

Rapid, highly diastereoselective addition of dialkylzinc reagents to atropisomeric 2-formyl arylamides

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Abstract—We have observed that dialkylzinc reagents add to atropisomeric 2-formyl arylamides many times faster than they react with other substituted benzaldehyde derivatives. Additionally, with diethylzinc the products were formed with very high diastereoselectivity, affording the *syn* product (d.r. greater than 95:5), except in one case where epimerization of the product is rapid. In contrast, Grignard and trialkylaluminum reagents afforded the *anti* diastereomers, with diminished stereoselectivity and formation of reduction products. © 2004 Elsevier Ltd. All rights reserved.

1. Introduction

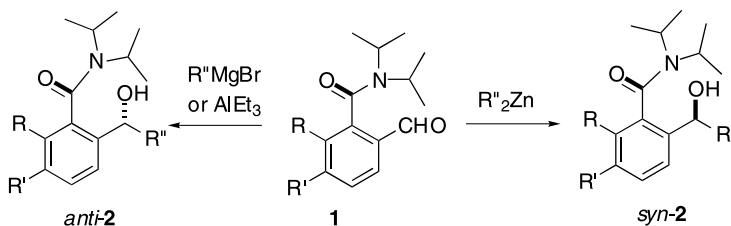
Atropisomeric amides, imides, and anilides are known to control a variety of stereoselective reactions¹ such as cycloadditions,^{2,3} radical additions,² lateral lithiations,^{4–9} and *ortho*-lithiations,^{10,11} among others.^{12–16} Atropisomeric *N,N*-diisopropyl amides have recently been used to control stereochemistry over long distances, as demonstrated by Clayden in the highly diastereoselective addition of phenylmagnesium chloride to a remote carboxaldehyde.^{17,18} Atropisomeric 1-naphthamides have also been shown to influence diastereoselectivity in the addition of organomagnesium and organolithium reagents to 2-formyl groups.¹⁸

In our continuing studies of atropisomeric amides,¹⁹ we have examined the addition of organometallic reagents to 2-formylaryl amides. We herein report surprising rate enhancements and excellent control of diastereoselectivity in the alkyl group addition to a series of racemic 2-formyl arylamides. We are not aware of related observations in this

system in the literature, despite the fact that substrate controlled diastereoselective reactions are well known.^{20,21} Dialkylzinc reagents were found to afford the *syn* products on addition to 2-formyl arylamides, whereas Grignard and trialkylaluminum compounds yielded the *anti* products as the major diastereomer under our reaction conditions (Scheme 1).

2. Results and discussion

During a study directed toward the dynamic kinetic resolution of atropisomeric amides, we found that diethylzinc added to amides **1** with excellent control over diastereoselectivity (Table 1). Surprisingly, the reaction took place equally as fast in the presence or absence of amino alcohols, finishing after 1 h at room temperature. These results were unexpected because it is known that diethylzinc reacts with benzaldehyde slowly in the absence of amino alcohols.²² Therefore, we propose that a mechanism involving activation of the diethylzinc by the



Scheme 1. Reagent controlled diastereoselection in the addition to 2-formyl arylamides.

Keywords: Dialkylzinc reagents; Atropisomeric amides; Stereochemistry; 1,2-Addition reactions.

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Table 1. Addition of organometallic reagents to 2-formyl arylamides

Entry	Substrate	R	R'	MR ^{II}	Product	Yield	d.r. (<i>syn/anti</i>)
1	1a	NMe ₂	H	ZnEt ₂	2a	99	>98:2
2	1b	CF ₃	H	ZnEt ₂	2b	96	95:5
3	1c	Ph	H	ZnEt ₂	2c	80	>98:2
4	1c	Ph	H	EtMgBr	2c	94	50:50
5	1c	Ph	H	AlEt ₃	2c	75 ^a	11:89
6	1d	OMe	H	ZnEt ₂	2d	95	>98:2
7	1d	OMe	H	EtMgBr	2d	83	33:67
8	1d	OMe	H	AlEt ₃	2d	39 ^b	14:86
9	1d	OMe	H	ZnMe ₂	3d	64 ^c	85:15
10	1d	OMe	H	MeMgBr	3d	97	33:67
11	1e	1-Naph ^d	H	ZnEt ₂	2e	68	>98:2
12	1e	1-Naph ^d	H	EtMgBr	2e	90	25:75
13	1e	1-Naph ^d	H	ZnMe ₂	3e	60 ^c	91:9
14	1e	1-Naph ^d	H	MeMgBr	3e	80	25:75
15	1f	SiMe ₃	H	ZnEt ₂	2f	57	33:67
16	1f	SiMe ₃	H	EtMgBr	2f	92	33:67

