Progress in Transition Metal-Based Enantioselective Catalysis

by

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B.S., Chemistry, 2003
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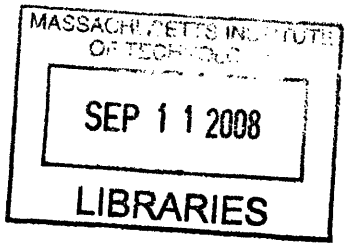

Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY
IN ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

September 2008

Signature of Author:_____
Department of Chemistry
July 14, 2008

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Gregory C. Fu
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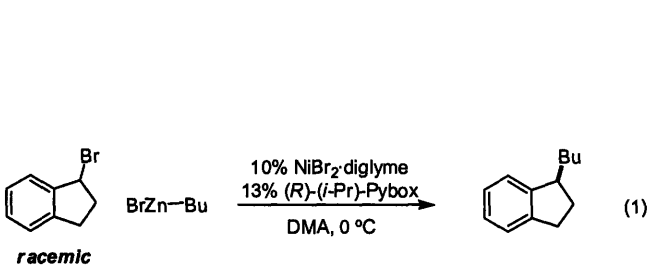
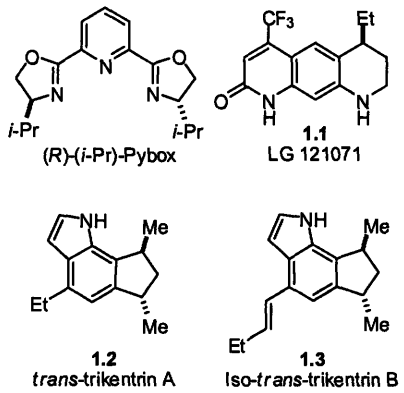
Abstract

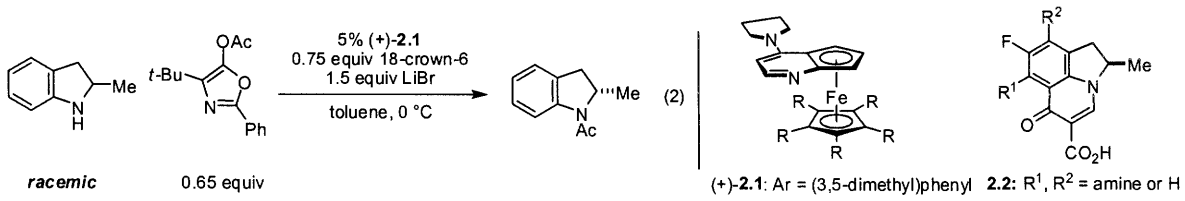
In Chapter 1, the first enantioselective cross-coupling reactions of racemic secondary benzylic halides are described (eq 1). This method was applied to the syntheses of intermediates employed by other groups in the generation of bioactive compounds, e.g., an androgen receptor agonist (**1.1**) and two members of the trikentrin family of natural products (**1.2** and **1.3**).





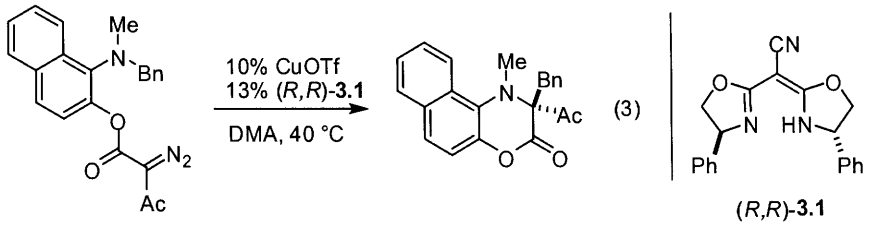
In Chapter 2, the first method for the kinetic resolution of indolines through catalytic N-acylation is described (eq 2). To improve the selectivity factor, a new planar-chiral PPY-derived catalyst (**2.1**) was prepared, wherein the chiral environment had been modified. The method was applied to the resolution of an intermediate prepared by K. Tsuji in the synthesis

of a series of novel antibiotics of core structure **2.2**. This work provides a rare example of a nonenzyme-based acylation catalyst for the kinetic resolution of amines.



racemic 0.65 equiv (+)-**2.1**: Ar = (3,5-dimethyl)phenyl **2.2**: R^1, R^2 = amine or H

Finally, in Chapter 3, the first examples of catalyzed, enantioselective insertion of carbenoid fragments into C–N sigma bonds are described (eq 3). The system uses commercially-available catalyst components and gives highly enantioselective rearrangements of benzylamine-, allylamine-, and α-aminocarbonyl-containing substrates. The method represents a new way to access 1,4-benzoxazinones, a subunit present in several pharmaceutical targets and chiral natural products.



(*R*,*R*)-**3.1**

Thesis Supervisor: Gregory C. Fu

Title: Professor of Chemistry

Portions of this document have appeared in the following publications:

Arp, F. O.; Fu, G. C. "Catalytic Enantioselective Negishi Reactions of Racemic Secondary Benzylic Halides" *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483.

Arp, F. O.; Fu, G. C. "Kinetic Resolutions of Indolines by a Non-Enzymatic Acylation Catalyst" *J. Am. Chem. Soc.* **2006**, *128*, 14264–14265.

Dedicated to my family, friends, labmates, and advisors

TABLE OF CONTENTS

Abbreviations

cod	1,4-cyclooctadiene
Boc	*t*-butoxycarbonyl
DIPEA	*N,N*-diisopropylethylamine
DMA	*N,N*-dimethylacetamide
DMAP	*N,N*-4-dimethylaminopyridine
DMI	*N,N*-dimethylimidazolidinone
DMF	*N,N*-dimethylformamide
DOSP	*N*-(*p*-dodecylphenylsulfonyl)prolinato
DPPP	1,3-bis(diphenylphosphino)propane
LHMDS	lithium bis(trimethylsilyl)amide
MOM	methoxymethyl
PPA	polyphosphoric acid
PPY	4-(pyrrolidin-1-yl)pyridine
Py	pyridine
TBA	tetra-*N*-butylammonium
TBAT	tetra-*N*-butylammonium triphenyldifluorosilicate
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TMEDA	*N,N,N',N'*-tetramethylethylenediamine

Chapter 1

Catalytic Enantioselective Negishi Reactions of Racemic Secondary Benzylic Halides

1.1 Background

Metal-catalyzed cross-coupling reactions are broadly defined as a set of reactions in which a new C–C bond (R^1–R^2; eq 1.1) is formed by union of an organometallic reagent (R^1–M) and an organic electrophile (R^2–X; X = halide, tosylate, etc.), through the agency of a transition-metal catalyst.[1]

$$R^1\text{–}M \quad R^2\text{–}X \xrightarrow{catalyst} R^1\text{–}R^2 \quad M\text{–}X \qquad (1.1)$$

The fundamental steps of a conventional, catalyzed cross-coupling are shown in Figure 1.1. The cycle initiates when the metal catalyst (L_nM^1) undergoes oxidative addition into the organic halide, producing an intermediate metal halide ($L_nM^1R^2X$). Then, in a transmetallation step, the metal halide and organometallic species transpose, producing a substituted metal intermediate ($L_nM^1R^1R^2$) and a second, terminal metal halide (M–X). Finally, the C–C bond is formed via reductive elimination of the substituted metal intermediate, and the metal catalyst is concomitantly regenerated. For differing cross-coupling systems, the precise mechanistic pathways of these fundamental steps can vary widely.[2]

[1] For reviews of metal-catalyzed cross-coupling reactions, see: (a) *Metal-catalyzed Cross-coupling Reactions,* 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed. Wiley Interscience: New York, 2002.

[2] For leading discussions and references on the fundamental steps of cross-couplings, see ref 1, and: *Principles and Applications of Organotransition Metal Chemistry* Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G., Eds.; University Science Books: Sausalito, 1987.

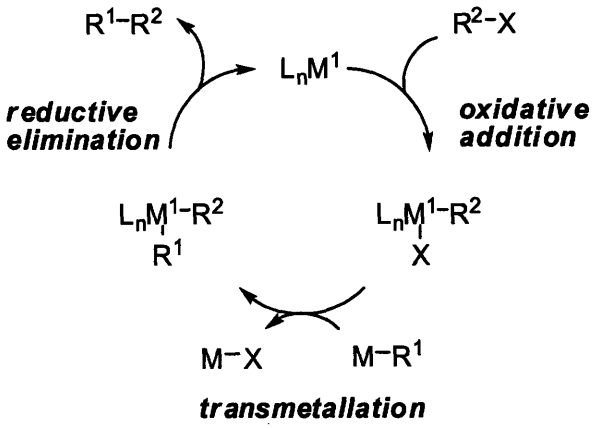


Figure 1.1. Conventional cross-coupling cycle.

Cross-coupling reactions are often called by common names, according to the family of organometallic nucleophile (Table 1.1). For the majority of this chapter, we will discuss reactions of organozinc nucleophiles, i.e., Negishi reactions.

Table 1.1. Named cross-coupling reactions.

Organometallic reagent	Reaction name
$R-BX_2$	Suzuki (Suzuki-Miyaura)
R–MgX	Kumada (Kumada-Corriu)
$R-SnX_3$	Stille (Migita-Kosugi-Stille)
$R-SiX_3$	Hiyama
R–ZnX	Negishi
$R-AlX_2$	
$R-ZrXCp_2$	

For decades, cross-coupling reactions have been a powerful way of synthesizing C–C bonds. Despite their utility, these reactions were seldom used for coupling β-hydride-containing substrates, owing to a general limitation that those substrates tended to preferentially undergo β-hydride elimination, rather than leading to coupling product formation (Figure 1.2). However, over the past several years, many nickel- and palladium-

based systems have emerged that are capable of circumventing the β-hydride elimination process and forming coupling products of alkyl fragments in useful yields.[3]

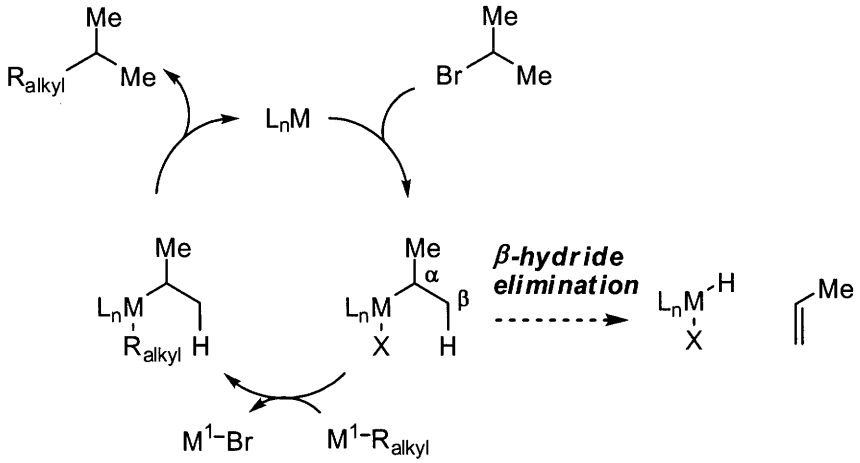
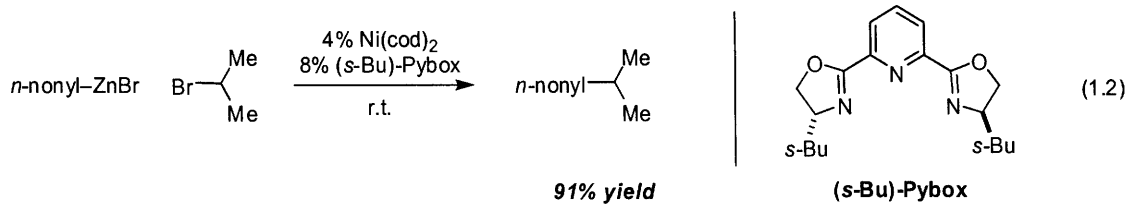


Figure 1.2. A conventional alkyl-alkyl cross-coupling cycle.

