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Highly Diastereoselective Addition of Alkynylmagnesium Chlorides to *N-tert*-Butanesulfinyl Aldimines: A Practical and General Access to Chiral α-Branched Amines

Bai-Ling Chen,[†] Bing Wang,*[,†,‡] and Guo-Qiang Lin[†,‡]

[†]*Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China and* [‡]*Institutes of Biomedical Sciences, Fudan University, 138 Yixueyuan Road, Shanghai 200032, China*

wangbing@fudan.edu.cn

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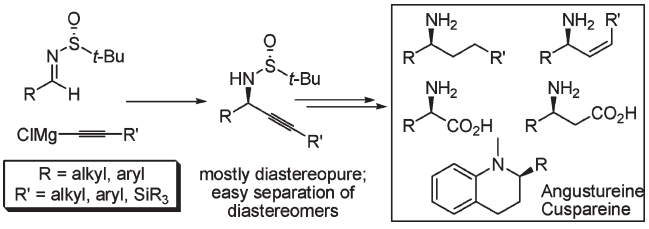

The addition of alkynylmagnesium chlorides to *N-tert*-butanesulfinyl imines proceeded with a remarkably high diastereoselectivity (dr > 13:1, mostly diastereopure), and with a general scope of both reaction partners. The high dr translated into simplified purification and higher optical purity for the synthesis of a wide array of chiral α-branched amines. The alkyne functionality also provides a multitude of opportunities for further synthetic transformations. The short asymmetric synthesis of (+)-angustureine **7** and (−)-cuspareine **10** was realized with use of this approach.

Nucleophilic additions to *N-tert*-butanesulfinyl (*t*-BS hereafter) imines constitute an immensely useful strategy for the synthesis of chiral amines,[1−4] thanks to the pioneering work of Davis, Ellman, and colleagues.[5] However, it should be noted that the level of asymmetric induction via this approach is not always perfect. A careful literature survey revealed that the diastereoselectivity is highly dependent on the nature of the imine *C*-appendage R, the incoming group R′, the metal countercation, the solvent and the additive. The lack of highly stereoselective preparation methods for some important types of chiral α-branched amines, such as 1-aryl-1-alkyl carbinamines and *Z*-allylic amines, is conspicuous and needs effective solutions. More importantly, the separation of diastereomeric products by conventional methods (flash chromatography or recrystallization) is not always possible in practice, often due to identical chromatographic behavior or undesirable physical properties. In these cases, the lower dr value is inevitably carried forward to the final products which, after removal of the chiral sulfinyl group, exhibit lower er values. Therefore, a high dr not only enhances the yield, but facilitates purification, especially on large scales. Prompted by the significance of chiral propargylic amines,[6,7] we see the addition of alkynyl Grignard reagents to *t*-BS imines not only as an access to this structural unit itself, but the solution to many other types of synthetically challenging chiral *N*-secondary alkyl amines (Figure 1). Interestingly, such alkynyl addition has not received its due attention, except that the Ellman group reported the addition to ketimines, using $AlMe_3$ as a mandatory additive,[8a] whereas Hou and co-workers investigated

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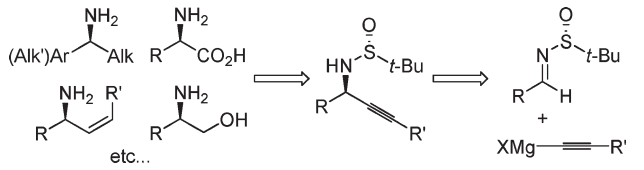

FIGURE 1. Proposed solutions to some synthetically challenging chiral *N*-secondary alkyl amines.

the addition of alkynyllithiums.[8b] As the continuation of our interest in the chemistry of *N-tert*-butanesulfinimine,[9] herein we report the details of a study on the alkynyl Grignard addition to *N-t*-BS aldimines.