^a 19% of reduction product.^b 44% of reduction product.^c After 2 days.^d *N,N*-Diisopropyl-2-formyl-1-naphthamide.

amide carbonyl is responsible for both the increase in reaction rate and the high diastereoselectivity, as outlined below. Dialkylzinc reagents can give excellent diastereoselectivity if a Lewis-basic functional group is in close proximity to the reaction center.^{23,24}

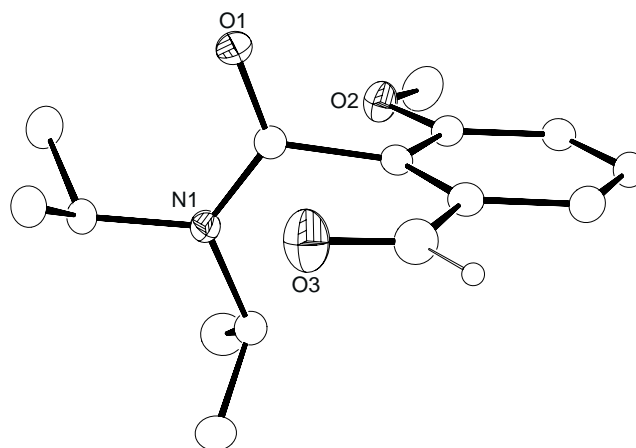
We applied this reaction to a series of atropisomeric aldehydes, achieving excellent diastereocontrol, as determined by ¹H and ¹³C{¹H} NMR spectroscopy (Table 1, entries 1–3, 6 and 11). Only the addition to **1f** afforded poor diastereoselectivity as discussed below (entry 15). Dimethylzinc additions required longer reaction times (approximately 2 d) and gave somewhat lower diastereoselectivities (Table 1, entries 9 and 13). It is well known that dimethylzinc is significantly less reactive than diethylzinc. For example, Noyori reported that dimethylzinc reacted 20 times slower with benzaldehyde than diethylzinc in the presence of catalyst formed from the amino alcohol ligand DAIB.²⁵ We attribute the decrease in the diastereoselectivity in the dimethylzinc additions to the prolonged reaction times, which permit the epimerization of the product through rotation about the Ar–carbonyl bond. Experimental support for this hypothesis is presented below.

To examine the diastereoselectivity with Grignard reagents, we carried out the addition of ethylmagnesium bromide to aldehydes **1c–f** (Table 1, entries 4, 7, 12, and 16) and methylmagnesium bromide to **1d** and **1e** (entries 10 and 14). Surprisingly, in contrast to the formation of the *syn* product with dialkylzinc reagents, the *anti* diastereomer predominated in these addition reactions. Under our conditions, where the Grignard reagent was used as a diethyl ether

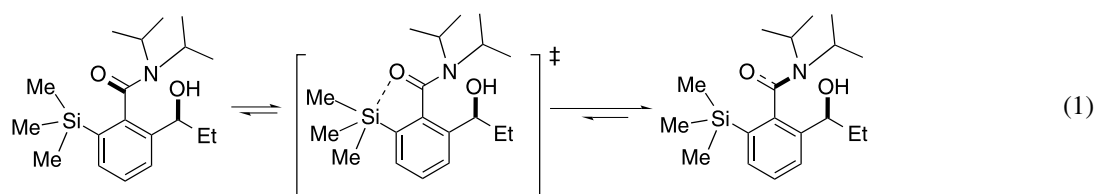
solution at 0 °C, we observed formation of the *anti* diastereomer. In contrast, Clayden and co-workers employed Grignard reagent in THF at low temperature and reported formation of the *syn* diastereomer.¹⁸ We repeated the experiment of the Clayden group and obtained the *syn* diastereomer under these conditions, in agreement with their report.²⁶ It is likely that the change in diastereoselectivity of the addition in diethyl ether and THF is related the higher affinity of magnesium for THF. The specific cause, however, remains unclear at this time.

