual skeletal structure found among the communesin family of alkaloids.

5. Experimental section

5.1. General

^{1}H NMR spectra were recorded on a Varian Unity Plus 300 (300 MHz) or 500 (500 MHz) FT spectrometer at ambient temperature. ^{13}C NMR spectra were recorded on a Varian Unity Plus 500 (125 MHz) FT spectrometer at ambient temperature. IR spectra were recorded on a Perkin–Elmer FT-IR 1600 Series spectrophotometer, ν_{max} (cm^{-1}) are partially reported. Analytical thin layer chromatography (TLC) was performed on SILICYCLE pre-coated TLC plates (silica gel 60 F-254, 0.25 mm). Flash column chromatography was performed on silica gel 60 (SILICYCLE 230–400 mesh). Visualization was

accomplished with UV light and/or with ceric ammonium molybdate (CAM) or $KMnO_4$ staining solutions. High resolution mass spectra were acquired from the Mass Spectrometry Laboratory of the University of Illinois (Urbana–Champaign, IL). Elemental Analyses were acquired from the QTI Analytical Research and Development Laboratory. All reactions were carried out in oven-dried glassware with magnetic stirring under nitrogen atmosphere unless otherwise noted. All solvents were freshly distilled. All other reagents and starting materials, unless otherwise noted, were purchased from commercial vendors and used without further purification.

5.1.1. General procedure. To a solution of **1** (0.28 mmol, 0.040 g) and **2** (0.14 mmol, 0.017 g) in DCE (0.41 mL) was added TFA (0.041 mmol, 0.0031 mL) at rt. The resulting solution was stirred at 50 °C overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (5.0 mL) and diluted with EtOAc (5.0 mL). The organic phase was washed with brine (10 mL), and then dried over Na_2SO_4. Solvent was removed using a rotary evaporator, and the residue was purified by silica gel chromatography (EtOAc/pentanes).

*5.1.2. Preparation of **3***. The compound **3** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a white solid in 86% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.10–7.07 (m, 2H), 7.04–7.01 (t, J=7.5 Hz, 1H), 6.97–6.95 (d, J=7.5 Hz, 1H), 6.74–6.71 (t, J=7.0 Hz, 1H), 6.67–6.62 (m, 2H), 6.49–6.48 (d, J=8.0 Hz, 1H), 4.69 (br s, 1H), 4.15 (s, 1H), 2.75 (s, 3H), 2.74–2.50 (m, 2H), 1.22 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 149.6, 141.8, 137.2, 129.0, 127.8, 127.2, 121.9, 121.5, 118.5, 118.0, 113.6, 107.7, 83.9, 39.8, 37.6, 32.0, 22.1; IR (film, cm^{-1}) 3402, 2956, 1608, 1482, 1371, 1287, 1098, 1080, 1018, 913, 796, 746. Elemental analysis: calculated for $C_{17}H_{18}N_2$ (250.34): C, 81.56; H, 7.25; N, 11.19; found: C, 81.31; H, 7.32; N, 11.06%.

*5.1.3. Preparation of **6***. The compound **6** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a white solid in 65% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.34–7.25 (m, 5H), 7.08–7.06 (m, 1H), 7.01–6.94 (m, 3H), 6.68–6.65 (m, 2H), 6.50–6.48 (d, J=8.0 Hz, 1H), 6.31–6.30 (d, J=7.5 Hz, 1H), 4.54–4.53 (br s, 1H), 4.52–4.25 (m, 2H), 4.46 (br s, 1H), 2.89–2.58 (m, 2H), 1.29 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 149.2, 142.3, 139.1, 136.6, 128.7, 128.7, 127.7, 127.7, 127.2, 127.1, 123.3, 121.8, 118.5, 118.1, 114.2, 107.2, 82.5, 49.6, 42.0, 38.0, 23.9; IR (film, cm^{-1}) 3403, 3024, 2924, 1607, 1494, 1359, 1285, 1126, 1101, 1026, 744, 698. Elemental analysis: calculated for $C_{23}H_{22}N_2$ (326.43): C, 84.63; H, 6.79; N, 8.58; found: C, 84.20; H, 6.97; N, 8.42%.