In 2003, Fu and Zhou reported the first nickel-based system that allowed coupling of primary nucleophiles with secondary electrophiles in good yield (91%, eq 1.2).[4] One salient feature of this system is the use of an enantiopure ligand, raising the question of whether *enantioselective* cross-couplings of chiral, secondary electrophiles are possible.



(1.2)

Prior to 2005, no enantioselective cross-couplings of β-hydride containing electrophiles were known, although many enantioselective cross-couplings with aryl and vinyl electrophiles had been reported.[5] For example, in 1983, Hayashi and Kumada

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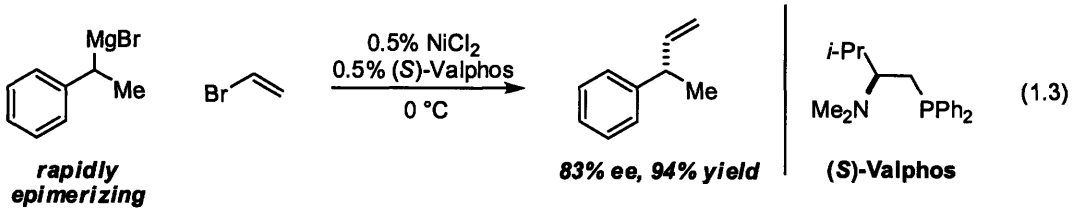
[3] Metal-catalyzed cross-coupling reactions of alkyl halides: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674–688. (b) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525–1532.

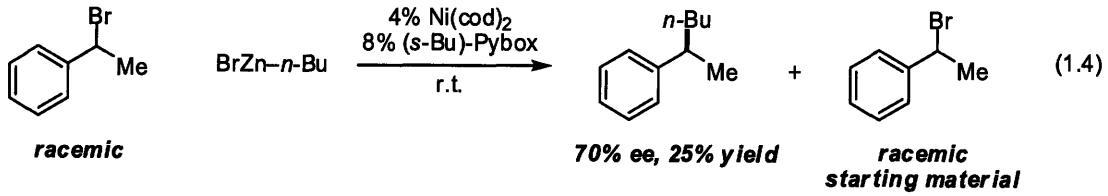
[4] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.

[5] Enantioselective cross-couplings of aryl and vinyl electrophiles: (a) Hayahi, T. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H. Eds.: Springer-Verlag: Berlin, Heidelberg, 2004; Chapter 25. (b) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453–3516. For a specific

demonstrated the use of $NiCl_2$ with a valine-derived phosphine to couple vinyl bromide fragments with benzylic Grignard nucleophiles in good enantioselectivities (83% ee, eq 1.3).[5c]



We felt that expanding the scope of enantioselective cross-couplings to include β-hydride-bearing alkyl coupling partners could ultimately be a valuable step forward in the methodology. In principle, it could be a highly convergent way to produce a wide variety of optically enriched stereocenters containing C–C bonds. In pursuit of that goal, Zhou obtained promising selectivities with the original $Ni(cod)_2$/Pybox system and racemic 1-bromoethylbenzene electrophile (70% ee, eq 1.4).[6] The reaction initially gave low yields of product, but with recovery of *racemic* starting material, indicating that the reaction may be exhibiting stereoconvergent product formation. This result marked the beginning of my studies in cross-coupling chemistry.



Concurrently with the studies of benzylic halides, Dr. Christian Fischer discovered high selectivities in cross-couplings of α-bromoamides (eq 1.5).[7] This reaction was certainly stereoconvergent (96% ee, 90% yield), and, if run to partial conversion, also gave racemic

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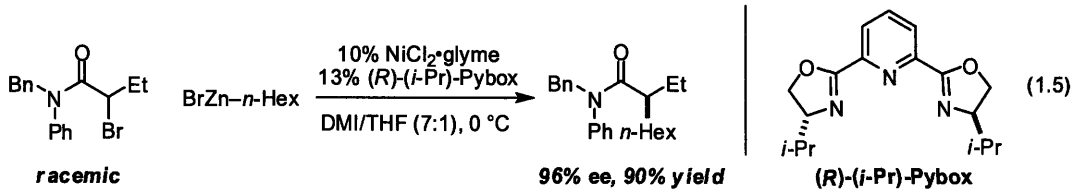
example, see: (c) Hayashi, T., Konishi, M., Fukushima, M.; Kanehira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195–2202.

[6] Zhou, J. Ph. D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, September 2005.

[7] Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595

recovered starting material. The catalyst is composed of commercially available ligands and $NiCl_2$·glyme, which is more stable to heat and light and is less toxic than $Ni(cod)_2$.



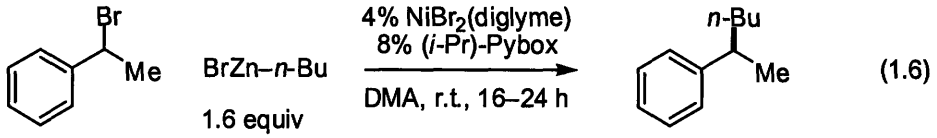
(1.5)

1.2 Results and Discussion

Initial efforts to improve the yields and enantioselectivities of benzyl halide cross-couplings gave limited success. As with the α-bromoamide system, a Ni(II)-source could be incorporated, but we could not bolster enantioselectivities beyond moderate levels (75% ee, eq 1.6).

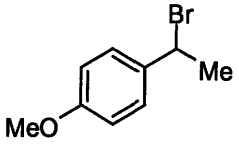
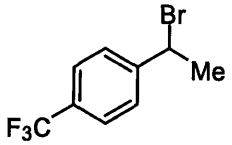
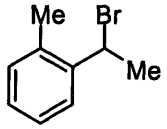
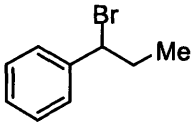
On exploration of substrate scope (Table 1.2), we found that electronic perturbations on the aryl ring did not improve selectivities (entries 1 and 2). Increased hindrance on the aryl ring or on the alkyl chain gave much lower product yields (entries 3 and 4). However, employing indane-based electrophiles resulted in higher enantioselectivities and yields of product (92% ee, 80% yield; entry 6). Other fused-ring systems were less effective in terms of both chemical yield and enantioselectivity.

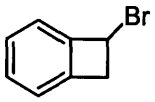
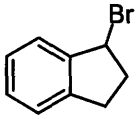
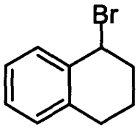
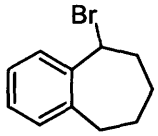
Table 1.2. Early substrate screening.



(1.6)

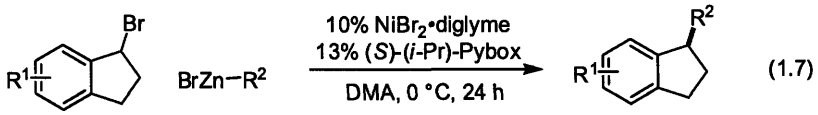
racemic ***75% ee, 50% yield***

entry	substrate	yield	ee
1		60	40
2		41	48
3		<5	–
4		8	64

entry	substrate	yield	ee
5		68	16
6		80	92
7		10	33
8		9	42

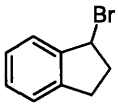
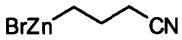
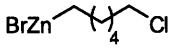
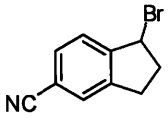
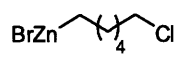
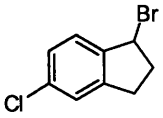
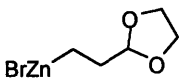
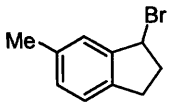
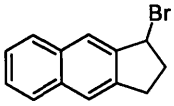
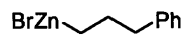
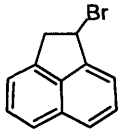
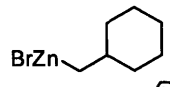
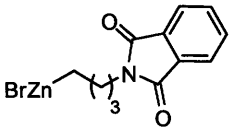
The optimized indane system (eq 1.7) gives high enantioselectivities across a range of indane coupling reactions (Table 1.3). As in the α-bromoamide-based system, the nickel-source and both enantiomers of ligand are commercially available. Additionally, the system does not appear to be highly air- or moisture-sensitive. The final entries were set up in air with untreated glassware, and the reaction vessels were purged with an inert gas (nitrogen or argon) prior to the reaction initiation.

Table 1.3. Catalytic enantioselective Negishi reactions of racemic bromoindanes.[a]



(1.7)

racemic

entry	R^1-X	R^2-ZnBr	yield (%)	ee (%)
1			64	91
2			69	94
3			47	91
4			82	91
5		BrZn–*n*-Hex	89	96
6			76	98
7		BrZn–*n*-Bu	72	98
8[b]			39	96
9[b]			41	99

[a] All data are the average of two experiments. [b] The coupling was performed at room temperature.

Organozinc reagents bearing a cyano, chloro, or acetal functional group cross-couple with high enantioselectivities (entries 1–4), as do those with alkyl branching at the β-carbon or with imines (entries 8 and 9), albeit with more modest chemical yield. Incorporation of a second fused benzo-ring bolsters enantioselectivities further (entries 6–9). In those cases, we may be benefiting from an enhanced substrate-ligand π-π interaction.

Although nickel-based cross-couplings of aryl and alkyl chlorides are known,[8] we did not observe the corresponding aryl- or alkyl-chloride coupling products in our system (entries 2–4). 1-Chloroindanes were suitable coupling partners in these systems (Figure 1.3). In comparison with 1-chloroindane and 1-bromoethylbenzene, the open-chain 1-chloroethylbenzene was repeatedly shown to give poor chemical yields and comparatively low conversion (ca. 33% recovered starting material).

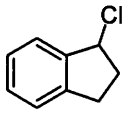
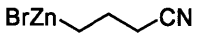
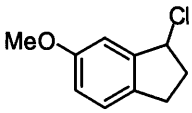
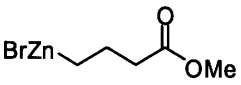
89% yield, 94% ee ca. 8% yield, 63% ee

Figure 1.3. Racemic benzylic chlorides, with yields and enantioselectivities resulting from cross-coupling reactions with *n*-Bu–ZnBr (eq 1.6).

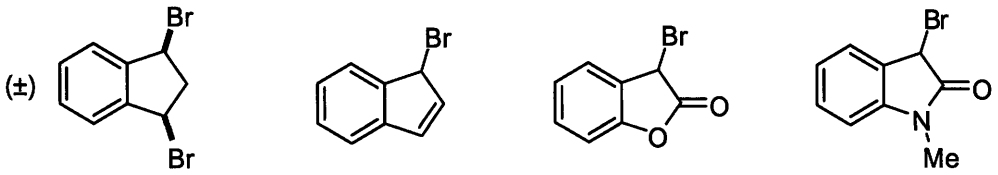
We demonstrated two chloroindane couplings under our finalized conditions (eq 1.7; Table 1.4). As with the parent chloroindane system used in preliminary studies (Figure 1.3), these chloroindane substrates coupled in comparable yield and enantioselectivity to their bromoindane counterparts.

[8] Nickel-based systems that cross-couple aryl chlorides: (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374–4376. (b) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058. A nickel-based system that cross-couples alkyl chlorides: (c) González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361.

Table 1.4. Final 1-chloroindane couplings.

entry	R^1-X	R^2-ZnBr	yield (%)	ee (%)
1			56	91
2			61	93

Some electrophiles containing a 6,5-fused ring architecture were not suitable reaction partners in our final system (Figure 1.4). *cis*-1,3-Dibromoindane (**1.4**) underwent full conversion, but produced 68% indene side product under the reaction conditions, with no other detectable products. The indene may arise from a decomposing benzylic radical intermediate (see Section 1.3). Bromoindene (**1.5**) also underwent full conversion, producing traces of product (<5% yield, <10% ee), with ca. 30% electrophile homocoupling side products detected. Coumaranone **1.6** and oxindole **1.7** both gave low conversion, with no detectable product.