Addition of representative Grignard reagents to aldimine **1a** under literature conditions afforded the expected adducts in modest to very good yields (entries 1−5). However, ^{1}H NMR of the purified products showed that significant amounts of diastereomers were present, which could not be separated by flash chromatography. After removal of the *t*-BS auxiliary from **2a**−**c** and derivatization, chiral HPLC analysis of the *N*-methyl carbamates revealed that the ee values of the α-branched amines were unsatisfactory, ranging from 77% to 92%. Using $AlMe_3$[8a] as an additive improved the dr only marginally in the case of phenyl addition (entry 3). On the other hand, the addition of alkynyl magnesium chlorides to **1a** resulted in good to very good yields and excellent diastereoselectivity (entries 6, 8, and 9). The reaction of commercial ethynylmagnesium bromide was complicated by proton exchange of the normal adduct **2f** with the excess reagent and further coupling with **1a**. Fortunately, this was remedied by using the readily removable trimethylsilyl to block the other end of ethynyl (entry 8).

This protocol turned out to cover a wide substrate scope (Table 2). Various *C*-alkyl, *C*-aryl, and *C*-heteroaryl *N-tert*-butanesulfinyl aldimines underwent smooth Grignard additions to afford the desired *N-t*-BS propargylic amines. The highly hindered imine **3b** and the α-oxygenated substrate **3c** were both suitable electrophiles (entries 4−9). 4-Nitrobenzaldehyde-derived *t*-BS imine **3f** also gave adducts **4fB** and **4fC** in decent yields, which in our hands were inaccessible via the analogous addition of alkynyllithiums.[8b] Meanwhile, electron-rich imine **3g** was less reactive, only the addition of 2-TMS-ethynyl was feasible (entry 17). Nevertheless, removal of TMS followed by Sonogashira coupling would allow further elaboration of the other end of the triple bond. The yields for heteroaromatic aldimines **3i**, **3j**, and **3k** were modest (30−70%); however, in view of the presence of adjacent heteroatoms capable of chelation to metal countercations, the high dr values were notable. Among the 28 examples listed in Tables 1 and 2, only four (**4eA**, **4eB**, **4eC**, and **4jC**) exhibited slightly lower dr values (13−25:1), in all other cases the adducts were virtually diastereopure. In addition, all four diastereomeric pairs are separable on silica gel column, suggesting the beneficial influence of the alkynyl group on product separation. The imine derived from pyrrole-2-carboxaldehyde did not react under this protocol, probably due to the unprotected acidic N−H or the electronic effects. The effect of the nucleophile structure was more subtle, the yields for phenylethynyl adducts were usually lower than those of alkyl- or silylethynyl analogues, with more side products.

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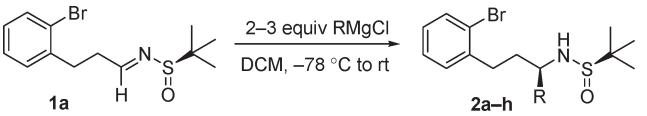
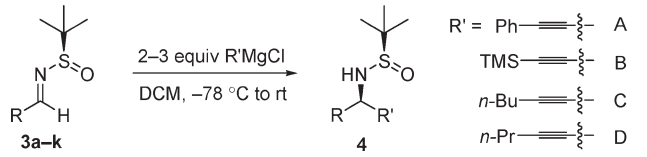
TABLE 1. Comparison of the Stereoselectivity of Carbanion Additions to *t*-BS aldimine 1a[a]

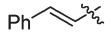


entry	R	adduct	yield (%)[b]	*ee* (%)[c]
1	*n*-C_5H_{11}	**2a**	83[d]	92
2	Ph	**2b**	87[d]	77
3[e]	Ph	**2b**	65[d]	81
4	cyclohexyl	**2c**	80[d]	80
5	*t*-Bu	**2d**	42	nd
6	Ph—	**2e**	78	99.0
7	H—	**2f**	38	nd
8	TMS—	**2g**	60	99.3
9	*n*-Pr—	**2h**	84	99.2

[a]All reactions run on 0.5−1.0 mmol scales. [b]Isolated yields. [c]Enantiomeric excess of *N*-methyl carbamate derivatives of the crude adducts, determined by chiral HPLC, see the Supporting Information. [d]Inseparable diastereomers. [e]$AlMe_3$ as the additive.