*5.1.4. Preparation of **8***. The compound **8** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a pale yellow solid in 71% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.10–7.07 (m, 2H), 6.94–6.93 (d, J=7.5 Hz, 1H), 6.85–6.84 (d, J=7.5 Hz, 1H), 6.75–6.71 (m, 1H), 6.61–6.58 (m, 1H), 6.50–6.48 (m, 1H), 4.52 (br s, 1H), 4.23 (s, 1H), 2.79 (s, 3H), 2.77–2.53 (m, 2H), 2.21 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 149.6, 139.7, 137.2, 128.4, 127.8, 126.9, 121.5, 120.8, 118.5, 117.6, 107.6, 84.0, 39.9, 37.8, 31.9, 22.3, 17.0; IR (film, cm^{-1}) 3428, 3048, 2956, 2923, 1603, 1501, 1479, 1418, 1372, 1296, 1244, 1110, 1085, 1019, 954, 919, 796, 743, 710. Exact mass calcd for [M+H]$^+$ requires m/z 265.1705; found 265.1703 (ES$^+$).

*5.1.5. Preparation of **9***. The compound **9** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a white solid in 96% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.09–7.05 (m, 2H), 6.84–6.83 (d, J=8.0 Hz, 1H), 6.78 (s, 1H), 6.73–6.69 (m, 1H), 6.54–6.53 (d, J=8.0 Hz, 1H), 6.47–6.45 (m, 1H), 4.57 (br s, 1H), 4.15 (s, 1H), 2.74 (s, 3H), 2.71–2.46 (m, 2H), 2.20 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 149.7, 139.4, 137.2, 129.5, 127.8, 127.6, 127.2, 122.1, 121.5, 118.3, 133.6, 107.5, 84.1, 40.3, 37.8, 31.9, 22.6, 20.4; IR (film, cm^{-1}) 3401, 2956, 1609, 1511, 1482, 1419, 1372, 1293, 1262, 1157, 1099, 1081, 1018, 951, 909, 799, 747, 711. Elemental analysis: calculated for $C_{18}H_{20}N_2$ (264.36): C, 81.78; H, 7.63; N, 10.60; found: C, 81.35; H, 7.89; N, 10.45%.

*5.1.6. Preparation of **10***. The compound **10** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a pale yellow solid in 64% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.11–7.07 (m, 2H), 7.00–6.98 (m, 1H), 6.95 (s, 1H), 6.75–6.72 (t, J=7.5 Hz, 1H), 6.59–6.57 (d, J=8.0 Hz, 1H), 6.50–6.48 (d, J=8.0 Hz, 1H), 4.73 (br s, 1H), 4.14 (s, 1H), 2.74 (s, 3H), 2.72–2.46 (m, 2H), 1.21 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 149.4, 140.5, 136.7, 128.6, 128.0, 126.9, 123.6, 122.2, 121.6, 118.7, 114.7, 107.9, 83.7, 39.5, 37.4, 32.0, 21.9; IR (film, cm^{-1}) 3409, 2957, 1606, 1497, 1419, 1372, 1289, 1078, 1018, 918, 796, 749. Exact mass calcd for [M+H]$^+$ requires m/z 285.1159; found 285.1162 (ES$^+$).