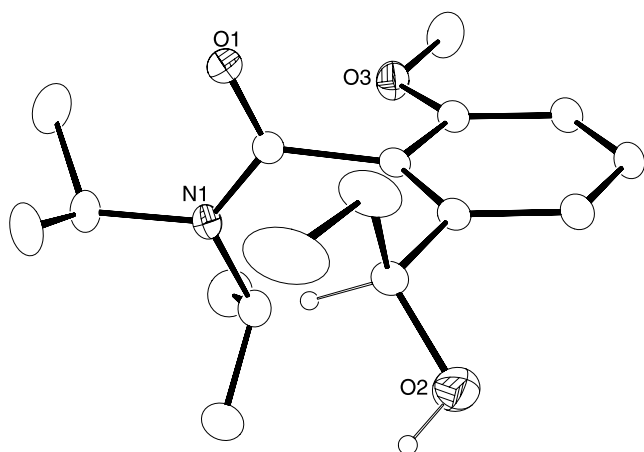
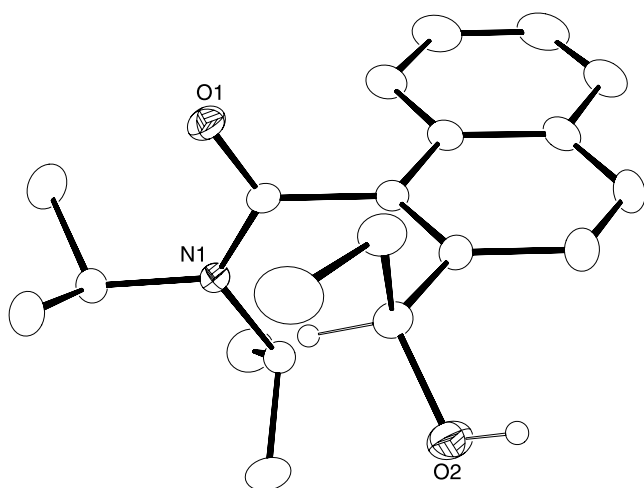
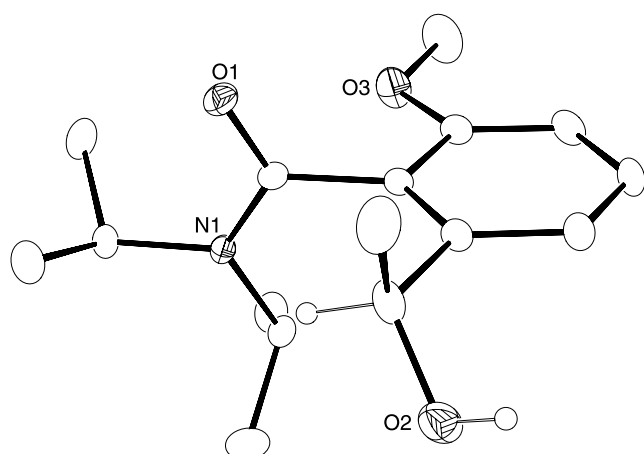
Only in the additions to **1f** (entries 15 and 16), which has a trimethylsilyl group *ortho* to the amide, was the same mixture of diastereomers isolated with the zinc and magnesium reagents. There are two possible explanations for this observation. The increased length of the carbon–silicon bond could result in a decrease in the barrier to rotation of the amide. Alternatively, the trimethylsilyl group could facilitate rotation about the aryl–amide bond by coordination of the carbonyl oxygen to the silicon in the transition state as illustrated in Eq. 1.¹⁹ Coordination of Lewis bases by trialkylsilyl in an intramolecular fashion has been proposed in many systems.²⁷ Similar *ortho* silyl effects have been observed previously by Clayden²⁸ and our group.¹⁹

To examine the aldehyde conformation in the solid state, an X-ray structure determination of **1d** was performed.²⁹ An ORTEP drawing is shown in Figure 1 where the perpendicular architecture of the atropisomeric amide can be seen.

