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Indazoles: Regioselective Protection and Subsequent Amine Coupling Reactions

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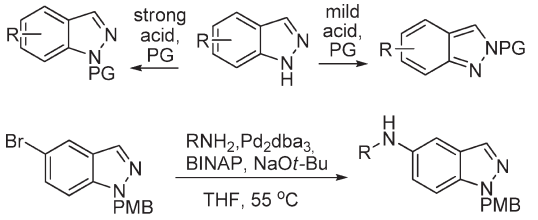
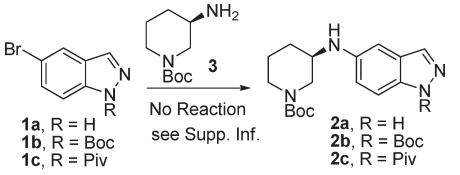


Indazoles are unselectively protected under strongly basic conditions to give a mixture at N-1 and N-2. Under mildly acidic conditions, regioselective protection at N-2 takes place. Thermodynamic conditions lead to regioselective protection at N-1. This trend applies to various substituted indazoles. Protected 5-bromoindazoles participate in Buchwald reactions with a range of amines to generate novel derivatives.

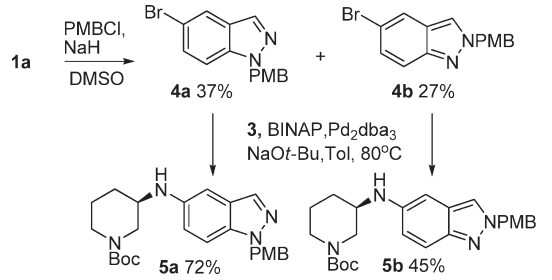
Medicinal chemists have benefited greatly from the recent availability of chiral amine fragments and the discovery of novel reactions[1−3] to integrate them into molecules of interest. Indazoles are a highly utilized pharmacophore found in many drugs[4] and are a good example of a building block that might be easily manipulated with this synthetic approach. Recently, we were interested in obtaining **2a**, **2b**, or **2c** in multigram quantities from the easily obtained 5-bromo-1*H*-indazole[5] (**1a**, Scheme 1). This paper describes our results for the selective protection of indazoles and the scope and behavior of these substrates in their subsequent Buchwald coupling reactions.

Initial attempts to couple *N*-Boc-3-aminopiperidine (**3**) or *N*-Boc-3-aminopyrrolidine with **1** using directly applicable

SCHEME 1. Initial Attempts Using Standard Buchwald Conditions



SCHEME 2. Base/PMB Protection and Buchwald Couplings



Buchwald coupling conditions[1−3] did not yield any desired product (conditions are listed in the Supporting Information). Hypothesizing that the free NH of the indazole was proving problematic, we examined the reactivity of the Boc- (**1b**) and Piv-protected (**1c**) versions of **1a**. Unfortunately, these reaction conditions led to complete deprotection[6] and no coupling related products.

The requirement for a less base labile protecting group under elevated temperatures led us to investigate PMB due to its subsequent ease of removal. Introduction of the PMB under strongly basic conditions led to a mixture of regioisomers at N-1 (**4a**) and N-2 (**4b**) (Scheme 2). Deprotonation of indazoles is known to give a delocalized anion[7] that is nonselectively trapped by electrophiles. In any case, we were pleased to find that both **4a** and **4b** gave the desired product under standard Buchwald conditions[1] (Pd_2dba_3, BINAP, NaO*t*-Bu, toluene, 80 °C), though under these conditions the 1-PMB isomer **4a** gave higher conversion and better yield.

While this sequence was serviceable to supply small amounts of the desired coupling products, it was found to be unacceptable on a larger scale. Though **4a** and **4b** are each crystalline solids, we were unable to successfully purify either by recrystallization. Chromatography was also found to be an inadequate solution on scale. What we required was a regioselective protection with a group stable to base and elevated temperature. Alonso et al. have reported THP protection of indazoles under strongly acidic conditions.[8] We decided to explore their findings further (Scheme 3).