1.4 **1.5** **1.6** **1.7**

Figure 1.4. Electrophiles with a 6,5-fused ring framework that perform inefficiently in cross-coupling reactions.

It is notable in the above context that control reactions run in the presence of a full equivalent of indene gave ca. 43% recovery of that indene, after the course of the reaction (eq

1.8). One explanation for the consumption of indene is its adventitious polymerization, possibly mediated by nickel.[9]

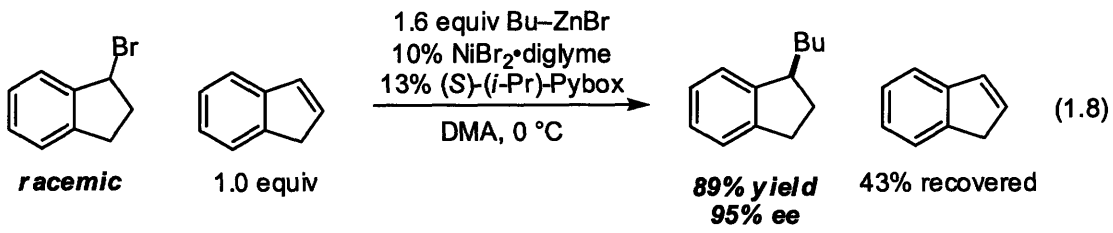


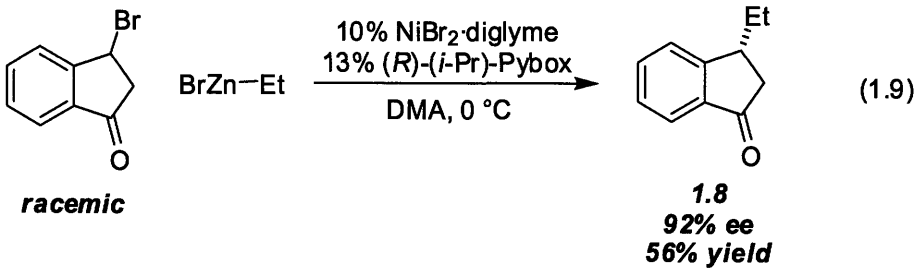
Figure 1.5 shows nucleophiles inefficient in bromoindane coupling systems. Poor yields were observed with phenylzinc, benzylzinc, and cyclohexylzinc reagents. Dimethylzinc did produce moderate amounts of product, but in decreased enantioselectivity.

Bn–ZnBr	Ph–ZnBr	Ph–ZnI
< 5% yield	12% yield, <10% ee	23% yield, <10% ee
$ZnMe_2$	$ZnPh_2$	Cy–ZnI
50% yield, 77% ee	5% yield, 38% ee	<10% yield

Figure 1.5. Organozinc nucleophiles that perform inefficiently in cross-coupling reactions.

Although our final system was highly enantioselective only in the case of indane electrophiles, we found several instances in the literature where the method could be employed in the formation of useful products. For example, compound **1.8** could be prepared in high ee's and moderate yields in only two steps from commercially available starting materials (eq 1.9).

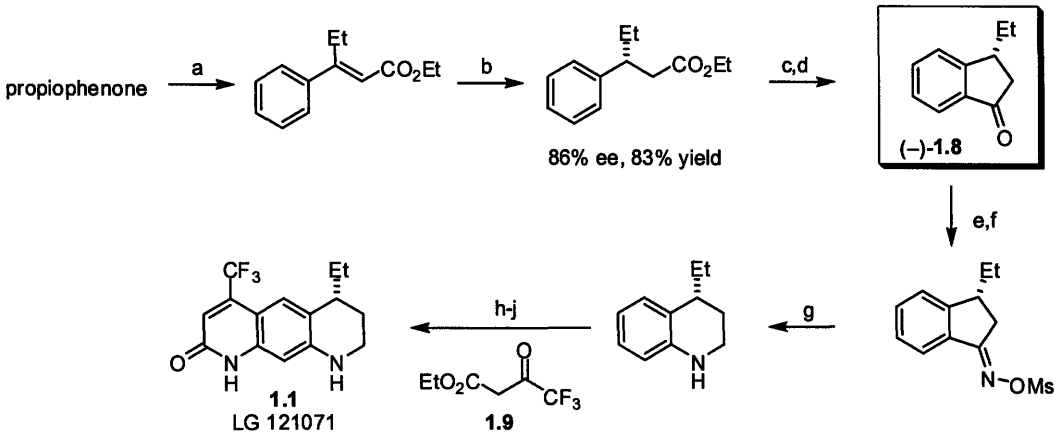
[9] For a review of nickel-catalyzed ethylene polymerization, including systems using oxazoline-based ligands, see: Speiser, F.; Braunstein, P.; Saussine, L. *Acc. Chem. Res.* **2005**, *38*, 784–793.



(1.9)

This compound had previously been used by Ligand Pharmaceuticals en route to target LG 121071 (**1.1**; Scheme 1.1), the first orally active non-steroidal androgen receptor agonist.[10] Their route proceeded in a four-step sequence that generated the benzylic stereocenter though a Cu-catalyzed hydrosilylation.[11] The 5-membered ring was formed by acid-mediated condensation, and then expanded to the 6-membered ring through a Beckman rearrangement.

Scheme 1.1. Synthesis of LG 121071 by Ligand Pharmaceuticals (**1.1**).[a]



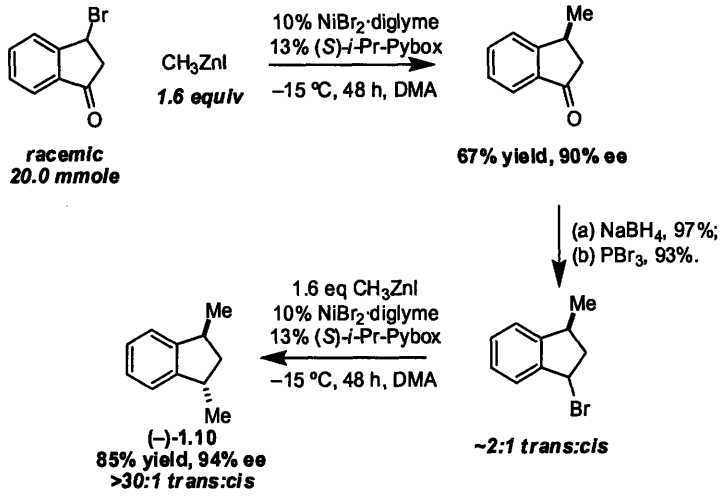
[a] Reagents and conditions: (a) triethylphosphonoacetate, NaH; (b) (*R*)-*p*-tol-BINAP, CuCl, NaO*t*-Bu, PMHS; (c) NaOH; (d) PPA; (e) NH_2OH•HCl, KOH; (f) MsCl, TEA; (g) DIBAL-H; (h) HNO_3, H_2SO_4; (i) H_2, Pd/C; (j) **1.9**, $ZnCl_2$.

We also synthesized the enantioenriched compound (–)-**1.10** in a five-step sequence, wherein our coupling methodology was used twice to set the two stereocenters (Scheme 1.2).

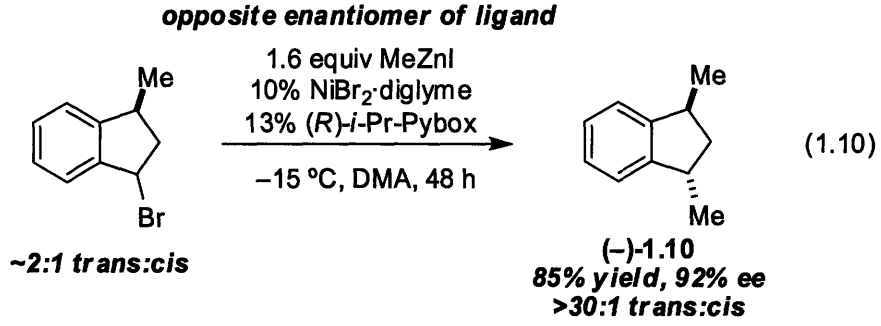
[10] (a) Hamann, L. G.; Mani, N. S.; Davis, R. L.; Wang, X.-N.; Marschke, K. B.; Jones, T. K.; *J. Med. Chem.* **1999**, *42*, 210–212. (b) Mani, N. S.; Wu, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4687–4691.

[11] Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473–9474.

Scheme 1.2. Synthesis of enantioenriched dimethylindane (–)-**1.10**.



This sequence also afforded us an opportunity to test whether the final methylation was occurring under catalyst or substrate control. Thus, in eq 1.10, when the opposite enantiomer of Pybox ligand was employed under otherwise identical conditions, we still obtained ca. 30:1 selectivity favoring *trans*-(–)-**1.10**, indicating that the second stereocenter is set under substrate control.



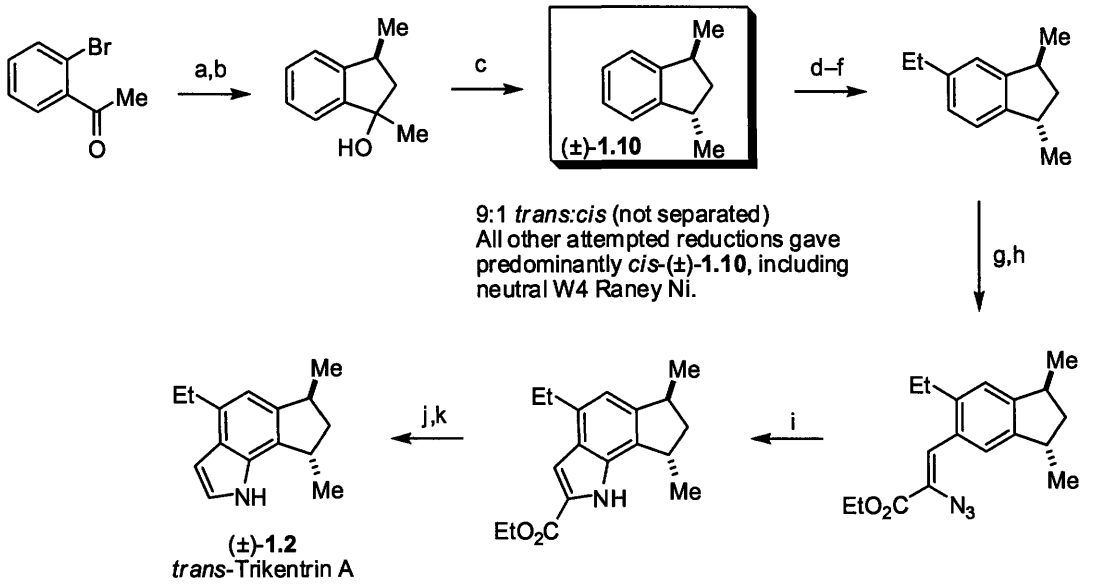
(1.10)

To our knowledge this was the first instance of an enantioselective preparation of **1.10**. However, racemic **1.10** had previously been used by MacLeod in the syntheses of *trans*-trikentrin A[12] and iso-*trans*-trikentrin B.[13]

[12] Monahan, L. C.; MacLeod, J. K. *Aust. J. Chem.* **1990**, *43*, 329–337.
[13] MacLeod, J. K.; Ward, A.; Willis, A. C. *Aust. J. Chem.* **1998**, *51*, 177–187.

The synthesis of *trans*-trikentrin A (Scheme 1.3) begins with Bu_3SnH-mediated radical ring-closure to produce the 6,5-fused core. After screening several reaction conditions, it was discovered that alkaline W4 Raney nickel reduction gave the target *trans*-(±)-**1.10** product in a 9:1 ratio versus *cis*-(±)-**1.10**. Friedel-Crafts acylation, followed by $C–H_{aryl}$ nitrene insertion produced the trikentrin core, and subsequent saponification-decarboxylation yielded the final natural product.