**Figure 1.** ORTEP drawing of **1d**.

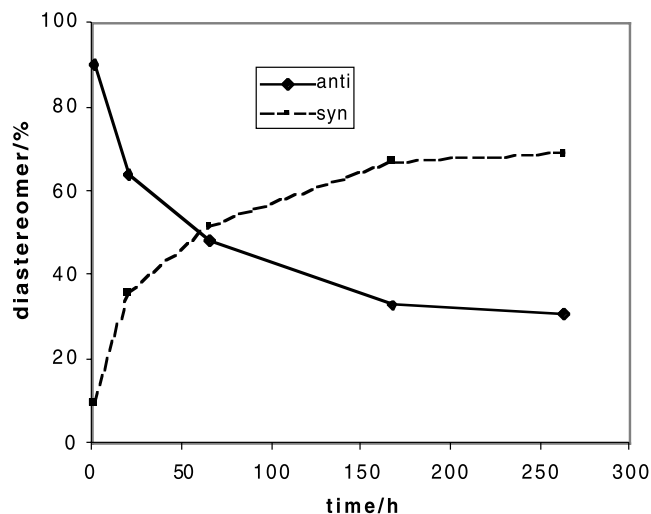
In order to assign the relative stereochemistry of each diastereomer, crystals of the *syn/anti* mixtures of **2d**, **2e**, and **3d** were grown,²⁹ and their structures determined by X-ray diffraction. Only the *anti* diastereomers crystallized under our conditions. ¹H NMR spectroscopy of those crystals



Figure 2. ORTEP drawing of *anti*-2d.Figure 3. ORTEP drawing of *anti*-2e.Figure 4. ORTEP drawing of *anti*-3d.

showed that they were the major diastereomer in the reactions with the Grignard reagents. Therefore, the *syn* diastereomer was formed in the dialkylzinc additions. Figures 2–4 show ORTEP drawings of **2d**, **2e**, and **3d** where the *anti* arrangement can be clearly seen.

To examine the rates of epimerization of the atropisomeric amide products a 90:10 mixture of *anti*-**3d**:*syn*-**3d** was

Figure 5. Epimerization of *anti*-**3d**. Plot of the diastereomer % vs time.

monitored at room temperature by ^1H NMR spectroscopy. From Figure 5 it is clear that the equilibration of the *syn* and *anti* diastereomers occurs slowly at room temperature eventually leading to the thermodynamic ratio (30:70 *anti*:*syn*).^{9,28} However, the epimerization rate is sufficiently fast to result in a decrease in the diastereoselectivities in the addition of dimethylzinc to aldehydes.

The diastereoselectivity in the Grignard addition reactions was only moderate, and thus we decided to explore other reagents in order to improve the *anti* selectivity. We were pleased to find that triethylaluminum added to **1c** and **1d** with much better diastereoselection, affording predominantly the *anti* diastereomer (Table 1, entries 5 and 8). However, variable amounts of reduction products were also isolated.

Next we compared the rates of reaction of diethylzinc with 2-formylatropisomeric amides and 2-substituted benzaldehyde derivatives. The reactions with **1d** and **1e** were complete after 3 h at room temperature, whereas reactions with 2-anisaldehyde, 2-tolualdehyde, and 2-trifluoromethylbenzaldehyde exhibited no conversion after 3 h by ^1H NMR spectroscopy. The results of these studies allow us to propose a mechanism for the addition of dialkylzinc reagents to 2-formylatropisomeric amides that explains the high level of diastereoselectivity observed. The rapid addition of diethylzinc to the amides **1d** and **1e** suggests that the zinc is activated by coordination to the amide carbonyl oxygen. It has been proposed that the alkyl groups in coordinated zinc complexes of the type LZnR_2 (where L is a Lewis-basic group) are significantly more reactive than those of ZnR_2 .^{25,30} Thus, the activated ZnR_2 can deliver the alkyl group as shown in Figure 6. The proposed conformation of the formyl group is that found in the crystal structure of **1d** in Figure 1. A model for the addition of Grignard reagents to 2-formylatropisomeric amides is also proposed in Figure 6. Activation of the aldehyde by the magnesium center is proposed to cause a conformational change of the aldehyde carbonyl–aryl bond as a result of steric interactions of the magnesium assembly with the substrate. Thus, the addition reaction takes place on the opposite face of the aldehyde.