*5.1.7. Preparation of **11***. The compound **11** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a pale yellow oil in 62% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.04–6.97 (m, 3H), 6.92–6.90 (d, J=7.5 Hz, 1H), 6.67–6.60 (m, 3H), 6.39–6.37 (d, J=8.0 Hz, 1H), 4.64 (br s, 1H), 4.42 (s, 1H), 2.80–2.60 (m, 2H), 2.77 (s, 3H), 1.70–1.55 (m, 2H), 1.35–1.19 (m, 2H), 0.87–0.84 (t, J=7.5 Hz, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 150.4, 142.7, 135.0, 128.6, 127.7, 127.0, 123.6, 122.2, 118.5, 117.9, 114.0, 106.8, 81.0, 46.1, 39.3, 37.6, 31.5, 18.0, 14.7; IR (film, cm^{-1}) 3405, 2955, 1607, 1498, 1370, 1287, 1095, 1022, 939, 800, 745. Exact mass calcd for [M+H]$^+$ requires m/z 279.1861; found 279.1860 (ES$^+$).

*5.1.8. Preparation of **12***. The compound **12** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a pale yellow solid in 50% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.21–7.14 (m, 3H), 7.05–6.99 (m, 5H), 6.97–6.95 (d, J=7.0 Hz, 1H), 6.69–6.62 (m, 3H), 6.36–6.35 (d, J=7.5 Hz, 1H), 4.61 (br s, 1H), 4.30 (s, 1H), 3.16–2.75 (m, 4H), 2.64 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 150.3, 142.6, 137.9, 134.1, 130.9, 128.9, 128.0, 127.9, 127.2, 126.5, 122.8, 122.8, 118.4, 117.9, 114.0, 107.3, 80.1, 46.6, 42.0, 37.1, 31.4; IR (film, cm^{-1}) 3408, 3025, 2922, 1608, 1497, 1371, 1288, 1117, 1095, 1025, 951, 800, 748, 702. Exact mass calcd for [M+H]$^+$ requires m/z 327.1861; found 327.1862 (ES$^+$).

*5.1.9. Preparation of **13***. The compound **13** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a white solid in 69% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.08–7.00 (m, 3H), 6.94–6.93 (d, J=7.0 Hz, 1H), 6.70–6.62 (m, 3H), 6.42–6.40 (d, J=7.5 Hz, 1H), 5.79–5.71 (m, 1H), 5.07–5.03 (m, 2H), 4.64 (br s, 1H), 4.41 (s, 1H), 2.82–2.67 (m, 2H), 2.76 (s, 3H), 2.55–2.51 (m, 1H), 2.34–2.30 (m, 1H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 150.3, 142.6, 134.7, 134.5, 128.7, 127.9, 127.1, 123.0, 122.4, 118.5, 118.1, 117.9, 114.1, 107.0, 80.7, 45.4, 41.0, 37.0, 31.6; IR (film, cm^{-1}) 3403, 3052, 2851, 1608, 1498, 1370, 1287, 1191, 1156, 1115, 1095, 1022, 917, 844, 799, 747. Exact mass calcd for [M+H]$^+$ requires m/z 277.1705; found 277.1709 (ES$^+$).

*5.1.10. Preparation of **14***. The compound **14** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a white solid in 73% yield that was

homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.18–7.15 (m, 2H), 7.04–7.01 (t, J=8.0 Hz, 1H), 6.97–6.95 (d, J=7.0 Hz, 1H), 6.68–6.62 (m, 2H), 6.35–6.34 (d, J=8.0 Hz, 1H), 4.67 (br s, 1H), 4.19–4.18 (d, J=4.5 Hz, 1H), 2.73 (s, 3H), 2.73–2.49 (m, 2H), 1.21 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 148.7, 141.5, 139.4, 130.4, 129.1, 127.3, 124.8, 121.7, 118.3, 113.8, 109.8, 109.0, 83.7, 40.3, 37.5, 31.7, 22.2; IR (film, cm^{-1}) 3406, 3055, 2956, 2925, 2856, 1606, 1496, 1475, 1454, 1416, 1358, 1286, 1260, 1232, 1188, 1125, 1086, 976, 952, 913, 865, 808, 749, 711, 655. Elemental analysis: calculated for $C_{17}H_{17}BrN_2$ (329.23): C, 62.02; H, 5.20; N, 8.51; found: C, 61.82; H, 5.30; N, 8.28%.