Introduction of a THP group under mildly acidic conditions led to a single product (**6b**) after 5 h (Scheme 3). A subsequent reaction provided a mixture of **6a** and **6b** (3:1)

(1) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
(2) Harris, M. C.; Huang, X.; Buchwald, S. *Org. Lett.* **2002**, *4*, 2885.
(3) Ericsson, A. M.; Burchat, A.; Frank, K., E.; Calderwood, D. J.; Abbott, L. K.; Argiriadi, M., A.; Borhani, D. W.; Cusack, K. P.; Dixon, R. W.; Gordon, T. D.; Mullen, K. D.; Talanian, R. V.; Wu, X.; Zhang, X.; Wang, Lu. X.; Li, B.; Barberis, C. E.; Wishart, N. Indazole Compounds. PCT Int. Appl. WO 2007/117465, April 2, **2007**.
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(5) Lukin, K.; Hsu, M. C.; Fernando, D.; Leanna, M. R. *J. Org. Chem.* **2006**, *71*, 8166.
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(7) Luo, G.; Chen, L.; Dubowchik, G. *J. Org. Chem.* **2006**, *71*, 5392.
(8) Alonso, G.; Diez, C.; Garcia-Munoz, G.; De las Heras, F. G.; Navarro, P. *J. Carbohydr. Nucleosides Nucleotides* **1976**, *3*, 157.

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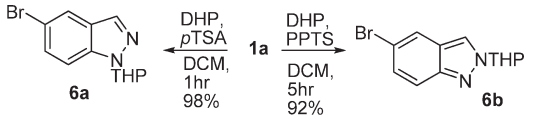
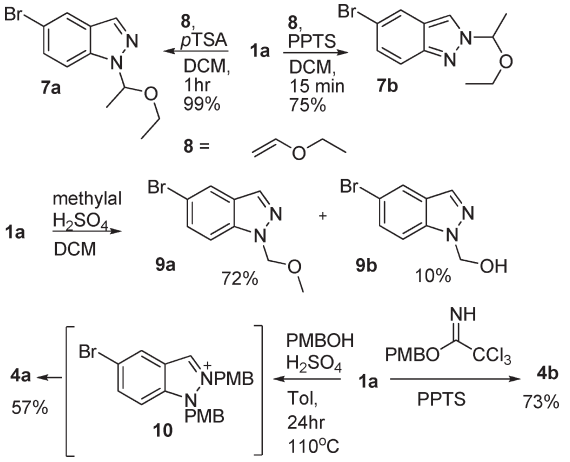
SCHEME 3. Regioselective THP Protection



SCHEME 4. Acidic Protections

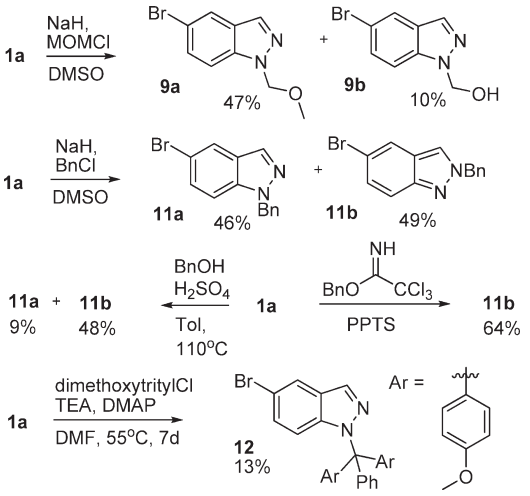


after 18 h. These data suggested that acid-catalyzed protection of indazoles at N-2 was favored kinetically and that the N-1 regioisomer was the thermodynamic product. Reports by Cheung[9] and Luo[7] suggest the N-2 lone pair is more kinetically accessible than the N-1 lone pair for neutral indazoles. The 1*H* tautomer of indazoles has been shown by Catalán[10] to be more stable than the 2*H* tautomer. Therefore, with extended reaction time **6b** should convert slowly to the more stable **6a**. Use of more forcing conditions (i.e., employing a stronger acid like *p*-TSA) allowed efficient, rapid access to thermodynamic product **6a** (98%).