TABLE 2. Highly Diastereoselective Addition of Alkynylmagnesium Chlorides to *N-tert*-Butanesulfinyl Aldimines[a]



entry	R	**3**	R'	adduct	yield (%), *dr*[b]
1		**3a**	A	**4aA**	88, >99:1
2			B	**4aB**	87, >99:1
3			D	**4aD**	88, >99:1
4		**3b**	A	**4bA**	70, >99:1
5			B	**4bB**	79, >99:1
6			C	**4bC**	78, >99:1
7	$TBDPSOCH_2$	**3c**	A	**4cA**	76, >99:1
8			B	**4cB**	73, >99:1
9			D	**4cD**	80, >99:1
10	Ph	**3d**	B	**4dB**	46, >99:1
11			D	**4dD**	45, >99:1
12	*p*-Cl-C_6H_4	**3e**	A	**4eA**	60, 20:1[c]
13			B	**4eB**	77, 16:1[c]
14			C	**4eC**	79, 13:1[c]
15	*p*-O_2N-C_6H_4	**3f**	B	**4fB**	33, >99:1
16			C	**4fC**	51, >99:1
17	*p*-MeO-C_6H_4	**3g**	B	**4gB**	49, >99:1
18		**3h**	B	**4hB**	29, >99:1
19			C	**4hC**	81, >99:1
20		**3i**	A	**4iA**	30, >99:1
21			B	**4iB**	55, >99:1
22			C	**4iC**	30, >99:1
23		**3j**	B	**4jB**	45, >99:1
24			C	**4jC**	70, 25:1[c]
25		**3k**	C	**4kC**	33, >99:1
26		**3l**	C	**4lC**	NR

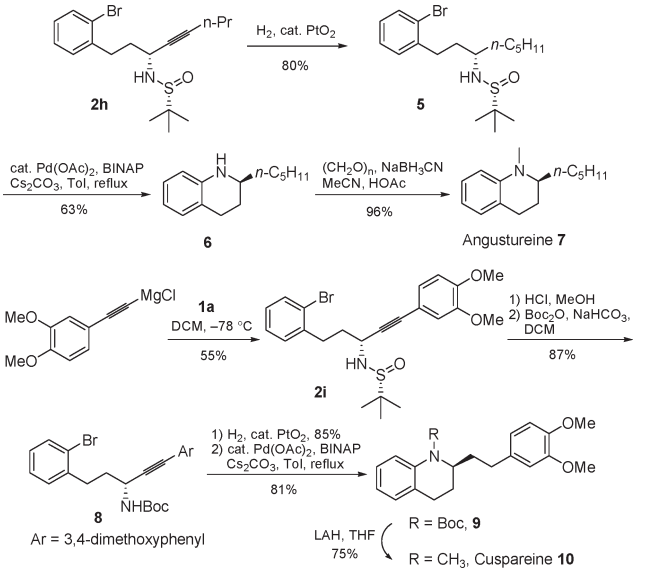
[a]All reactions run on 0.5−1.0 mmol scales. [b]Isolated yields of pure diastereomers. Distereoselectivity determined by ^{1}H NMR of the crude adducts. [c]Separable diastereomers.

The absolute configuration of adduct **4aB** was established by single-crystal X-ray analysis, which showed that R_S-imine produced (R_S,*R*)-adduct (see the Supporting Information for the ORTEP plot). Other representative adducts (**4cC**, **4dC**, and **4iA**) were also correlated with known compounds for unambiguous determination of stereochemistry (see the Supporting Information). Thus, the sense of chiral induction was the same as that of the addition of lithioalkynes,[8b] although the reaction conditions was quite different with regard to the solvent, metal countercation, and temperature. Moreover, alkynyl Grignard reagents afforded generally higher dr (mostly diastereopure) than their lithium counterparts (88−95% de).