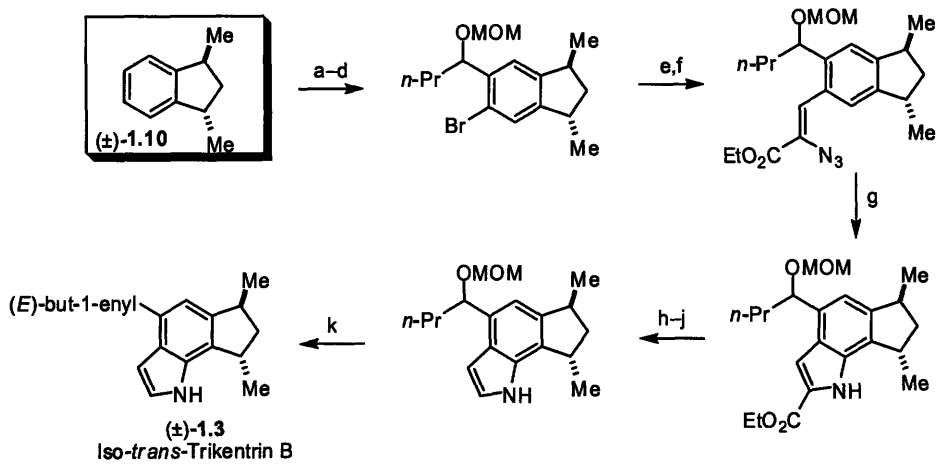
Scheme 1.3. Synthesis of (±)-*trans*-trikentrin A by MacLeod.[a]



[a] Reagents and conditions: (a) allylmagnesium bromide; (b) Bu_3SnH; (c) alkaline W4 Raney Ni, H_2; (d) AcCl, $AlCl_3$; (e) $NaBH_4$; (f) H_2, Pd/C; (g) dichloromethyl methyl ether, $TiCl_4$, then H_2O; (h) ethyl 2-azidoacetate, base; (i) toluene, reflux; (j) KOH, 1,4-dioxane, reflux; (k) flash vacuum pyrolysis.

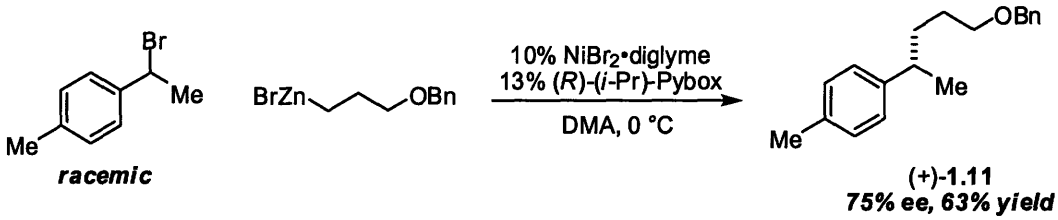
Iso-*trans*-trikentrin B (**1.3**) was also prepared from the intermediate (±)-**1.10** (Scheme 1.4). This sequence proceeded first through installation of a MOM ether fragment, and then indole formation through nitrene insertion. The MOM ether was eliminated with dimethyl bromoborane, producing the final (*E*)-but-1-enyl side chain, and target **1.3**.

Scheme 1.4. Synthesis of Iso-*trans*-trikentrin B by MacLeod.[a]



[a] Reagents and conditions: (a) butyryl chloride, $AlCl_3$; (b) $NaBH_4$; (c) n-BuLi, CBr_4; (d) DMAP, DIPEA, MOM–Cl; (e) n-BuLi, DMF; (f) ethyl azidoacetate, Na^0, EtOH; (g) 135 °C; (h) DIBAL–H; (i) MnO_2; (j) $RhCl(CO)(PPh_3)_3$, DPPP; (k) BMe_2Br.

We were also able to access an open-chain target (+)-**1.11** in a two-step sequence, albeit with more modest enantioselectivity (eq 1.11). This molecule had previously been used by Takano in the syntheses of a series of natural products.

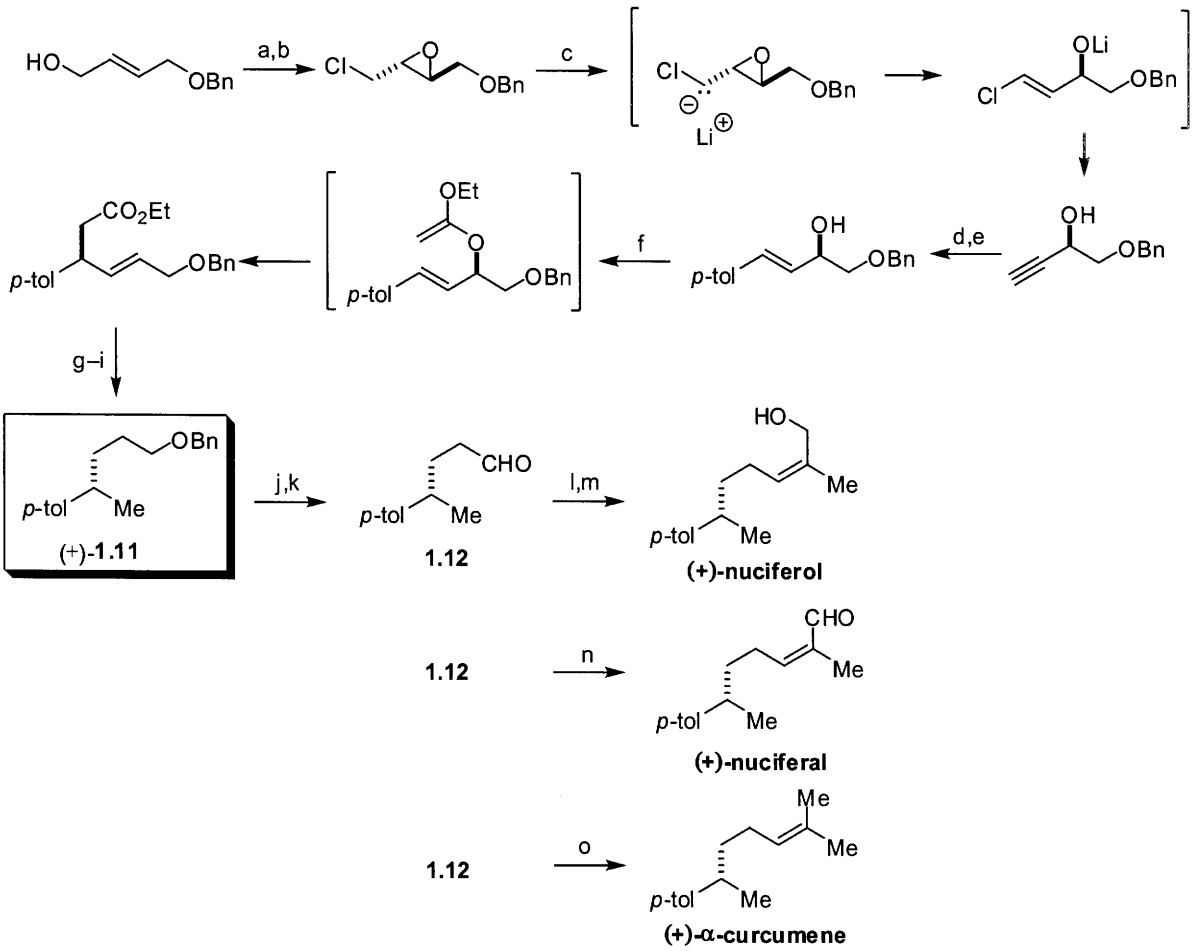


(1.11)

Takano previously synthesized fragment (+)-**1.11** through a 9-step sequence from *trans*-2-butene-1,4-diol (Scheme 1.5).[14] The route features a Sharpless asymmetric epoxidation, base-mediated epoxide opening, and a Claisen rearrangement to set the benzylic stereocenter. After deprotection and oxidation, they access aldehyde intermediate **1.12**, which is used to prepare three natural products: (+)-nuciferol, (+)-nuciferal, (+)-α-curcumene.

[14] Takano, S.; Sugihara, T.; Samuzi, K.; Akiyama, M.; Ogasawara, K. *Chem. Lett.* **1989**, 1781–1784. Previously, (+)-**1.11** had been synthesized in a 13-step route from mannitol: Takano, S.; Goto, E.; Ogasawara, K. *Tetrahedron Lett.* **1982**, *23*, 5567–5570.

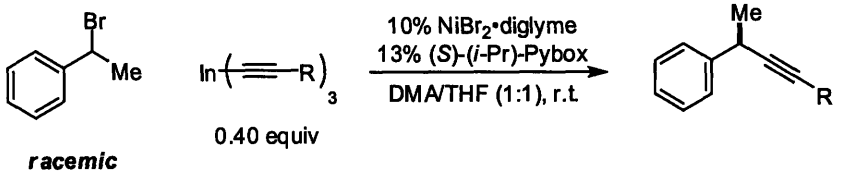
Scheme 1.5. Synthesis of three natural products from (+)-**1.11**, by Takano.[a]



[a] Reagents and conditions: (a) Sharpless AE; (b) PPh_3, CCl_4; (c) *n*-BuLi; (d) *p*-tol–I, cat. $PdCl_2(PPh_3)_2$, cat. CuI, TEA; (e) $LiAlH_4$; (f) $MeC(OEt)_3$, cat. pivalic acid; (g) cat. $Hg(I)(OAc)_2$, ethyl vinyl ether; (h) H_2, Pd/C; (i) $(PPh_3)_3RhCl$; (j) H_2, Pd/C; (k) Swern; (l) $Ph_3P{=}CHMe$; (m) *n*-BuLi; CH_2O; (n) EtCH=N*t*-Bu, LDA; H_3O^+; (o) $Ph_3P{=}CH(i\text{-}Pr)$.

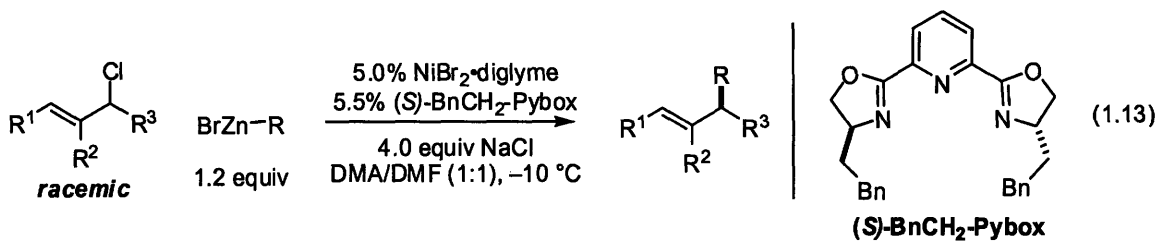
Recent Work

In 2008, Sestelo and Sarandeses reported a closely related Ni/pybox system that is capable of coupling alkynylindium nucleophiles with benzylic bromides in good enantioselectivities (eq 1.12).[15]



(1.12)

Within the Fu group, Sunghee Son reported a pybox-based system capable of coupling allylic chloride substrates with organozinc reagents in high enantioselectivities (eq 1.13) in 2008.[16] Other group members have observed excellent selectivities for Ni/pybox-based systems that couple α-bromoketones and propargylic halide substrates.