*5.1.11. Preparation of **15**.* The compound **15** was prepared following the general procedure and isolated by silica gel column chromatography (5% EtOAc/pentanes) as a clear colorless oil in 88% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.00–6.85 (m, 4H), 6.67–6.61 (m, 2H), 6.52–6.49 (m, 1H), 6.09–6.07 (d, J=7.5 Hz, 1H), 4.65 (br s, 1H), 3.05–2.78 (m, 2H), 2.74 (s, 3H), 2.15–2.04 (m, 3H), 1.95–1.90 (m, 1H), 1.84–1.77 (m, 1H), 1.57–1.48 (m, 1H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 151.4, 144.9, 134.7, 127.9, 127.8, 127.7, 127.1, 122.4, 119.9, 116.4, 115.5, 103.5, 92.1, 59.5, 42.9, 39.4, 38.9, 27.2, 24.1; IR (film, cm^{-1}) 3357, 3048, 2949, 2866, 1606, 1496, 1423, 1376, 1309, 1256, 1190, 1109, 1021, 952, 738, 709. Elemental analysis: calculated for $C_{19}H_{20}N_2$ (276.38): C, 82.57; H, 7.29; N, 10.14; found: C, 82.57; H, 7.47; N, 9.88%.

*5.1.12. Preparation of **19a**.* The compound **19a** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a pale yellow solid in 77% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (br s, 1H), 7.61–7.59 (d, J=7.5 Hz, 1H), 7.39–7.37 (m, 1H), 7.27–7.18 (m, 2H), 7.14–7.09 (m, 2H), 6.86 (s, 1H), 6.80–6.77 (t, J=7.5 Hz, 1H), 6.71–6.69 (d, J=8.0 Hz, 1H), 4.03 (s, 2H), 3.65 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.0, 136.8, 130.7, 127.6, 127.6, 125.5, 122.5, 122.5, 119.7, 119.3, 119.0, 116.1, 114.0, 111.4, 28.4; IR (film, cm^{-1}) 3408, 1618, 1493, 1455, 1338, 1226, 1091, 744. Exact mass calcd for $[M+H]^+$ requires m/z 223.1235; found 223.1241 (ES^+).

*5.1.13. Preparation of **19b**.* The compound **19b** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a pale yellow solid in 52% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (br s, 1H), 7.46–7.44 (m, 1H), 7.19–7.17 (m, 1H), 7.12–7.08 (m, 1H), 7.06–7.02 (m, 2H), 6.87 (s, 1H), 6.79–6.76 (m, 1H), 6.70–6.69 (m, 1H), 4.02 (s, 2H), 3.67 (br s, 2H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.1, 136.4, 130.7, 127.6, 127.2, 125.6, 123.0, 122.2, 120.6, 120.0, 119.0, 117.1, 116.0, 114.5, 28.6, 16.8; IR (film, cm^{-1}) 3387, 3179, 1619, 1492, 1452, 1253, 1230, 1114, 801, 767, 746. Exact mass calcd for $[M+H]^+$ requires m/z 237.1392; found 237.1398 (ES^+).

*5.1.14. Preparation of **19c**.* The compound **19c** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a pale yellow solid in 77% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (br s, 1H), 7.53–7.51 (m, 2H), 7.46–7.35 (m, 5H), 7.24–7.21 (m, 1H), 7.09–7.05 (m, 2H), 7.02–7.00 (d, J=7.5 Hz, 1H), 6.72–6.67 (m, 2H), 4.08 (s, 2H), 3.67 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.6, 136.3, 135.8, 132.9, 129.7, 129.5, 129.2, 128.1, 127.2, 125.4, 122.7, 120.1, 120.0, 119.0, 115.6, 111.0, 109.8, 27.0; IR (film, cm^{-1}) 3399, 3056, 1620, 1492, 1455, 1342, 1306, 1156, 908, 742, 699. Exact mass calcd for $[M+H]^+$ requires m/z 299.1548; found 299.1552 (ES^+).