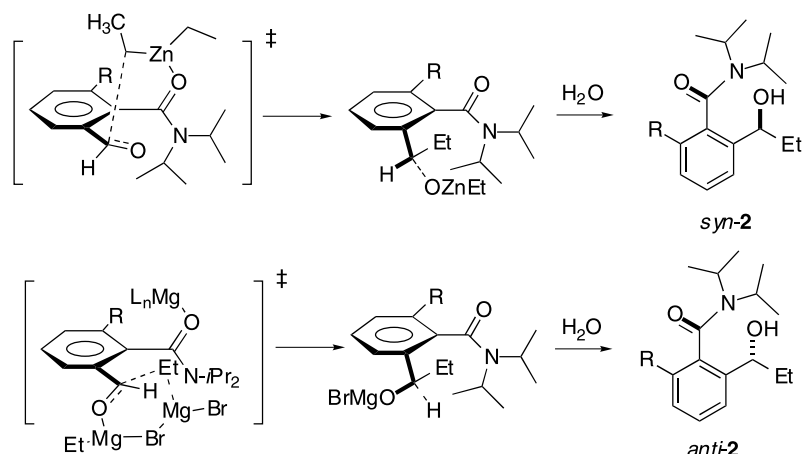


Figure 6. Proposed models for the diethylzinc and the Grignard additions to 2-formylaryl amides. Solvent molecules coordinated to magnesium are not shown.

3. Conclusions

In summary, we report that dialkylzinc reagents react rapidly with atropisomeric 2-formyl arylamides relative to 2-substituted benzaldehyde derivatives. It is proposed that this large difference in reactivity is due to an internal activation of the organozinc reagent by the amide carbonyl. Furthermore, the alkyl zinc reagents add in a highly diastereoselective fashion, affording the *syn* adducts in high yields and diastereoselectivities. The *anti* diastereomers have also been synthesized through the addition of Grignard reagents to the same starting material. A promising alternative to this latter reaction is the use of trialkylaluminum compounds, which provides the *anti* diastereomer with high diastereoselectivity. We are currently examining the possibility of using other reactions to achieve the dynamic kinetic resolution of these interesting substrates.

4. Experimental

4.1. General experimental section

^1H NMR spectra were obtained on a 500 MHz Fourier transform NMR spectrometer at the University of Pennsylvania NMR facility. ^1H NMR spectra were recorded relative to tetramethylsilane. $^{13}\text{C}\{^1\text{H}\}$ NMR spectra were obtained at 125 MHz on the 500 MHz instrument, and chemical shifts were recorded relative to the solvent resonance. Chemical shifts are reported in units of parts per million downfield from tetramethylsilane and all coupling constants are reported in Hz. IR spectra were obtained on a Perkin–Elmer 1600 series spectrometer. Unless otherwise specified, all reagents were either purchased from Aldrich Chemical Co. or Acros Organics, and used without further purification. TMEDA was distilled over CaH_2 prior to use. Aldehyde precursors to compounds **2** and **3** were synthesized by the literature methods.

4.2. Procedure A. Addition of dialkylzinc reagents to compounds 1a–f

The aldehyde (0.4 mmol) was weighed into a dry, round

bottom flask and dissolved in 2 mL of dry toluene under nitrogen. 1 M solutions of either diethyl- or dimethylzinc in hexanes (0.8 mmol, 0.8 mL) were added dropwise. The reaction was quenched with aq. sat. NH_4Cl after 1 h when diethylzinc was used, and after 2 d when dimethylzinc was used. The mixture was extracted with diethyl ether ($\times 3$), dried (MgSO_4), and solvents removed in vacuo. The crude reaction product was purified by column chromatography on silica gel when necessary using ethyl acetate and hexanes. The d.r. was determined prior and after purification by ^1H NMR spectroscopy.

4.3. Procedure B. Addition of Grignard reagents to compounds 1c–f

The aldehyde (0.4 mmol) was weighed into a dry, round bottom flask and dissolved in 2 mL of dry diethyl ether under nitrogen. The solution was cooled to 0°C and 3 M solutions of either ethyl- or methylmagnesium bromide in diethyl ether (0.8 mmol, 0.27 mL) were added dropwise. The mixture was allowed to warm to room temperature. After 4 h, the reaction was quenched with aq. sat. NH_4Cl , extracted with diethyl ether ($\times 3$), dried (MgSO_4), and solvents removed in vacuo. The crude reaction product was purified by column chromatography on silica gel when necessary using ethyl acetate and hexanes. The d.r. was determined prior and after purification by ^1H NMR spectroscopy.