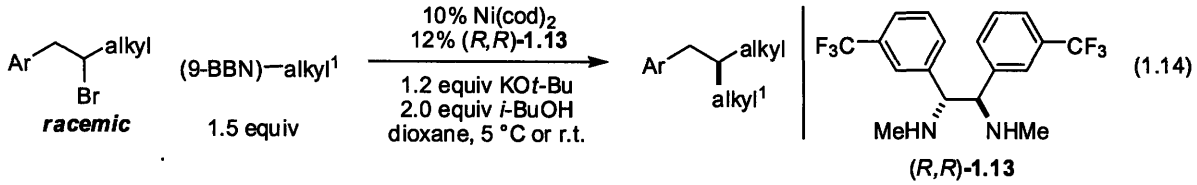


(1.13)

In 2006, Dr. Francisco Gonzalez-Bobes reported that aminoalcohol ligands are suitable components in systems that mediate the couplings of arylboronic acids and alkyl halides (non-asymmetric).[8c] Soon thereafter, Dr. Bunnai Saito applied diamine ligands to cross-couplings of alkyl-9-BBN nucleophiles,[17] and then he demonstrated asymmetric couplings of 9-BBN nucleophiles with unactivated homobenzylic bromides (eq 1.14).[18]

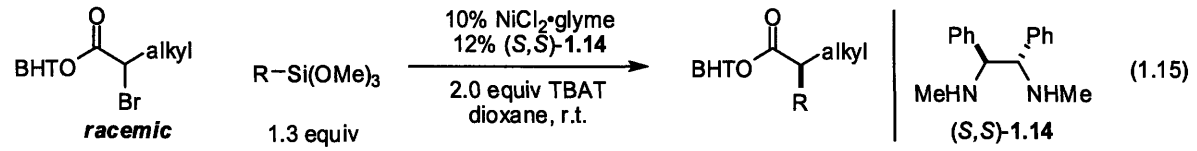
---

[15] Caeiro, J.; Sestelo, J. P.; Sarandeses, L. A. *Chem. Euro. J.* **2008**, *14*, 741–746.
[16] Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 2756–2757.
[17] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603.
[18] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695.



(1.14)

Earlier in 2008, Drs. Xing Dai and Neil Strotman had demonstrated that diamine ligands could also be used in asymmetric couplings of Hiyama couplings of α-bromoester electrophiles (eq 1.15).[19] Additionally, our group has obtained preliminary high selectivities in couplings of α-bromoketones using Ni/bisoxazoline systems.



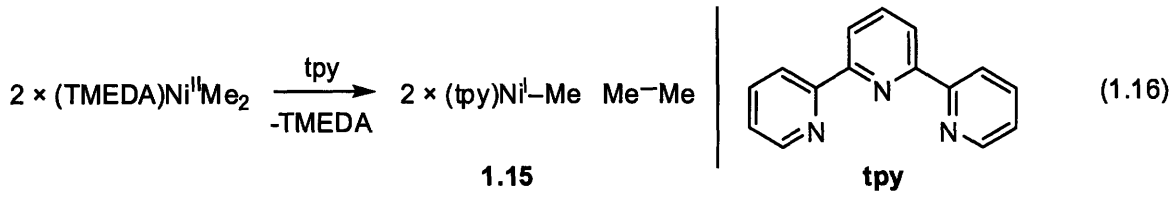
(1.15)

[19] Dai, X.; Strotman, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 3302–3303.

1.3 Mechanistic Discussion

In the two-year interim between the achiral secondary cross-coupling by Zhou and the 2005 reports of enantioselective couplings, the Vicic lab advanced a mechanistic hypothesis for alkyl-alkyl cross-couplings.[20]

They initially believed, on the basis of stoichiometric control experiments, that the active catalyst was an alkylated Ni(I) species (**1.15**), which was produced through ligand exchange of the dialkylated Ni(II) precursor, along with concomitant expulsion of a free methyl radical that homocouples in situ to form ethane (eq 1.16).



(1.16)

Vicic went on to propose that the active catalytic cycle proceeded via a Ni(I)/Ni(II) shuttle (Figure 1.6), wherein two free alkyl radical fragments were expelled during successive steps, and that final C–C bond formation was a result of free radical coupling (eq 1.17), as opposed to classic reductive elimination. Vicic isolated complex **1.15**, characterized it by X-ray crystallography, and demonstrated its chemical competence as a catalyst for alkyl-alkyl cross-coupling reactions.

[20] Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100–8101.

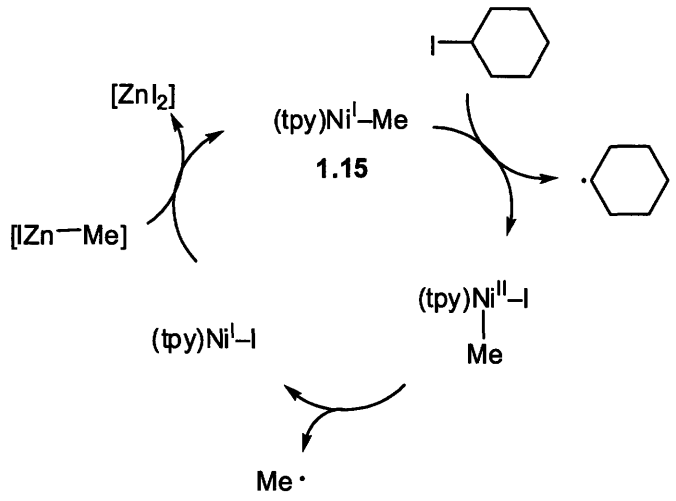
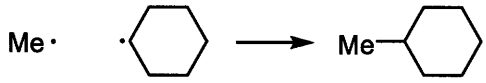
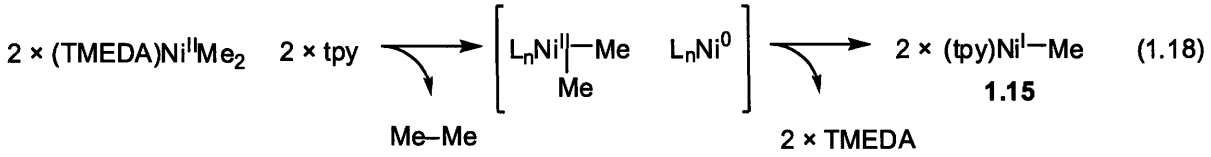


Figure 1.6. The first mechanistic proposal regarding alkyl-alkyl cross-couplings by Vicic.



(1.17)

In 2005, Vicic issued a revised mechanism, on the basis of updated stoichiometric control experiments.[21] The revised mechanism is thought to initiate via ligand-initiated loss of ethane, and then comproportionation of the resulting Ni(II) and Ni(0) species to generate the proposed active catalyst, **1.15** (eq 1.18).



(1.18)

The revised catalytic cycle proceeds through a Ni(I)/Ni(III) shuttle, wherein the final C–C bond is produced through a classic reductive elimination (Figure 1.7). This Ni(I)/(III) cycle was evaluated computationally, and the mechanism was deemed feasible for primary

[21] (a) Jones, G. D.; McFarland, C.; Anderson, T. J.; Vicic, D. A. *Chem. Comm.* **2005**, 4211–4213. (b) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183.

alkyl halides, but less likely for secondary alkyl halides, due to an unfavorable reductive elimination step.[22,23]

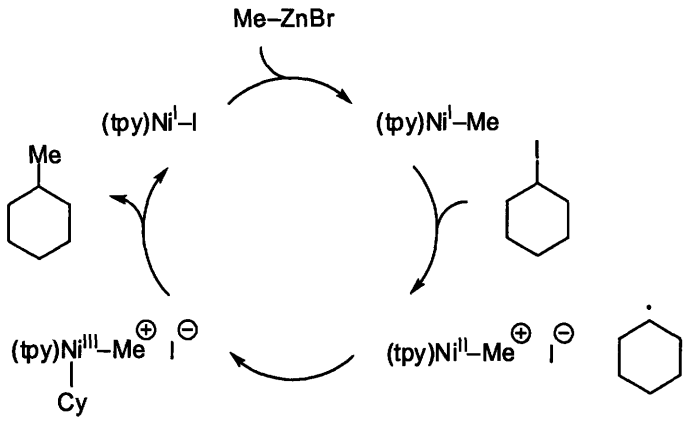


Figure 1.7. The revised catalytic cycle by Vicic.

Both of these mechanisms propose that oxidative addition proceeds first through radical formation at the formerly halogenated carbon, and then combination of alkyl radical and metal center, to generate the Ni–C bond. This is notable in that it provides a rationale for stereoconvergence, i.e., that a free alkyl radical, having a rapidly-inverting geometry, could lose its stereoinformation during the oxidative addition step.

Kochi has studied oxidative additions of Ni(0) complexes into aryl halides (Figure 1.8).[24] Through a fairly rigorous investigation, Kochi concluded that the Ni(0) species likely forms a π-complex with the aryl halide (**1.16**), and then transfers a single electron into that aryl halide, producing a close radical-ion pair (**1.17**). Then, C–X bond fragmentation and Ni–Br bond formation occur, through either concerted or stepwise processes, resulting in a *neutral* radical pair that undergoes collapse within a solvent cage to afford the Ni(II) adduct.

[22] Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680–3688.
[23] Kochi has proposed a Ni(I)/(III) cycles in the past for nickel-mediated aryl-aryl couplings: Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 7547–7560.
[24] Tsou, T. T.; Kochi, J. K. J. Am. Chem. Soc. 1979, 101, 6319–6332

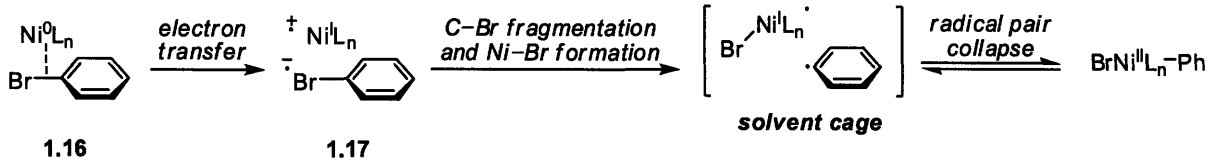


Figure 1.8. The proposed mechanism for Ni(0) insertion into an Ar–X bond, by Kochi.

Although he did not undertake in-depth studies on the corresponding alkyl electrophiles, Kochi speculates that those species are more likely to pre-coordinate to the Ni(0) in an end-on η^1-complex, and that electron transfer proceeds through an inner-sphere route, as opposed to an η^2 π-complex with outer-sphere electron transfer as in the case of Ar–X.[25]

Our lab has also obtained other preliminary evidence, pointing to the possibility of alkyl radical intermediates. In two nickel-based systems for Suzuki couplings of arylboronic acids and alkyl electrophiles, we have observed that *endo*- and *exo*-2-bromonorbornane both convert to the same *exo*-cross-coupling product, each in greater than 20:1 selectivity over the *endo*-product (Figure 1.9).[26,8c]

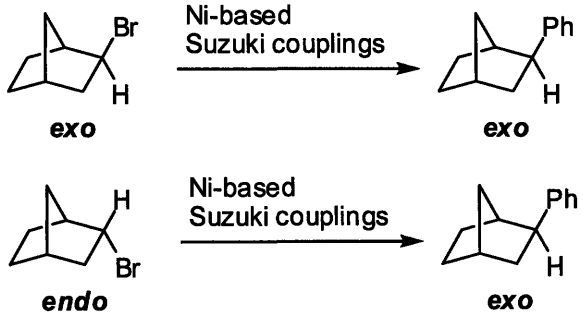
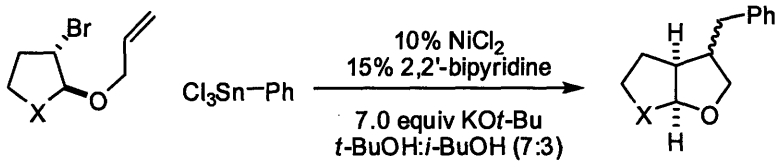


Figure 1.9. Convergent product formation in Ni-based Suzuki cross-couplings.