We decided to pursue other protections (Scheme 4) under acidic conditions. Either PMB regioisomer can be selectively obtained under acidic conditions. Trichloroacetimidate[11] conditions with mild acid PPTS provide **4b**, while forcing conditions using *p*-methoxybenzyl alcohol and catalytic H_2SO_4 give **4a** in high selectivity. By HPLC, the reaction clearly forms **4b** first, which slowly converts to **4a**, presumably through some transient dialkylated intermediate such as **10**. The harsh conditions do cause significant decomposition byproducts which are easily separated by chromatography, in direct contrast to the difficult separation of mixtures of **4a** and **4b** obtained under basic conditions.

Basic protections of indazoles remained nonselective in our hands (Scheme 5). Alkali MOM protection gave a similar distribution of products to its acidic counterpart, albeit with a lower yield of **9a** (47% vs 72%). Use of benzyl chloride/NaH unsurprisingly gave a mixture of **11a** and **11b**, and the mildly acidic PPTS conditions gave the expected **11b**. Interestingly, equilibration of **11b** to **11a** is possible, though exceedingly slow, with the reaction being halted after 1 week

SCHEME 5. Alternative Protection Strategies



at 110 °C. Curious as to the regioisomeric outcome under more S_N1-like conditions, we mixed **1a**, dimethoxytrityl chloride, triethylamine, and catalytic DMAP in DMF with heating to 55 °C for 1 week and observed very slow albeit very selective (by HPLC) formation of **12**.

Interested in the possible application of this equilibrium to other indazoles, we examined a variety of substituents and subjected them to both acidic and basic conditions. Selectivity does not appear to depend on the electronic nature of the substituent: basic conditions lead to a mixture of products (Table 1), but acidic protections provide good regioselectivity.

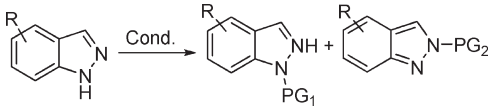
Having established various selective protections of **1**, it was time to optimize the cross-coupling. Bromide **4a** was selected for its crystallinity. Among the byproducts isolated, the two most prominent were aniline **13** and dehalogenated indazole **14** (Scheme 6). The source of **13** was not readily apparent, but it appeared to derive from coupling of the amine with a phenyl ring and was directly dependent on temperature. Only 32% conversion of **4a** to **5a** is achieved in 18 h at 55 °C, and 30% conversion at 30 °C requires 48 h. However, changing the solvent to pyridine drove the reaction to completion within 12 h at 55 °C while reducing the amount of **13** formed. It was later proven that formation of **13** occurred via transfer of a phenyl ring from the BINAP. This was confirmed by using tolyl-BINAP as the ligand and obtaining tolyl-derived byproduct **15** (Scheme 6). We decided to attempt a further scan of literature[1−3] conditions to explore the need for BINAP as the ligand used (Table 2).

Experiments revealed that high-quality sodium *tert*-butoxide was paramount for success. Commercial sodium *tert*-butoxide (from Alfa Aesar) was used without further purification. The base was stored in the desiccator after opening, with a shelf life of 4−6 weeks before rapidly diminishing yields were obtained in Buchwald aminations. We strongly recommend use-testing a given batch of sodium *tert*-butoxide immediately prior to large-scale work.

In an attempt to eliminate this shortcoming, other combinations of bases and solvents were surveyed (Table 2). Unfortunately, neither LiHMDS nor Cs_2CO_3 proved to be a viable base, and the use of pyridine as the solvent/base failed as well (Table 2, entry 6). In a pleasant surprise, THF accelerated the reaction further and minimized byproducts

(9) Cheung, M.; Boloor, A.; Stafford, J. A. *J. Org. Chem.* **2003**, *68*, 4093.
(10) Catalan, J.; del Valle, J. C.; Claramunt, R. M.; Boyer, G.; Laynez, J.; Gomez, J.; Jimenez, P.; Tomas, F.; Elguero, J. *J. Phys. Chem.* **1994**, *98*, 10606.
(11) Patil, V. J. *Tetrahedron Lett.* **1996**, *37*, 1481.
(12) Nakajima, N.; Saito, M.; Ubukata, M. *Tetrahedron* **2002**, *58*, 3561.