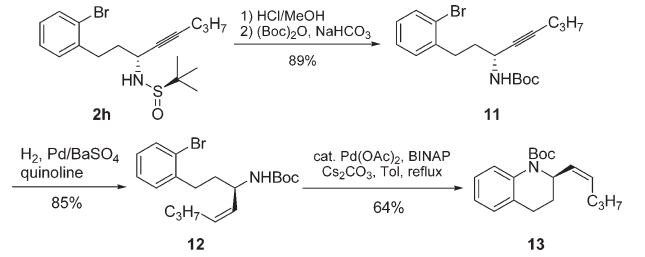
With this protocol in hand, we applied it to the asymmetric synthesis of two chiral 2-substituted tetrahydroquinoline[10] alkaloids, namely, angustureine[11] and cuspareine.[12] Saturation of the triple bond of **2h** afforded **5** in very good yield. By using the classic Pd-catalyzed Buchwald−Hartwig amination reaction,[13] the free amine **6** was obtained in 63% yield. It was noteworthy that the *t*-BS auxiliary was concomitantly removed from the aniline nitrogen under *basic* conditions. Analogous intramolecular amination with CuI as the catalyst did not work, and **5** was recovered. Reductive *N*-methylation afforded the target molecule (+)-**7**, the antipode of the natural product, in excellent yield (41% overall yield from **1a**). In a similar vein, the native (−)-cuspareine (**10**) was prepared in a short six-step sequence from imine **1a** and the readily available (3,4-dimethoxyphenyl)ethyne,[14] with an overall yield of 24% (Scheme 1).

Moreover, the propargylic adducts are also ideal building blocks for the synthesis of *Z*-allylic amines which were otherwise difficult to access. In this connection, the *t*-BS group was first replaced by Boc, partial hydrogenation of alkyne **11** using Lindlar's catalyst established the cis configuration of **12**, and the latter underwent Pd-catalyzed intramolecular amination smoothly to afford 2-*Z*-alkenyl tetrahydroquinoline **13** in 64% yield (Scheme 2). Under the same conditions, the *N*-*t*-BS analogue of **12** could also cyclize to give tetrahydroquinoline, however, in a diminished yield (34%). This approach complemented the iridium-catalyzed asymmetric hydrogenation of quinolines[10] in that the olefin in the side chain could be tolerated.

SCHEME 1. Short Asymmetric Synthesis of (+)-Angustureine and (−)-Cuspareine



SCHEME 2. Synthesis of 2-*Z*-Alkenyl tetrahydroquinolines



In conclusion, we have demonstrated that the addition of alkynylmagnesium chlorides to *t*-BS imines proceeded in a highly diastereoselective manner (dr > 13:1), without the need of additives. The propargylic adducts are versatile intermediates for the syntheses of natural products and synthetically challenging chiral *N*-secondary alkyl amines. The short asymmetric synthesis of two representative 2-substituted tetrahydroquinoline alkaloids **7** and **10** were realized. Unexpected deblocking of *t*-BS auxiliary from aniline nitrogen under basic conditions was encountered. This sulfinimine-based approach is synthetically useful for its wide scope in both the imine and the nucleophile, consistently high stereoselectivity, and easy separation of diastereomeric adducts.

Experimental Section

General Procedure. To a cooled (−78 °C) solution of sulfinylimine (1.0 mmol) in CH_2Cl_2 (5 mL) under Ar was added dropwise the freshly prepared alkynyl Grignard reagent (2−3 mmol

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(13) For reviews on the Buchwald−Hartwig amination, see: (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (b) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (c) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (d) Buchwald, S. L.; Muci, A. *Top. Curr. Chem.* **2002**, *219*, 133.

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in THF/ether), and the solution was stirred at the same temperature for 2 h, then gradually warmed to room temperature and stirred overnight. The reaction was quenched by sat. aq NH_4Cl then extracted by EtOAc, and the combined organic phase was washed with brine, dried ($NaSO_4$), and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography eluted with EtOAc/hexane.