Additionally, in a study of nickel/bipyridine-mediated Stille couplings of secondary alkylbromides **1.18** and **1.19**, we observe formation of the corresponding 5-exo-trig cyclization products (**1.20** and **1.21**; eq 1.19), where the cis/trans ratios of cross-coupling

[25] For a discussion on inner-sphere vs. outer-sphere electron transfer, see: *Principles and Applications of Organotransition Metal Chemistry* Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G., Eds.; University Science Books: Sausalito, 1987; pp 308–309.
[26] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341.

products correlate with the ratios of previous radical cyclization studies of these substrates.[27] The same phenomenon was observed in nickel-mediated Suzuki couplings of arylboronic acids and alkyl halides,[8c] and in a study by Cárdenas of alkyl-alkyl Negishi cross-couplings.[28]

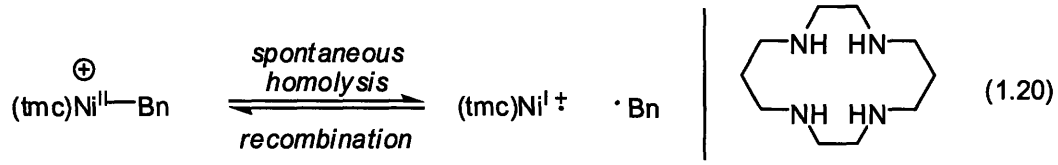


(1.19)

1.18, X = CH_2
1.19, X = O

1.20, X = CH_2; 67% (2:1 endo:exo)
1.21, X = O; 57% (>20:1 endo:exo)

Another possible explanation for our observed stereoconvergence, apart from radical formation during oxidative addition, is spontaneous in situ Ni–C bond homolysis. Ni–C bond homolysis has long been discussed as a route to observed side products in cross-couplings, and in 2003 Schofield and Halpern reported an empirical bond-dissociation energy for the homolysis of Ni(tmc) species (ΔH = 19 kcal/mol; eq 1.20).[29] This process was facile at room temperature.



(1.20)

BDE: 19±1 kcal/mol

tmc

[27] Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *127*, 510–511.
[28] Cárdenas also observed instances of cyclopropyl ring-opening cross-coupling products: Phapale, V. B.; Buñuel, E.; García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790–8795.
[29] Schofield, M. H.; Halpern, J. *Inorg. Chim. Acta* **2003**, *345*, 353–358.

1.4 Conclusion

The first enantioselective cross-coupling reactions of racemic secondary benzylic halides have been described, and the method was applied to the syntheses of intermediates used by other groups in the generation of bioactive compounds.[30]

[30] Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483.

1.5 Experimental Section

I. General

N,N-Dimethylacetamide (DMA; anhydrous in a Sure-Seal® bottle; Fluka), $NiBr_2$·diglyme (Aldrich), I-(*i*-Pr)-Pybox (Aldrich), (*S*)-(*i*-Pr)-Pybox (Fluka), and pyridine (anhydrous in a Sure-Seal® bottle; Fluka) were used as received. CH_2Cl_2 was dried by passage through a neutral alumina column under argon pressure prior to use. All other chemicals were reagent-grade and used as received.

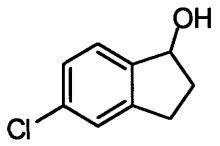
Note: Although $NiBr_2$·diglyme and (*i*-Pr)-Pybox can be left in the air without any impact on cross-coupling efficiency, we recommend that, for long-term storage, they be kept under an inert atmosphere.

HPLC analyses were carried out on an Agilent 1100 Series system with Daicel Chiralpak® columns in hexanes/isopropanol mixtures. GC analyses were performed on a Hewlett-Packard HP 6850 Series apparatus with a Chrompack capillary column 'CP Chirasil-Dex CB' (25 m x 0.25 mm x 0.25 mm), unless otherwise noted.

II. Preparation of Substrates

The yields in this section have not been optimized.

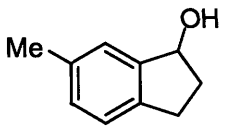
$NaBH_4$ Reduction Procedure. A 250-mL round-bottomed flask was charged with the indanone and a mixture of 1,2-dichloroethane/methanol (1:1; 50 mL). $NaBH_4$ (2 equiv) was then added to the stirred mixture, and the resulting clear, colorless solution was allowed to stir open to the air for 30 min. Then, the reaction mixture was transferred to a separatory funnel with the aid of water (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to furnish the product as either a white solid or a clear, colorless oil.



5-Chloro-1-indanol [33781-38-3]. This compound was reduced according to the Reduction Procedure using 5-chloro-1-indanone (2.08 g, 12.5 mmol) and $NaBH_4$ (946 mg, 25.0 mmol). The product was obtained as a white solid (2.01 g, 95%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.20 (m, 1H), 7.23-7.20 (m, 2H), 5.20 (t, J = 6.0 Hz, 1H), 3.07-2.99 (m, 1H), 2.84-2.76 (m, 1H), 2.54-2.46 (m, 1H), 2.00-1.91 (m, 2H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.3, 143.4, 134.0, 126.9, 125.3, 125.0, 75.7, 36.1, 29.6.

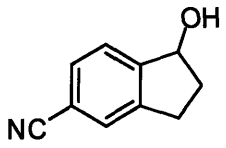


6-Methyl-1-indanol [200425-63-4]. This compound was reduced according to the Reduction Procedure using 6-methyl-1-indanone (0.989 g, 6.77 mmol) and $NaBH_4$ (500 mg,

13 mmol). The product was obtained as a clear, colorless oil (0.947 mg, 94%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.25 (s, 1H), 7.17-7.15 (m, 1H), 7.11-7.09 (m, 1H), 5.24-5.19 (m, 1H), 3.06-2.99 (m, 1H), 2.83-2.75 (m, 1H), 2.53-2.45 (m, 1H), 2.38 (s, 3H), 1.99-1.89 (m, 2H);

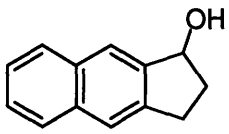
^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.1, 140.2, 136.3, 129.1, 124.7, 124.6, 76.4, 36.2, 29.3, 21.2.



5-Cyano-1-indanol [125114-88-7]. This compound was reduced according to the Reduction Procedure using 5-cyano-1-indanone[31] (540 mg, 3.44 mmol) and $NaBH_4$ (260 mg, 6.87 mmol). The product was obtained as a white solid (498 mg, 91%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55-7.51 (m, 3H), 5.31-5.26 (m, 1H), 3.10-3.04 (m, 1H), 2.89-2.83 (m, 1H), 2.60-2.53 (m, 1H), 2.09 (br s, 1H), 2.02-1.95 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.3, 144.1, 130.7, 128.4, 124.9, 119.1, 111.3, 75.5, 35.5, 29.4.



1-Benz[*f*]indanol [123332-18-3]. This compound was reduced according to the Reduction Procedure using benz[*f*]indanone[32] (499 mg, 2.74 mmol) and $NaBH_4$ (200 mg, 5.3 mmol). The product was obtained as a white solid (503 mg, 100%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87-7.84 (m, 2H), 7.81-7.79 (m, 1H), 7.70 (s, 1H),

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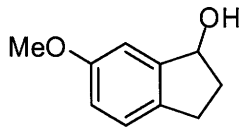
[31] Arnold, D. R.; Du, X.; Chen, J. *Can. J. Chem.* **1995**, *73*, 307–318.
[32] (a) Becker, C. L.; McLaughlin, M. L. *Synlett* **1991**, 642. (b) Jones, D. W.; Marmon, R. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3271–3275.

7.48-7.41 (m, 2H), 5.39 (dd, J = 6.0, 6.1 Hz, 1H), 3.26-3.19 (m, 1H), 3.02-2.94 (m, 1H), 2.60-2.52 (m, 1H), 2.09-2.01 (m, 1H), 1.81 (d, J = 6.6 Hz, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.2, 141.5, 133.9, 132.9, 128.1, 127.6, 125.8, 125.2, 122.9, 122.6, 75.9, 36.7, 29.3.

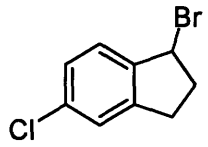


6-Methoxy-1-indanol [3469-09-8]. This compound was reduced according to the Reduction Procedure using 6-methoxy-1-indanone (2.23 g, 13.7 mmol) and $NaBH_4$ (1.04 g, 27.5 mmol). The product was obtained as a white solid (2.18 g, 97%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.15 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.83 (dd, J = 2.5, 8.3 Hz, 1H), 5.22-5.21 (m, 1H), 3.82 (s, 3H), 3.02-2.95 (m, 1H), 2.80-2.72 (m, 1H), 2.57-2.48 (m, 1H), 1.99-1.91 (m, 1H), 1.81 (br s, 1H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.0, 146.3, 135.0, 125.5, 115.0, 108.7, 76.6, 55.5, 36.6, 28.9.

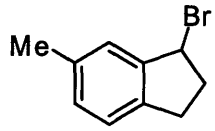
PBr_3/PCl_3 Halogenation Procedure. A dry 250-mL round-bottomed flask was charged with the benzylic alcohol and then placed under a nitrogen atmosphere. Dry CH_2Cl_2 (~50 mL) and dry pyridine (0.1 mL) were added, and then the reaction mixture was cooled to –10 °C in an *iso*-propanol/ice bath. PBr_3 (0.5 equiv) was dissolved separately in dry CH_2Cl_2 (5 mL), and the resulting solution was added portionwise over a period of 10 min to the solution of the alcohol. The mixture was allowed to stir for an additional 20 min, and then the solution was transferred to a separatory funnel with the aid of 5% aqueous Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum to give a yellow residue that was taken up in ether (10 mL), passed through an Acrodisc®, and then concentrated, furnishing the desired benzylic halide as either a clear, colorless oil or a white solid.



1-Bromo-5-chloroindane [192702-71-9]. This compound was prepared according to the Halogenation Procedure using 5-chloro-1-indanol (2.01 g, 11.9 mmol), PBr_3 (1.61 g, 5.95 mmol), and dry pyridine (0.1 mL). The product was obtained as a clear, light-pink oil (1.57 g, 57%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.34 (m, 1H), 7.26 (s, 1H), 7.23-7.21 (m, 1H), 5.54 (dd, J = 2.2, 6.2 Hz, 1H), 3.25-3.23 (m, 1H), 2.88 (ddd, J = 2.6, 7.6, 16.3 Hz, 1H), 2.67-2.59 (m, 1H), 2.58-2.50 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.5, 142.4, 134.7, 127.4, 126.1, 125.0, 53.4, 37.8, 30.5.



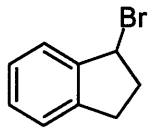
6-Methyl-1-bromoindane. This compound was prepared according to the Halogenation Procedure using 6-methyl-1-indanol (0.920 g, 6.21 mmol), PBr_3 (870 mg, 3.2 mmol), and dry pyridine (0.1 mL). The product was obtained as a clear, colorless oil (1.03 g, 79%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.26 (s, 1H), 7.18-7.16 (m, 1H), 7.10-7.08 (m, 1H), 5.58 (dd, J = 2.3, 6.0 Hz, 1H), 3.20-3.12 (m, 1H), 2.89-2.82 (m, 1H), 2.64-2.50 (m, 2H), 2.37 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 143.9, 140.6, 136.8, 129.9, 125.5, 124.5, 55.2, 37.9, 30.6, 21.2;

IR (film) 3011, 2976, 2945, 2916, 2846, 1493, 1442, 1184, 1162, 861, 812 cm^{-1};

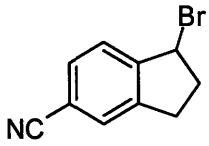
EIMS (70 eV) *m/z*: M^+ 210, 208, 130, 115, 102, 89.



1-Bromoindane [24373-98-6]. This compound was prepared according to the Halogenation Procedure using 1-indanol (4.00 g, 29.8 mmol), PBr_3 (4.03 g, 14.9 mmol), and dry pyridine (0.1 mL). The product was obtained as a clear, colorless oil (5.47 g, 93%) that contained ~5% 1-indene according to ^1H NMR.

^1H NMR ($CDCl_3$, 500 MHz): δ 7.48-7.46 (m, 1H), 7.31-7.25 (m, 3H), 5.63 (dd, J = 2.4, 6.1 Hz, 1H), 3.27-3.19 (m, 1H), 2.96-2.89 (m, 1H), 2.67-2.53 (m, 2H);

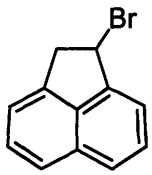
^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.8, 143.6, 128.8, 127.1, 125.1, 124.8, 54.8, 37.7, 30.6.