*5.1.15. Preparation of **19d**.* The compound **19d** was prepared following the general procedure and isolated by silica gel column chromatography (25% EtOAc/pentanes) as a pale yellow solid in 75% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.83 (br s, 1H), 7.39–7.37 (m, 1H), 7.30–7.27 (m, 1H), 7.14–7.11 (m, 1H), 7.08–7.01 (m, 3H), 6.74–6.71 (m, 1H), 6.68–6.66 (m, 1H), 3.95 (s, 2H), 3.67 (br s, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.0, 135.5, 132.3, 130.0, 129.1, 127.3, 125.6, 121.4, 119.6, 118.8, 118.6, 115.8, 110.4, 108.3, 27.2, 12.1; IR (film, cm^{-1}) 3398, 1619, 1492, 1458, 1299, 908, 744. Exact mass calcd for $[M+H]^+$ requires m/z 237.1392; found 237.1395 (ES^+).

*5.1.16. Preparation of **19e**.* The compound **19e** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a light brown solid in 61% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.02 (br s, 1H), 7.71 (s, 1H), 7.29–7.26 (m, 1H), 7.22–7.21 (m, 1H), 7.13–7.09 (m, 2H), 6.82 (s, 1H), 6.79–6.76 (m, 1H), 6.71–6.70 (d, J=7.5 Hz, 1H), 3.94 (s, 2H), 3.61 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.9, 135.4, 130.6, 129.4, 127.8, 125.3, 125.0, 123.8, 121.9, 119.1, 116.1, 113.8, 113.0, 112.9, 28.1; IR (film, cm^{-1}) 3411, 1618, 1493, 1457, 1224, 1093, 880, 794, 754. Exact mass calcd for $[M+H]^+$ requires m/z 301.0340; found 301.0345 (ES^+).

*5.1.17. Preparation of **19f**.* The compound **19f** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a pale yellow solid in 68% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (br s, 1H), 7.39 (s, 1H), 7.28–7.26 (d, J=8.0 Hz, 1H), 7.17–7.16 (m, 1H), 7.12–7.09 (m, 1H), 7.06–7.04 (m, 1H), 6.81 (s, 1H), 6.79–6.76 (m, 1H), 6.71–6.69 (m, 1H), 3.99 (s, 2H), 3.65 (br s, 2H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.0, 135.1, 130.6, 129.0, 127.9, 127.6, 125.6, 124.1, 122.7, 118.9, 118.9, 116.0, 113.5, 111.0, 28.3, 21.8; IR (film, cm^{-1}) 3407, 2916, 1618, 1492, 1456, 1226, 1090, 795, 753. Exact mass calcd for $[M+H]^+$ requires m/z 237.1392; found 237.1393 (ES^+).

*5.1.18. Preparation of **19g**.* The compound **19g** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a pale yellow solid in 64% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.89 (br s, 1H), 7.27–7.25 (m, 1H), 7.20–7.18 (m, 1H), 7.13–7.09 (m, 1H), 7.01 (d, J=2.5 Hz, 1H), 6.89–6.87 (m, 1H), 6.84 (s, 1H), 6.80–6.77 (m, 1H), 6.71–6.70 (m, 1H), 3.99 (s, 2H), 3.83 (s, 3H), 3.65 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.2, 145.1, 131.9, 130.7, 128.0, 127.7, 125.5, 123.3, 119.0, 116.1, 113.6, 112.7, 112.1, 101.0, 56.1, 28.5; IR (film, cm^{-1}) 3408, 2935, 2829, 1620, 1583, 1486, 1454, 1278, 1213, 1170, 1048, 923, 833, 798, 754. Exact mass calcd for $[M+H]^+$ requires m/z 253.1341; found 253.1343 (ES^+).