Compound **2h**: $[\alpha]^{28}_D$ −33.6 (*c* 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 1H, J = 7.8 Hz), 7.25−7.21 (m, 2H), 7.09−7.04 (m, 1H), 4.14−4.07 (m, 1H), 3.37 (d, 1H, J = 5.8 Hz), 2.96−2.85 (m, 2H), 2.21 (td, 2H, J = 7.0, 2.1 Hz), 2.04−1.94 (m, 2H), 1.55 (sextet, 2H, J = 7.2 Hz), 1.23 (s, 9H), 1.00 (t, 3H, J = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6, 132.8, 130.4, 127.7, 127.5, 124.3, 85.9, 79.5, 55.9, 47.5, 37.1, 32.3, 22.5, 22.0, 20.7, 13.5. HR-ESI-MS m/z calcd for $C_{18}H_{27}BrNOS$ ($M + H^+$) 384.0997, found 384.0975.

A suspension of **2h** (104 mg, 0.27 mmol) and PtO_2 (5 mg) in EtOH (3 mL) was stirred under H_2 atmosphere (1 atm) for 5 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (EtOAc/hexane = 1/4) to afford **5** (84 mg, 80%).

Compound **5**: $[\alpha]^{27}_D$ −23.8 (*c* 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 1H, J = 7.8 Hz), 7.26−7.18 (m, 2H), 7.08−7.03 (m, 1H), 3.34−3.27 (m, 1H), 3.07 (d, 1H, J = 6.8 Hz), 2.89 (ddd, 1H, J = 13.0, 11.0, 4.5 Hz), 2.70 (ddd, 1H, J = 13.0, 11.0, 5.5 Hz), 1.90−1.81 (m, 1H), 1.76−1.57 (m, 3H), 1.45−1.35 (m, 2H), 1.35−1.27 (m, 4H), 1.25 (s, 9H), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 132.8, 130.2, 127.6, 127.5, 124.3, 56.6, 55.8, 36.4, 35.8, 32.4, 31.7, 25.3, 22.7, 22.5, 14.0; HR-ESI-MS m/z calcd for $C_{18}H_{31}BrNOS$ ($M + H^+$) 388.1310, found 388.1339.

Under Ar atmosphere, a mixture of **5** (107 mg, 0.27 mmol), $Pd(OAc)_2$ (2.0 mg, 3.3 mmol %), *rac*-BINAP (8.0 mg, 5 mol %), and Cs_2CO_3 (123 mg, 1.4 equiv) in toluene (2 mL) was heated at 100 °C overnight, cooled, and concentrated. The residue was purified by column chromatography (EtOAc/hexane = 1/20) to afford **6** (36 mg, 63%). The aniline **6** was dissolved in MeCN (3 mL), to the solution was added sequentially 30% aq CH_2O (0.4 mL), $NaBH_3CN$ (95 mg, 1.53 mmol), and HOAc (0.1 mL), then additional HOAc (0.1 mL) was added after 30 min; after full conversion of the starting material (1 h), the mixture was diluted with ether (30 mL), washed with 1 M KOH (3 × 5 mL), dried over K_2CO_3, and concentrated. The residue was purified by column chromatography (hexane) to afford **7** (37 mg, 96%).

(+)-Angustureine **7**: $[\alpha]^{24}_D$ +9.50 (*c* 0.40, $CHCl_3$) {lit.: $[\alpha]_D$ −7.16 for enantiomer,[11a] $[\alpha]^{23}_D$ +7.9 (*c* 1.00, $CHCl_3$)[11c]}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (t, 1H, J = 7.5 Hz), 6.96 (d, 1H, J = 7.2 Hz), 6.62−6.48 (m, 2H), 3.26−3.19 (m, 1H), 2.92 (s, 3H), 2.84−2.75 (m, 1H), 2.68−2.61 (m, 1H), 1.92−1.85 (m, 2H), 1.65−1.54 (m, 1H), 1.43−1.22 (m, 7H), 0.89 (t, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4, 128.6, 127.0, 121.9, 115.2, 110.4, 59.0, 37.9, 32.0, 31.3, 25.7, 24.5, 23.6, 22.6, 14.0; HR-ESI-MS m/z calcd for $C_{15}H_{24}N$ ($M + H^+$) 218.1909, found 218.1892.