4.4. Procedure C. Addition of triethylaluminum to aldehydes 1c–d

The aldehyde (0.4 mmol) was weighed into a dry, clean, round bottom flask, and dissolved in 2 mL of dry toluene under nitrogen. A 1 M solution of triethylaluminum in hexanes (0.8 mmol, 0.8 mL) was added dropwise. The reaction was quenched with aq. sat. NH_4Cl after 12 h, extracted with diethyl ether ($\times 3$), dried (MgSO_4), and solvents removed in vacuo. The crude product was purified by column chromatography on silica gel. The d.r. was determined after purification by ^1H NMR spectroscopy.

4.4.1. *syn* *N,N*-Diisopropyl 1-(dimethylamino)-3-(1-hydroxypropyl)-2-benzamide, *syn-2a*. Prepared according

to general procedure A. *syn-2a* was isolated as a clear oil in 99% yield (120 mg). ^1H NMR (500 MHz, CDCl_3) δ 7.21 (t, $J=8$ Hz, 1H), 7.01 (d, $J=8$ Hz, 1H), 6.86 (d, $J=8$ Hz), 4.38 (m, 1H), 3.79 (broad s, 1H), 3.53 (m, 1H), 3.45 (m, 1H), 2.67 (s, 6H), 1.92 (m, 1H), 1.82 (m, 1H), 1.55 (d, $J=7$ Hz, 3H), 1.50 (d, $J=7$ Hz, 3H), 1.12 (d, $J=7$ Hz, 3H), 0.93–0.89 (m, 6H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 171.0, 149.8, 141.6, 132.9, 129.1, 119.3, 117.4, 72.0, 51.2, 45.8, 44.1, 26.5, 20.6, 20.5, 20.1, 20.0 11.1 ppm; IR (film) 3420, 3065, 2963, 1600, 1466, 1336 cm^{-1} ; HRMS (ES+) m/z 329.2218 (calcd for $[\text{C}_{18}\text{H}_{30}\text{N}_2\text{O}_2+\text{Na}]=329.2205$).

4.4.2. *syn N,N*-Diisopropyl 1-(trifluoromethyl)-3-(1-hydroxypropyl)-2-benzamide, *syn-2b*. Prepared according to general procedure A. *syn-2b* was isolated in 96% yield as a clear oil (115 mg). ^1H NMR (500 MHz, CDCl_3) δ 7.62 (d, $J=8$ Hz, 1H), 7.52 (d, $J=8$ Hz, 1H), 7.45 (t, $J=8$ Hz, 1H), 4.54 (m, 1H), 3.48 (m, 2H), 3.10 (broad s, 1H), 2.00 (m, 1H), 1.75 (m, 1H), 1.56 (d, $J=7$ Hz, 3H), 1.47 (d, $J=7$ Hz, 3H), 1.09 (d, $J=7$ Hz, 3H), 1.01 (m, 3H), 0.99 (d, $J=7$ Hz, 3H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 167.9, 141.7, 135.2, 129.8, 129.1, 128.4, 126.1, 71.2, 51.2, 46.4, 26.9, 20.7, 20.2, 19.6, 19.4, 11.1 ppm; IR (film) 3420, 3080, 2969, 1614, 1440, 1372, 1319 cm^{-1} ; HRMS (ES+) m/z 354.1671 (calcd for $[\text{C}_{17}\text{H}_{24}\text{F}_3\text{NO}_2+\text{Na}]=354.1657$).

4.4.3. *syn N,N*-Diisopropyl 1-phenyl-3-(1-hydroxypropyl)-2-benzamide, *syn-2c*. Prepared according to general procedure A. *syn-2c* was isolated as a white solid (105 mg) in 80% yield. ^1H NMR (500 MHz, CDCl_3) δ 7.47–7.24 (m, 8H), 4.48 (m, 1H), 3.39 (m, 1H), 3.32 (m, 1H), 1.99 (m, 1H), 1.84 (m, 1H), 1.49 (d, $J=7$ Hz, 3H), 1.23 (d, $J=7$ Hz, 3H), 0.95 (t, $J=7$ Hz, 3H), 0.79 (d, $J=7$ Hz, 3H), 0.14 (d, $J=7$ Hz, 3H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 170.5, 140.9, 139.9, 137.9, 136.8, 129.4, 128.8, 128.7, 128.3, 127.6, 124.7, 72.1, 50.8, 46.0, 26.7, 20.5, 20.4, 19.3, 19.2, 11.1 ppm; IR (film) 3407, 3057, 2964, 1603, 1444, 1370, 1335 cm^{-1} ; HRMS (ES+) m/z 362.2083 (calcd for $[\text{C}_{22}\text{H}_{29}\text{NO}_2+\text{Na}]=362.2096$).