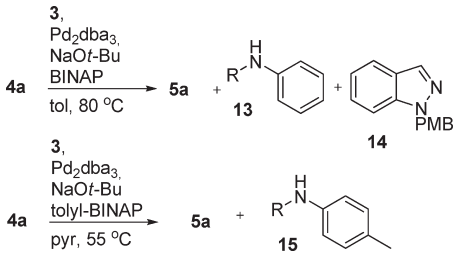
TABLE 1. Scope of Protection Conditions



entry	R =	conditions[a]	PG_1 =	yield (%)	PG_2 =	yield (%)
1	H	base	PMB	55	PMB	25
2	H	S.A. T.	THP	99	THP	
3	H	M.A. T.	THP		THP	91
4	H	S.A. P.	PMB	37	PMB	
5	H	M.A. P.	PMB	5	PMB	50
6	5-NO_2	base	PMB	68	PMB	31
7	5-NO_2	S.A. T.	THP	99	THP	
8	5-NO_2	M.A. T.	THP		THP	75
9	4-F	base	PMB	58	PMB	34
10	4-F	S.A. T.	THP	90	THP	
11	4-F	M.A. T.	THP		THP	83
12	4-F	S.A. P.	PMB	38	PMB	
13	4-F	M.A. P.	PMB	7	PMB	70
14	6-F	base	PMB	47	PMB	26
15	6-F	S.A. T.	THP	86	THP	
16	6-F	M.A. T.	THP		THP	80
17	6-F	S.A. P.	PMB	38	PMB	
18	6-F	M.A. P.	PMB	6	PMB	66
19	4-OMe	base	PMB	56	PMB	42
20	4-OMe	S.A. T.	THP	97	THP	
21	4-OMe	M.A. T.	THP		THP	71
22	6-OMe	Base	PMB	68	PMB	21
23	6-OMe	S.A. T.	THP	97	THP	
24	6-OMe	M.A. T.	THP		THP	80

[a]Base = NaH, PMBCl, DMSO. S.A. T. = 3,4-dihydropyran and *p*-TSA (0.1 equiv). M.A. T. = 3,4-dihydropyran and PPTS (0.1 equiv). S.A. P. = PMBOH and H_2SO_4, toluene 110 °C. M.A. P. = PMBOC(=NH)CF_3 and PPTS (0.1 equiv).[12]

SCHEME 6. Buchwald Coupling Byproducts



(Table 2, entry 2). Choice of a ligand with no phenyl groups eliminated the formation of **13** but led to an increase of other byproducts, notably **14** (Table 2, entry 15). Therefore, we settled on THF, NaO-*t*-Bu, Pd_2dba_3, and BINAP as the optimized system for future Buchwald couplings.

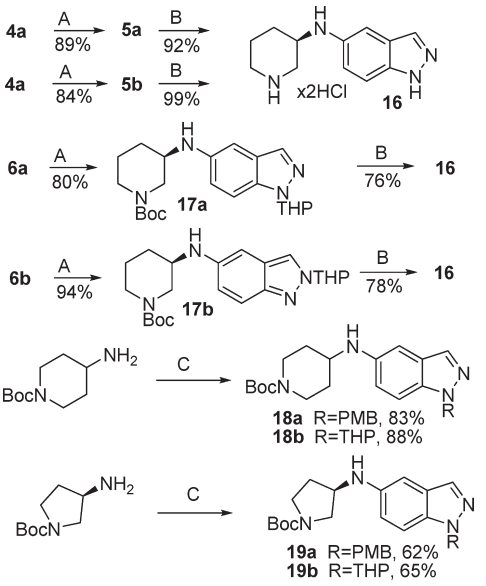
Upon optimization of the coupling conditions, the indazole scope was expanded to include the most efficient protections we had discovered (i.e., **6a**, **6b**, Scheme 7). We were very pleased to find that all analogues assayed (i.e., **4a**, **4b**, **6a**, **6b**) performed comparably well in couplings with **3** and closely related amines. Coupled THP products **17a**, **17b**, **18b**, and **19b** should be formed as mixtures of diastereomers, but we did not see evidence of diastereoisomerism either by HPLC or NMR (see NMR spectra in the Supporting Information). Presumably, this is due to the chiral centers being relatively remote. The choice of protecting group could thus be decided by the desirability of either crystalline intermediates (**4a**, **4b**) or the overall efficiency of the process (**6a**, **6b**).