*5.1.19. Preparation of **19h**.* The compound **19h** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as an orange oil in 67% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 (d, J=2.0 Hz, 1H), 7.32–7.30 (m, 1H), 7.18–7.10 (m, 3H), 6.80–6.77 (m, 1H), 6.72–6.71 (m, 1H), 6.68 (s, 1H), 3.94 (s, 2H), 3.70 (s, 3H), 3.62 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.9, 136.2, 130.6, 129.7, 128.4, 127.8, 125.2, 124.8, 121.9, 119.0, 116.1, 112.6, 112.1, 111.0, 33.1, 28.0; IR (film, cm^{-1}) 3443, 3368, 3022, 2917, 2243, 1619, 1583, 1493, 1475, 1457, 1422, 1374, 1288, 1202, 1142, 1044, 908, 864, 832, 812, 792, 752, 732. Exact mass calcd for $[M+H]^+$ requires m/z 315.0497; found 315.0491 (ES^+).

*5.1.20. Preparation of **19i**.* The compound **19i** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a pale yellow solid in 82%

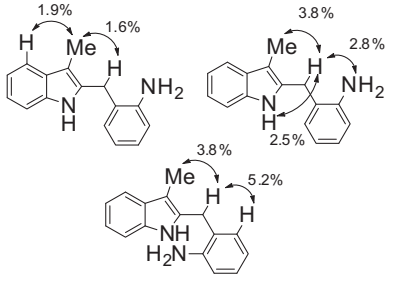
yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.61–7.60 (d, J=7.5 Hz, 1H), 7.32–7.31 (m, 1H), 7.27–7.24 (m, 1H), 7.20–7.18 (m, 1H), 7.13–7.10 (m, 2H), 6.80–6.77 (m, 1H), 6.71–6.70 (m, 2H), 4.02 (s, 2H), 3.72 (s, 3H), 3.66 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.1, 137.5, 130.7, 128.0, 127.6, 127.2, 125.7, 122.0, 119.4, 119.1, 118.9, 116.0, 112.3, 109.5, 32.9, 28.3; IR (film, cm^{-1}) 3440, 3363, 3051, 2924, 1618, 1583, 1549, 1493, 1424, 1372, 1327, 1251, 1198, 1154, 1130, 1058, 1011, 909, 741. Exact mass calcd for $[M+H]^+$ requires m/z 237.1392; found 237.1393 (ES^+).

*5.1.21. Preparation of **19j**.* The compound **19j** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a pale yellow solid in 79% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40–7.39 (d, J=8.0 Hz, 1H), 7.29–7.28 (m, 1H), 7.18–7.15 (m, 1H), 7.07–7.01 (m, 3H), 6.72–6.69 (m, 1H), 6.67–6.65 (m, 1H), 3.97 (s, 2H), 3.70 (s, 3H), 3.67 (br s, 2H), 2.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.0, 136.9, 134.2, 130.0, 128.1, 127.2, 125.9, 120.9, 119.2, 118.8, 118.6, 115.7, 108.8, 107.5, 29.8, 27.4, 10.6; IR (film, cm^{-1}) 3439, 3365, 3048, 2910, 1619, 1582, 1492, 1472, 1456, 1409, 1367, 1332, 1289, 1249, 1183, 1153, 1055, 1016, 922, 839, 741. Exact mass calcd for $[M+H]^+$ requires m/z 251.1548; found 251.1556 (ES^+).

*5.1.22. Preparation of **19k**.* The compound **19k** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a pale yellow solid in 73% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.21–7.19 (m, 2H), 7.13–7.10 (m, 1H), 7.02 (d, J=2.5 Hz, 1H), 6.92–6.90 (m, 1H), 6.81–6.77 (m, 1H), 6.72–6.70 (m, 1H), 6.67 (s, 1H), 3.98 (s, 2H), 3.84 (s, 3H), 3.69 (s, 3H), 3.64 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.0, 145.1, 132.9, 130.6, 128.2, 127.8, 127.6, 125.7, 118.9, 116.0, 112.2, 111.6, 110.3, 101.1, 56.1, 33.1, 28.4; IR (film, cm^{-1}) 3440, 3365, 2996, 2938, 2830, 1620, 1580, 1491, 1454, 1423, 1377, 1302, 1257, 1222, 1172, 1136, 1057, 1034, 899, 836, 796, 752. Exact mass calcd for $[M+H]^+$ requires m/z 267.1497; found 267.1500 (ES^+).