4.4.4. *syn N,N*-Diisopropyl 1-methoxy-3-(1-hydroxypropyl)-2-benzamide, *syn-2d*. Prepared according to general procedure A. *syn-2d* was isolated in 95% yield as a clear oil (98 mg). ^1H NMR (500 MHz, CDCl_3) δ 7.24 (t, $J=8$ Hz, 1H), 6.99 (d, $J=8$ Hz, 1H), 6.73 (d, $J=8$ Hz, 1H), 4.41 (m, 1H), 3.73 (s, 3H), 3.63 (m, 1H), 3.45 (m, 1H), 3.40 (broad s, 1H), 1.89 (m, 1H), 1.78 (m, 1H), 1.52 (d, $J=7$ Hz, 3H), 1.50 (d, $J=7$ Hz, 3H), 1.12 (d, $J=7$ Hz, 3H), 0.97 (d, $J=7$ Hz, 3H), 0.91 (t, $J=7$ Hz, 3H) ppm; $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 168.5, 154.9, 142.1, 129.5, 127.6, 118.0, 109.5, 72.1, 55.3, 51.2, 46.0, 27.2, 20.8, 20.6, 20.3, 20.2, 10.9 ppm; IR (film) 3396, 3055, 2964, 1608, 1469, 1440, 1337, 1262 cm^{-1} ; HRMS (ES+) m/z 316.1877 (calcd for $[\text{C}_{17}\text{H}_{27}\text{NO}_3+\text{Na}]=316.1889$).

4.4.5. *syn N,N*-Diisopropyl 1-methoxy-3-(1-hydroxyethyl)-2-benzamide, *syn-3d*. Prepared according to general procedure A. *syn-3d* was isolated in 64% yield (99 mg) as a clear oil. ^1H NMR (500 MHz, CDCl_3) δ 7.23 (t, $J=8$ Hz, 1H), 7.04 (d, $J=8$ Hz, 1H), 6.73 (d, $J=8$ Hz, 1H), 4.73 (q, $J=6$ Hz, 1H), 3.72 (s, 3H), 3.60 (m, 1H), 3.44 (m, 1H), 1.51 (d, $J=7$ Hz, 3H), 1.49 (d, $J=7$ Hz, 3H), 1.45 (d, $J=6$ Hz, 3H), 1.10 (d, $J=7$ Hz, 3H), 0.96 (d, $J=7$ Hz, 3H) ppm;

$^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz, CDCl_3) δ 168.6, 154.7, 143.1, 129.5, 126.8, 117.6, 109.6, 66.0, 55.3, 51.2, 46.0, 20.8, 20.6, 20.5, 20.2, 20.1 ppm; HRMS (CI+) m/z 279.1835 (calcd for $[\text{C}_{16}\text{H}_{25}\text{NO}_3+\text{Na}]=279.1834$).

4.4.6. *anti N,N*-Diisopropyl 1-methoxy-3-(1-hydroxyethyl)-2-benzamide, *anti-3d*. Prepared according to procedure C and isolated as a white solid in 39% yield (42 mg). Sample characterized from the crystals used for X-ray diffraction. ^1H NMR (500 MHz, CDCl_3) δ 7.22 (t, $J=8$ Hz, 1H), 7.02 (d, $J=8$ Hz, 1H), 6.72 (d, $J=8$ Hz, 1H), 4.78 (q, $J=6$ Hz, 1H), 3.71 (s, 3H), 3.62 (m, 1H), 3.44 (m, 1H), 1.50 (m, 6H), 1.46 (d, $J=6$ Hz, 3H), 1.08 (d, $J=7$ Hz, 3H), 1.02 (d, $J=7$ Hz, 3H).

4.4.7. *syn N,N*-Diisopropyl 2-(1-hydroxypropyl)-1-naphthamide, *syn-2e*. Spectroscopic data identical to that reported in the literature.²⁸

4.4.8. *anti N,N*-Diisopropyl 2-(1-hydroxypropyl)-1-naphthamide, *anti-2e*. Spectroscopic data identical to that reported in the literature.²⁸

4.4.9. *syn N,N*-Diisopropyl 2-(1-hydroxyethyl)-1-naphthamide, *syn-3e*. Spectroscopic data identical to that reported in the literature.²⁸

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