1-Bromo-5-cyanoindane [475475-78-6]. This compound was prepared according to the Halogenation Procedure using 5-cyano-1-indanol (498 mg, 3.13 mmol), PBr_3 (425 mg, 1.57 mmol), and dry pyridine (0.1 mL). The product was obtained as a white solid (472 mg, 68%).

^1H NMR ($CDCl_3$, 500 MHz): δ 7.56-7.51 (m, 3H), 5.51 (dd, J = 2.5, 6.5 Hz, 1H), 3.25-3.17 (m, 1H), 2.98-2.92 (m, 1H), 2.70-2.60 (m, 1H), 2.58-2.51 (m, 1H);

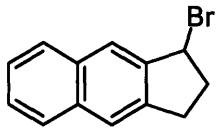
^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.8, 144.3, 131.0, 128.4, 125.7, 118.7, 112.1, 51.8, 37.1, 30.2.



Bromoacenaphthene [24171-73-1]. This compound was prepared according to the Halogenation Procedure using 1-acenaphthenol (1.00 g, 5.88 mmol), PBr_3 (796 mg, 2.94 mmol), and dry pyridine (0.1 mL). The resulting yellow solid was further purified by recrystallization from benzene/hexanes (1:5; 6 mL) to give the desired product as a lustrous, white crystalline solid (0.925 g, 68%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77-7.75 (m, 1H), 7.70-7.69 (m, 1H), 7.60-7.56 (m, 2H), 7.55-7.52 (m, 1H), 7.36-7.34 (m, 1H), 5.95 (dd, J = 2.1, 7.3 Hz, 1H), 4.14 (dd, J = 7.3, 18.4 Hz, 1H), 3.84 (d, J = 18.5 Hz, 1H);

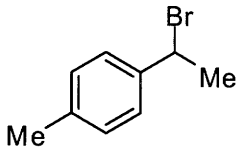
^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.7, 140.6, 136.5, 131.1, 128.3, 128.2, 125.2, 123.1, 121.6, 120.0, 47.6, 43.6.



Bromobenz[*f*]indane [146000-51-3]. This compound was prepared according to the Halogenation Procedure using 1-benz[*f*]indanol (503 mg, 2.73 mmol), PBr_3 (371 mg, 1.37 mmol), and dry pyridine (0.1 mL). The product was obtained as a white solid (598 mg, 89%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (s, 1H), 7.85-7.79 (m, 2H), 7.72 (s, 1H), 7.49-7.42 (m, 2H), 5.74 (dd, J = 3.1, 5.1 Hz, 1H), 3.42-3.33 (m, 1H), 3.10-3.03 (m, 1H), 2.65-2.59 (m, 2H);

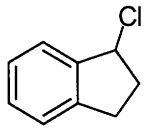
^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.8, 141.3, 134.0, 132.9, 128.3, 127.6, 126.3, 125.4, 124.0, 123.0, 53.9, 38.4, 30.1.



1-(1-Bromoethyl)-4-methylbenzene [69150-78-3]. This compound was prepared according to the Halogenation Procedure using 1-(4-methylphenyl)ethanol (1.50 g, 11.0 mmol), PBr_3 (1.49 g, 5.50 mmol), and dry pyridine (0.1 mL). The product was obtained as a clear, colorless oil (1.93 g, 88%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 5.23 (q, J = 6.9 Hz, 1H), 2.35 (s, 3H), 2.05 (d, J = 6.9 Hz, 3H);

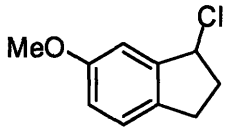
^{13}C NMR ($CDCl_3$, 100 MHz): δ 140.3, 138.3, 129.3, 126.7, 49.8, 26.8, 21.2.



Chloroindane [35275-62-8]. This compound was prepared according to the Halogenation Procedure using 1-indanol (1.00 g, 7.45 mmol), PCl_3 (512 mg, 3.73 mmol), and dry pyridine (0.1 mL). The product was obtained as a clear, colorless oil (0.866 g, 76%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44-7.43 (m, 1H), 7.29-7.24 (m, 3H), 5.44 (dd, J = 3.3, 6.7 Hz, 1H), 3.23-3.16 (m, 1H), 2.93-2.87 (m, 1H), 2.64-2.57 (m, 1H), 2.42-2.36 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.3, 143.0, 128.8, 127.0, 124.9, 124.7, 63.2, 36.9, 30.3.



Chloro-6-methoxyindane [128226-43-7]. This compound was prepared according to the Halogenation Procedure using 6-methoxy-1-indanol (651 mg, 3.96 mmol), PCl_3 (272 mg, 1.98 mmol), and dry pyridine (0.1 mL). The product was obtained as a clear, colorless oil (510 mg, 70%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18-7.16 (m, 1H), 6.97-6.96 (m, 1H), 6.86-6.84 (m, 1H), 5.40 (dd, J = 3.4, 6.7 Hz, 1H), 3.82 (s, 3H), 3.15-3.09 (m, 1H), 2.87-2.81 (m, 1H), 2.67-2.59 (m, 1H), 2.42-2.37 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.1, 144.3, 135.2, 125.4, 115.8, 109.3, 63.4, 55.5, 37.4, 29.5.

Preparation of the Organozinc Reagents.[33] A 25-mL Schlenck tube was charged with zinc powder (1.47 g, 22.5 mmol) and heated to 70 °C under high vacuum for 30 min. After back-filling with argon, iodine (0.19 g, 0.75 mmol) and DMA (to give a total volume of 10 mL) were added, and the resulting heterogeneous red mixture was allowed to stir until the red color of the iodine had faded (typically 1-2 min). Then, the alkyl halide (16 mmol; freshly distilled) was added. The colorless reaction mixture was allowed to stir for 12 h at 70 °C (exceptions: For MeI, the reaction was *not* heated; for cyclohexylmethylbromide, the reaction was heated for 24 h at 85 °C; for EtBr the reaction was *not* heated and it was allowed to stir for 48 h), then the mixture was allowed to cool to room temperature (the disappearance of the starting material and the formation of the organozinc reagent can readily be monitored by no-D NMR). The gray solution (~1.6 M) was passed through an Acrodisc® and stored under argon in a dry container with a pierceable septum.

These organozinc solutions can be stored at room temperature for several weeks without deterioration.

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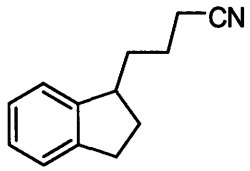
[33] This is based on the work of Huo: Huo, S. *Org. Lett.* **2003**, *5*, 423–425.

III. Negishi Cross-Coupling Reactions

General Procedure. In the air (no special precautions are necessary), a 4-mL glass vial was charged with $NiBr_2$·diglyme (35.3 mg, 0.100 mmol), I-(*i*-Pr)-Pybox (39.2 mg, 0.130 mmol), and the benzylic halide (1.00 mmol). The vial was fitted with a septum cap and purged with argon for 15 min. DMA (1.75 mL) was then added, and the resulting orange mixture was allowed to equilibrate for 15 min under argon in an isopropanol bath cooled to 0 °C. The organozinc solution (~1.6 M in DMA; 1.0 mL, 1.6 mmol) was then added in a single portion to the heterogeneous mixture, which rapidly became a clear, red-brown solution. The reaction mixture was allowed to stir for 24 h at 0 °C. Then, the excess organozinc reagent was quenched by the addition of ethanol (0.3 mL), and the resulting orange liquid was purified directly by flash chromatography.

The ee was determined on Chirasil® DEX-CB or Daicel Chiralpak® columns.

The second runs were conducted with (*S*)-(*i*-Pr)-Pybox.



4-Indan-1-yl-butyronitrile (Table 1.3, entry 1). This compound was prepared according to the General Procedure using (±)-1-bromoindane (197 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (6% EtOAc in hexanes), the title compound was isolated as a clear, colorless oil.

1st run: 122 mg (66%; 92% ee); 2nd run: 116 mg (63%; 91% ee).

The ee's were determined via HPLC on an OD-H column (eluent: 1.0% isopropanol in hexanes; flow rate: 1.0 mL/min) with t_r (major): 20.8 min, t_r (minor): 26.7 min.

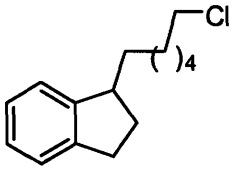
$[\alpha]^{23}_D = -4.2$ ($c = 0.56$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.25-7.23 (m, 1H), 7.21-7.17 (m, 3H), 3.17-3.15 (m, 1H), 2.95-2.93 (m, 1H), 2.90-2.85 (m, 1H), 2.41 (t, J = 7.0 Hz, 2H), 2.34-2.29 (m, 1H), 2.02-1.98 (m, 1H), 1.83-1.58 (m, 4H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.3, 143.8, 126.6, 126.2, 124.6, 123.5, 119.7, 44.0, 33.9, 31.8, 31.3, 23.5, 17.4;

IR (film) 3068, 3019, 2942, 2850, 2245, 1477, 1457, 1424, 747 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 185, 117, 91.



1-(6-Chlorohexyl)indane (Table 1.3, entry 2) [361541-11-9]. This compound was prepared according to the General Procedure using (±)-1-bromoindane (197 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (pentane), the title compound was isolated as a clear, colorless oil.

1st run: 163 mg (69%; 95% ee); 2nd run: 166 mg (70%; 94% ee).

The ee's were determined via HPLC on an OD-H column (eluent: 0.5% isopropanol in hexanes; flow rate: 1.0 mL/min) with t_r (major): 5.1 min, t_r (minor): 5.6 min.

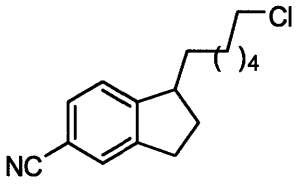
$[\alpha]^{23}_D = -11$ (c = 0.79, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24-7.14 (m, 4H), 3.56 (t, J = 6.7 Hz, 2H), 3.13-3.07 (m, 1H), 2.93 (ddd, J = 4.6, 8.5, 15.5 Hz, 1H), 2.87-2.81 (m, 1H), 2.32-2.26 (m, 1H), 1.88-1.78 (m, 3H), 1.72-1.64 (m, 1H), 1.51-1.34 (m, 7H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.6, 144.0, 126.2, 125.9, 124.4, 123.5, 45.2, 44.8, 34.9, 32.6, 32.1, 31.4, 29.1, 27.5, 26.9;

IR (film) 2930, 2852, 2359, 2336, 1698, 1648, 1558,1474, 1457, 1312, 752 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 236, 128, 117, 91.



1-(6-Chlorohexyl)indan-5-carbonitrile (Table 1.3, entry 3). This compound was prepared according to the General Procedure using (±)-1-bromo-5-cyanoindane (222 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (5% EtOAc in hexanes), the title compound was isolated as a clear, colorless oil.

1st run: 128 mg (49%; 91% ee); 2nd run: 120 mg (46%; 90% ee).

The ee's were determined via HPLC on an AS-H column (eluent: 0.5% isopropanol in hexanes; flow rate: 1.0 mL/min) with t_r (major): 24.6 min, t_r (minor): 28.1 min.

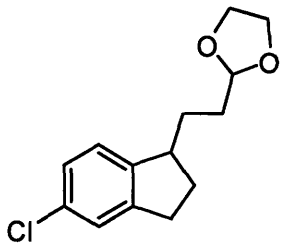
$[\alpha]^{23}_D = +3.8$ ($c = 0.54$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.25 (m, 2H), 7.25 (s, 1H), 3.54 (t, $J = 6.7$ Hz, 2H), 3.15-3.07 (m, 1H), 2.98-2.92 (m, 1H), 2.88-2.82 (m, 1H), 2.35-2.28 (m, 1H), 1.85-1.68 (m, 4H), 1.49-1.34 (m, 7H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.4, 145.2, 130.4, 128.0, 124.3, 119.6, 109.8, 45.1, 45.1, 34.4, 32.5, 31.8, 31.1, 29.0, 27.3, 26.8;

IR (film) 3380, 2930, 2856, 2226, 1608, 1483, 1442, 827 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 261, 142, 115.