*5.1.23. Preparation of **19l**.* The compound **19l** was prepared following the general procedure and isolated by silica gel column chromatography (10% EtOAc/pentanes) as a pale yellow solid in 64% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39 (s, 1H), 7.21–7.17 (m, 2H), 7.13–7.06 (m, 2H), 6.80–6.76 (m, 1H), 6.71–6.69 (m, 1H), 6.64 (s, 1H), 3.98 (s, 2H), 3.69 (s, 3H), 3.64 (br s, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 145.0, 135.9, 130.6, 128.4, 128.2, 127.5, 127.3, 125.8, 123.6, 118.9, 118.9, 116.0, 111.7, 109.2, 32.9, 28.2, 21.7; IR (film, cm^{-1}) 3362, 3021, 2914, 1619, 1492, 1456, 1376, 1304, 1147, 1054, 791, 750. Exact mass calcd for $[M+H]^+$ requires m/z 251.1548; found 251.1548 (ES^+).

*5.1.24. Characterization of **23**.* The compound **23** was isolated from the reaction depicted in Table 1 entry 5. Purification was performed by silica gel column chromatography (10% EtOAc/pentanes). The product was isolated as a white solid in 16% yield that was homogeneous as judged by ^{1}H NMR spectroscopy. ^{1}H NMR (CD_2Cl_2, 500 MHz) δ 7.96 (br s, 1H), 7.49–7.48 (m, 1H), 7.19–7.17 (m, 1H), 7.11–7.10 (d, J=8.0 Hz, 2H), 7.08–7.02 (m, 2H), 6.78–6.74 (td, J_1=7.5 Hz, J_2=1.0 Hz, 1H), 6.71–6.69 (d, J=7.5 Hz, 1H), 4.00 (s, 2H), 3.67 (br s, 2H), 2.34 (s, 3H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 145.2, 135.7, 132.3, 130.5, 129.4, 128.2, 123.6, 121.4, 119.1, 119.1, 118.3, 116.3, 110.5, 107.6, 29.1, 8.4; IR (film, cm^{-1}) 3405, 3055, 2921, 1620, 1583, 1495, 1458, 1384, 1332, 1241, 1157, 1008, 744.



Acknowledgements

The authors are grateful to Dartmouth College and the Walter and Constance Burke Foundation for their generous financial support.