TABLE 2. Optimizing Buchwald Conditions for the Coupling of 4a and 3

entry	ligand	solvent	base	conv[a] (%)	bypdts[b] (%)
1	BINAP	Pyr	NaO-*t*-Bu	70	40.4
2	BINAP	THF	NaO-*t*-Bu	>99	9.7
3	BINAP	THF	LiHMDS	0	
4	BINAP	THF	Cs_2CO_3	0	
5	BINAP	Pyr	Cs_2CO_3	0	
6	BINAP	Pyr		0	
7[2]	XANTPHOS	dioxane	Cs_2CO_3	0.3	
8	XANTPHOS	Pyr	Cs_2CO_3	0	
9	XANTPHOS	Pyr	NaO-*t*-Bu	80	27.9
10	XANTPHOS	THF	LiHMDS	0	
11	XANTPHOS	THF	NaOt-Bu	38	43.3
12[3]	Buch[c]	THF	LiHMDS	0	
13	Buch[c]	Pyr	Cs_2CO_3	2.5	>100
14	Buch[c]	Pyr	NaO-*t*-Bu	22.5	26.5
15	Buch[c]	THF	NaO-*t*-Bu	>99	11.4

[a]Conversion defined as Pdt/(Pdt + SM) by HPLC area. [b]Bypdts defined as (sum of bypdts)/Pdt by HPLC area. [c]Buch = 2'-(dicyclohexylphosphino)-*N*,*N*-dimethylbiphenyl-2-amine, 100 mg of **4a**, 1.1 equiv of **3**, 0.05 equiv of Pd_2dba_3, 0.12 equiv of ligand, 1 mL of solvent, and 3.00 equiv of base, stirred under N_2 for 8 h at 55 °C.

SCHEME 7. Comparison of the Regioisomers in Buchwald Couplings and Subsequent Deprotections[a]

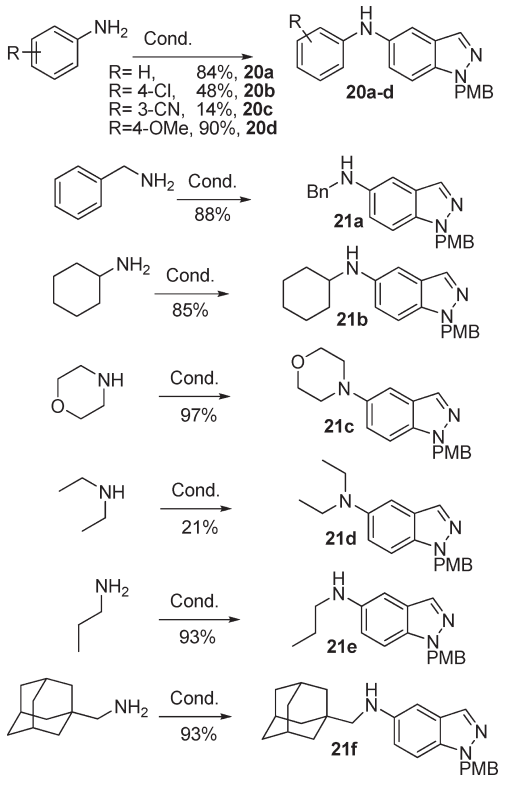


[a]A = 3, Pd2dba3, BINAP, NaO-*t*-Bu, THF, 55 °C. B = EtOH, 4 N HCl in 1,4-dioxane (2 equiv). C = 4a or 6a, Pd^2dba_3, BINAP, NaO-*t*-Bu, THF, 55 °C.

All protecting groups employed in Scheme 7 can be removed in ethanol with 2 equiv of HCl and heating to 80 °C. In all cases, a thick white slurry of di-HCl salt **16** formed which was easily isolated by filtration. Yields were comparable in all cases, and further product could be recovered from the mother liquor if desired (Scheme 7).

The final component of the Buchwald reaction to be studied was the amine. We again chose the PMB analogue **4a** for its crystallinity. The following partners were studied: substituted anilines, benzylamine, primary amines, and secondary amines (Scheme 8). Electron-withdrawing groups on the aniline (**20b**, **20c**) result in longer reaction times and low yield, whereas an electron-donating group results in a

SCHEME 8. Scope of Buchwald Coupling with Respect to Amine[a]



[a]**Conditions: 1.0 equiv of 4a or 10a, 1.1 equiv of amine, 0.05 equiv of Pd2dba3, 0.12 equiv of BINAP, 3.00 equiv of NaO*t*-Bu, THF, 55 °C, 18 h.**

very fast reaction and good yield (**20d**, Scheme 8). Morpholine was an excellent substrate for the cross-coupling, but diethylamine gave a poor yield, possibly due to its low boiling point.