Adduct **2i** (260 mg, 0.54 mmol) dissolved in MeOH (2 mL) was treated with 2 M HCl−MeOH (0.4 mL) at rt for 4 h, the volatiles were removed under reduced pressure, then to the residue was added DCM (5 mL), $NaHCO_3$ (90 mg, 1.08 mmol), and Boc_2O (175 mg, 0.80 mmol). The mixture was stirred at rt overnight, diluted with DCM, filtered, and concentrated. The residue was purified by column chromatography (hexane/EtOAc = 1/10) to afford **8** (224 mg, 87%).

Compound **8**: $[\alpha]^{25}_D$ −3.5 (*c* 0.37, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, 1H, J = 8.0 Hz), 7.27 (dd, 1H, J = 7.5, 1.5 Hz), 7.23 (td, 1H, J = 7.5, 1.0 Hz), 7.08−7.01 (m, 2H), 6.94 (d, 1H, J = 2.0 Hz), 6.79 (d, 1H, J = 8.5 Hz), 4.91 (s br, 1H), 4.71 (s br, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.01−2.89 (m, 2H), 2.09−2.02 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 149.5, 148.5, 140.5, 132.8, 130.4, 127.7, 127.5, 124.9, 124.4, 114.8, 114.4, 110.9, 86.7, 83.5, 79.8, 55.8, 43.2, 36.4, 32.4, 28.3; HR-ESI-MS m/z calcd for $C_{24}H_{28}BrNNaO_4$ ($M + Na^+$) 496.1099, found 496.1130.

Conversion of **8** to **9** followed the procedure for **2h** to **6**. To a solution of **9** (50 mg, 0.12 mmol) in THF (10 mL) was added $LiAlH_4$ (30 mg, 0.79 mmol) under rt, and the mixture was refluxed for 5 h, cooled to 0 °C, quenched by several drops of water, and basified by 10% NaOH. The mixture was extracted with ether (3 × 20 mL), then the combined organic phase was dried over K_2CO_3 and concentrated. The residue was purified by column chromatography (EtOAc/hexane = 1/6) to afford **10** (28 mg, 75%).

(−)-Cuspareine **10**: $[\alpha]^{25}_D$ −30.3 (*c* 0.27, $CHCl_3$); {lit.: $[\alpha]^{25}_D$ −22.8 (*c* 1.00, $CHCl_3$),[12a] $[\alpha]^{25}_D$ −30.2 (*c* 0.95, $CHCl_3$)[10b]}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (t, 1H, J = 7.7 Hz), 6.98 (d, 1H, J = 7.2 Hz), 6.78 (d, 1H, J = 8.0 Hz), 6.74−6.69 (m, 2H), 6.59 (t, 1H, J = 7.0 Hz), 6.53 (t, 1H, J = 7.8 Hz), 3.86 (s, 3H), 3.85 (s, 3H), 3.32−3.25 (m, 1H), 2.91 (s, 3H), 2.89−2.81 (m, 1H), 2.73−2.63 (m, 2H), 2.57−2.49 (m, 1H), 1.99−1.87 (m, 3H), 1.77−1.69 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 147.3, 145.3, 134.6, 128.6, 127.1, 121.8, 120.1, 115.4, 111.7, 111.4, 110.6, 58.4, 56.0, 55.9, 38.1, 33.1, 31.9, 24.4, 23.6; HR-ESI-MS m/z calcd for $C_{20}H_{26}NO_2$ ($M + H^+$) 312.1964, found 312.1962.

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Supporting Information Available: Characterization data, ^{1}H and ^{13}C NMR spectra for all new compounds, and crystallographic data for **4aB** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.