References and notes

1. Robertson, F.; Wu, J. *Org. Lett.* **2010**, *12*, 2668.
2. Han, X.; Zhang, Y.; Wu, J. *J. Am. Chem. Soc.* **2010**, *132*, 4104.
3. Han, X.; Wu, J. *Org. Lett.* **2010**, *12*, 5780.
4. (a) Numata, A.; Takahashi, C.; Ito, Y.; Takada, T.; Kawai, K.; Usami, Y.; Matsumura, E.; Imachi, M.; Ito, T.; Hasegawa, T. *Tetrahedron Lett.* **1993**, *34*, 2355; (b) Ratnayake, A. S.; Yoshida, W. Y.; Mooberry, S. L.; Hemscheidt, T. K. *J. Org. Chem.* **2001**, *66*, 8717; (c) Nielsen, K. F.; Smedsgaard, J. *J. Chromatogr., A* **2003**, *102*, 111; (d) Anderson, B.; Smedsgaard, J.; Frisvad, J. C. *J. Agric. Food Chem.* **2004**, *52*, 2421; (e) Dalsgaard, P. W.; Blunt, J. W.; Munro, M. H. G.; Frisvad, J. C.; Christophersen, C. *J. Nat. Prod.* **2005**, *68*, 258; (f) Siengalewicz, P.; Gaich, T.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 8170.
5. (a) Jadulco, R.; Edrada, R. A.; Ebel, R.; Berg, A.; Schaumann, K.; Wray, B.; Steube, K.; Proksch, P. *J. Nat. Prod.* **2004**, *67*, 78; (b) Hayashi, H.; Matsumoto, H.; Akiyama, K. *Biosci. Biotechnol. Biochem.* **2004**, *68*, 753.
6. (a) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169; (b) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203; (c) May, J. A.; Stoltz, B. *Tetrahedron* **2006**, *62*, 5262; (d) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995; (e) George, J. H.; Adlington, R. M. *Synlett* **2008**, 2093.
7. (a) Yang, J.; Wu, H.; Shen, L.; Qin, Y. *J. Am. Chem. Soc.* **2007**, *129*, 13794; (b) Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2000; (c) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226.
8. Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317.
9. Steinhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928.
10. For leading references see: (a) Nishimoto, Y.; Onishi, Y.; Yasuda, M.; Baba, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9131; (b) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 793.
11. For leading references see: (a) Sanz, R.; Martínez, A.; Miguel, D.; Álvarez-Gutiérrez, J. M.; Rodríguez, F. *Adv. Synth. Catal.* **2006**, *348*, 1841; (b) Qiao, Z.; Shafiq, Z.; Liu, L.; Yu, Z.-B.; Zheng, Q.-Y.; Wang, D.; Chen, Y.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7294.
12. (a) Cozzi, P. G.; Zoli, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4162; (b) Cozzi, P. G.; Zoli, L. *Green. Chem.* **2007**, *9*, 1292.
13. (a) Olah, G. A.; Farooq, O.; Farnia, S. M. F.; Olah, J. A. *J. Am. Chem. Soc.* **1988**, *110*, 2560; (b) Prakash, G. K. S.; Mathew, T.; Panja, C.; Alconcel, S.; Vaghoo, H.; Do, C.; Olah, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 3703; (c) Prakash, G. K. S.; Mathew, T.; Panja, C.; Vaghoo, H.; Venkataraman, K.; Olah, G. A. *Org. Lett.* **2007**, *9*, 179; (d) Yan, P.; Batamack, P.; Prakash, G. K. S.; Olah, G. A. *Catal. Lett.* **2005**, *103*, 165; (e) Parakash, G. K. S.; Yan, P.; Török, B.; Bucsi, I.; Tanaka, M.; Olah, G. A. *Catal. Lett.* **2003**, *85*, 1.
14. Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314.
15. (a) Bell, M. G.; Gernert, D. L.; Grese, T. A.; Belvo, M. D.; Borromeo, P. S.; Kelley, S. A.; Kennedy, J. H.; Kolis, S. P.; Lander, P. A.; Richey, R; Scott Sharp, V.; Stephenson, G. A.; Williams, J. D.; Hannah, Yu; Zimmerman, K. M.; Steinberg, M. I.; Jadhav, P. K. *J. Med. Chem.* **2007**, *50*, 6443; (b) Sanz, R.; Miguel, D.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Synlett* **2008**, 975.
16. (a) Sanz, R.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Eur. J. Org. Chem.* **2006**, 1383; (b) Bras, J. L.; Muzart, J. *Tetrahedron* **2007**, *63*, 7942.
17. Chung, J. Y. L.; Mancheno, D.; Dormer, P. G.; Variankaval, N.; Ball, R. G.; Tsou, N. N. *Org. Lett.* **2008**, *10*, 3037.
18. (a) Iyer, R.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 2* **1973**, 878; (b) Jackson, A. H.; Smith, P. *J. Chem. Soc., Chem. Commun.* **1967**, 265; (c) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119; (d) Williams, J. R.; Unger, L. R. *J. Chem. Soc., Chem. Commun.* **1970**, 1605.