In conclusion, the work described herein represents a useful way to obtain regioselectivity via acid-catalyzed protection of substituted indazoles, particularly with the THP group. Suitably protected and functionalized indazoles participated in Buchwald amine coupling reactions with a variety of substrates. Deprotections can be effected easily with HCl in EtOH to provide the desired indazole substrates as HCl salts.

Experimental Section

General *p*-TSA Protection Procedure. Preparation of 5-bromo-1-(tetrahydro-2*H*-pyran-2-yl)-1*H*-indazole **6a**: To a solution of **1a** (5.00 g, 25.4 mmol, 1 equiv) in 100 mL of DCM were added 3,4-dihydropyran (6.94 mL, 76.1 mmol, 3.00 equiv) and *p*-TSA (483 mg, 2.54 mmol, 0.1 equiv). The solution was stirred for 1 h, whereupon HPLC analysis revealed complete conversion to the 1-isomer product. The solution was further diluted with DCM, washed with saturated $NaHCO_3$, and evaporated. The residue was purified by flash chromatography, eluting with 10% EtOAc/hexanes to give 7.0 g of **6a** as a thick colorless oil (98.2%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.86 (d, J = 1.5 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.45 (dd, J = 1.5, 8.7 Hz, 1H), 5.69 (dd, J = 2.7, 9.0 Hz, 1H), 4.00 (m, 1H), 3.73 (m, 1H), 2.53 (m, 1H), 2.20−2.00 (m, 2H), 1.80−1.65 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 133.2, 129.8, 126.4, 123.6, 114.5, 111.9, 85.7, 67.6, 29.5, 25.3, 22.6; 1D NOE (300 MHz, DMSO-d_6) irradiation of the doublet at 7.49 ppm gave 13.9% NOE with a doublet at 7.49 ppm and 8.8% NOE with double doublet at 5.69 ppm; HRMS $[M + H]^+$ calcd for $C_{12}H_{14}BrN_2O$ 281.0284, found 281.0281.

General Coupling Procedure. Preparation of (*R*)-*tert*-butyl-3-(1-(4-methoxybenzyl)-1*H*-indazol-5-ylamino)piperidine-1-carboxylate **5a**: To a vial with a septum top were added 160 mg of **4a** (0.5 mmol 1.0 equiv), 110 mg of (*R*)-3-amino-*N*-Boc-piperidine (0.55 mmol, 1.10 equiv), 40 mg of *rac*-BINAP (0.12 equiv), 23 mg of Pd_2dba_3 (0.05 equiv), and 150 mg of sodium *tert*-butoxide (1.5 mmol, 3.0 equiv). The vial was degassed, and then 5 mL of THF was added. The resulting deep purple solution was stirred at 55 °C for 18 h. The reaction was diluted with EtOAc and filtered through Celite, washing with EtOAc. The filtrate was concentrated, and the residue was purified via flash chromatography (40% EtOAc/hexanes) to give 194 mg of **5a** as a pale-brown foam (89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.16 (m, 3H), 6.85 (d, J = 1.8 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.73 (dd, J = 1.8, 9.0 Hz, 1H), 5.46 (s, 2H), 4.05 (m, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 3.51 (bs, 1H), 3.38 (m, 1H), 3.10 (m, 1H), 2.90 (m, 1H), 2.00 (m, 1H), 1.73 (m, 1H), 1.50 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 155.0, 141.2, 134.7, 131.8, 129.3, 128.6, 125.6, 118.4, 114.1, 110.4, 110.2, 79.7, 55.3, 52.7, 49.9, 49.2, 44.1, 30.9, 28.5, 23.6; HRMS $[M + H]^+$ calcd for $C_{25}H_{33}N_4O_3$, 437.2547, found 437.2542.

Supporting Information Available: Experimental procedures for all new compounds, including general procedures for the strong acid protection conditions and for mild acid protection conditions. Full characterization data and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.