2-[2-(5-Chloroindan-1-yl)ethyl]-[1,3]dioxolane (Table 1.3, entry 4). This compound was prepared according to the General Procedure using (±)-1-bromo-5-chloroindane (232 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (8% EtOAc in hexanes), the title compound was isolated as a clear, colorless oil.

1st run: 210 mg (83%; 91% ee); 2nd run: 204 mg (81%; 91% ee).

The ee's were determined via HPLC on an OD-H column (eluent: 0.5% isopropanol in hexanes; flow rate: 1.0 mL/min) with t_r (major): 16.3 min, t_r (minor): 15.3 min.

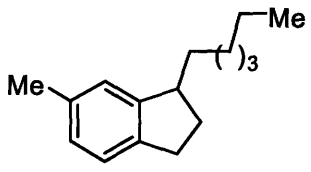
$[\alpha]^{23}_D = -2.0$ ($c = 0.83$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.18 (s, 1H), 7.12 (s, 2H), 4.90 (t, $J = 4.7$ Hz, 1H), 4.00-3.98 (m, 2H), 3.89-3.86 (m, 2H), 3.13-3.07 (m, 1H), 2.91 (ddd, $J = 4.8, 8.6, 15.9$ Hz, 1H), 2.85-2.78 (m, 1H), 2.34-2.27 (m, 1H), 1.98-1.92 (m, 1H), 1.82-1.67 (m, 3H), 1.58-1.49 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.0, 145.6, 131.9, 126.1, 124.6, 124.6, 104.5, 64.9, 44.0, 32.1, 31.7, 31.2, 28.9;

IR (film) 2949, 2883, 2860, 1600, 1474, 1410, 1131, 1034, 875, 813 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 252, 190, 164, 151, 129, 115, 73, 45.



1-Hexyl-6-methylindane (Table 1.3, entry 5). This compound was prepared according to the General Procedure using (±)-6-methyl-1-bromoindane (211 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (pentane), the title compound was isolated as a clear, colorless oil.

1st run: 188 mg (87%; 96% ee); 2nd run: 196 mg (91%; 95% ee).

The ee's were determined by chiral GC: CP Chirasil-Dex CB, t_r (major) 33.8 min, t_r (minor) 33.3 min; heating program: 125 °C; flow: 1.0 mL/min.

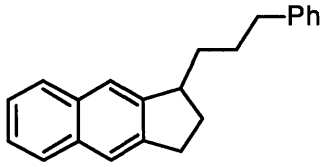
$[\alpha]^{23}_D = -23$ ($c = 0.99$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13-7.11 (m, 1H), 7.04 (s, 1H), 6.99-6.97 (m, 1H), 3.10-3.05 (m, 1H), 2.93-2.75 (m, 2H), 2.36 (s, 3H), 2.33-2.25 (m, 1H), 1.89-1.82 (m, 1H), 1.72-1.63 (m, 1H), 1.48-1.29 (m, 9H), 0.93 (t, $J = 6.8$ Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.1, 141.0, 135.5, 126.9, 124.3, 124.1, 44.8, 35.1, 32.5, 31.9, 31.0, 29.6, 27.7, 22.7, 21.4, 14.2;

IR (film) 3005, 2954, 2924, 2854, 1614, 1491, 1377, 1457, 877, 808, 723 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 216, 131, 91.



1-(3-Phenylpropyl)benz[*f*]indane (entry 1.3, entry 6). This compound was prepared according to the General Procedure using (±)-1-bromobenz[f]indane (247 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (2% EtOAc in hexanes), the title compound was isolated as a white solid.

1st run: 211 mg (74%; 97% ee); 2nd run: 227 mg (79%; 99% ee).

The ee's were determined via HPLC on an OD-H column (eluent: 2% isopropanol in

hexanes; flow rate: 0.9 mL/min) with t_r (major): 11.8 min, t_r (minor): 10.8 min.

$[\alpha]^{23}_D = -47$ ($c = 0.80$, $CHCl_3$);

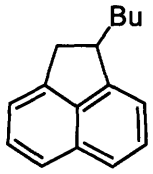
^1H NMR ($CDCl_3$, 500 MHz): δ 7.79-7.75 (m, 2H), 7.65 (s, 1H), 7.59 (s, 1H), 7.41-7.37 (m, 2H), 7.33-7.30 (m, 2H), 7.24-7.20 (m, 3H), 3.28-3.23 (m, 1H), 3.10-3.04 (m, 1H), 3.01-2.94 (m, 1H), 2.78-2.66 (m, 2H), 2.40-2.34 (m, 1H), 2.08-2.01 (m, 1H), 1.86-1.71 (m, 3H), 1.61-1.54 (m, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 146.8, 143.3, 142.6, 133.0, 132.8, 128.4, 128.3, 127.6, 127.4, 125.7, 124.9, 124.8, 122.1, 121.4, 44.3, 36.2, 34.4, 32.8, 31.1, 29.5;

IR ($CDCl_3$ solution) 3155, 2984, 2254, 1794, 1647, 1472, 1382, 911 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 286, 167, 152, 91;

mp 117–119 °C.



1-Butylacenaphthene (Table 1.3, entry 7). This compound was prepared according to the General Procedure using (±)-1-bromoacenaphthene (233 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (pentane), the title compound was isolated as a clear, colorless oil.

1st run: 148 mg (70%; 98% ee); 2nd run: 154 mg (73%; 98% ee).

The ee's were determined via HPLC on an OD-H column (eluent: 0.5% isopropanol in hexanes; flow rate: 0.7 mL/min) with t_r (major): 7.6 min, t_r (minor): 8.9 min.

$[\alpha]^{23}_D = -15$ ($c = 0.80$, $CHCl_3$);

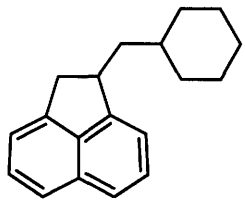
^1H NMR ($CDCl_3$, 500 MHz): δ 7.63-7.61 (m, 2H), 7.50-7.45 (m, 2H), 7.30-7.27 (m, 2H), 3.71-3.66 (m, 1H), 3.59 (dd, $J = 8.0$, 17.1 Hz, 1H), 3.08 (dd, $J = 3.4$, 17.1 Hz, 1H), 1.99-1.92 (m, 1H), 1.69-1.61 (m, 1H), 1.54-1.39 (m, 4H), 0.96 (t, $J = 7.1$ Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.8, 144.8, 138.6, 131.4, 127.8, 127.7, 122.5,

122.2, 119.1, 118.7, 43.4, 37.5, 36.3, 29.7, 22.9, 14.1;

IR (film) 3036, 2955, 2926, 2856, 1604, 1496, 1466, 1368, 796, 774 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 210, 167, 153.



1-Cyclohexylmethyl-acenaphthene (Table 1.3, entry 8). This compound was prepared according to the General Procedure **at room temperature** using (±)-1-bromo-acenaphthene (233 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (pentane), the title compound was isolated as a clear, colorless oil.

1st run: 96 mg (38%; 97% ee); 2nd run: 98 mg (39%; 96% ee).

The ee's were determined via HPLC on an OD-H column (eluent: 1.0% isopropanol in hexanes; flow rate: 0.7 mL/min) with t_r (major): 8.6 min, t_r (minor): 9.7 min.

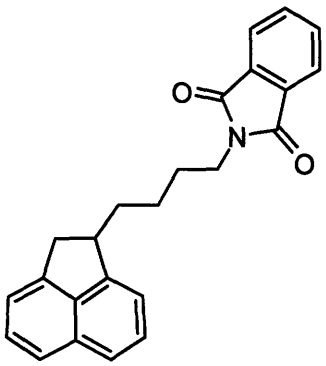
$[\alpha]^{23}_D = -24$ ($c = 0.60$, $CHCl_3$);

^1H NMR ($CDCl_3$, 500 MHz): δ 7.62-7.61 (m, 2H), 7.49-7.44 (m, 2H), 7.28-7.25 (m, 2H), 3.81-3.76 (m, 1H), 3.59 (dd, $J = 7.9$, 17.2 Hz, 1H), 3.05 (dd, $J = 3.2$, 17.5 Hz, 1H), 1.96-1.93 (m, 1H), 1.82-1.72 (m, 5H), 1.66-1.50 (m, 2H), 1.38-1.19 (m, 3H), 1.10-0.99 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.3, 144.8, 138.5, 131.5, 127.8, 127.7, 122.4, 122.2, 119.1, 118.7, 45.0, 40.6, 38.0, 35.9, 34.2, 32.9, 26.7, 26.5, 26.4;

IR (film) 3036, 2920, 2849, 1604, 1448, 1369, 795, 771 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 250, 165, 153, 55.



2-(4-Acenaphthen-1-yl-butyl)isoindole-1,3-dione (Table 1.3, entry 9). This compound was prepared according to the General Procedure **at room temperature** using (±)-1-bromoacenaphthene (233 mg, 1.00 mmol), 0.75 mL (rather than 1.75 mL) of DMA, and the appropriate organozinc reagent (~0.80 M in DMA; 2.0 mL, 1.6 mmol). After purification by column chromatography (12% EtOAc in hexanes), the title compound was isolated as a clear, colorless oil, which solidified after a period of time.

1st run: 138 mg (39%; 99% ee); 2nd run: 151 mg (42%; 99% ee).

The ee's were determined via HPLC on an OD-H column (eluent: 10% isopropanol in hexanes; flow rate: 1.0 mL/min) with t_r (major): 18.0 min, t_r (minor): 16.9 min.

$[\alpha]^{23}_D = +6.0$ ($c = 0.45$, $CHCl_3$);

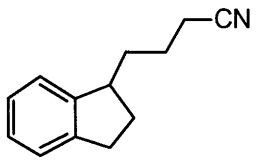
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87-7.85 (m, 2H), 7.74-7.72 (m, 2H), 7.61-7.59 (m, 2H), 7.47-7.43 (m, 2H), 7.27-7.26 (m, 2H), 3.73 (t, J = 7.3 Hz, 2H), 3.70-3.65 (m, 1H), 3.58 (dd, J = 8.0, 17.1 Hz, 1H), 3.05 (dd, J = 3.4, 17.1 Hz, 1H), 2.02-1.95 (m, 1H), 1.83-1.65 (m, 3H), 1.61-1.52 (m, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.4, 149.3, 144.6, 138.5, 133.9, 132.1, 131.4, 127.8, 127.7, 123.2, 122.6, 122.2, 119.1, 118.8, 43.3, 37.9, 37.5, 36.1, 28.8, 24.8;

IR ($CDCl_3$ solution) 3155, 2936, 2254, 1772, 1712, 1469, 1398, 1096 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 355, 207, 165, 153, 133, 104, 71;

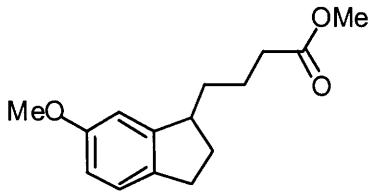
mp 80–83 °C.



4-Indan-1-yl-butyronitrile (Table 1.4, entry 1). This compound was prepared (using (±)-1-chloroindane (153 mg, 1.00 mmol)) and assayed as described for Table 1.3, entry 1.

1st run: 99 mg (53%; 91% ee); 2nd run: 108 mg (58%; 91% ee).

$[\alpha]^{23}_{D} = -4.4$ ($c = 0.54$, $CHCl_3$).



4-(6-Methoxy-indan-1-yl)butyric acid methyl ester (Table 1.4, entry 2) [102062-86-2]. This compound was prepared according to the General Procedure using (±)-1-chloro-6-methoxyindane (182 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (4% → 6% EtOAc in hexanes), the title compound was isolated as a clear, colorless oil.

1st run: 152 mg (61%; 94% ee); 2nd run: 153 mg (62%; 92% ee).

The ee's were determined via HPLC on an OD-H column (eluent: 0.75% isopropanol in hexanes; flow rate: 1.0 mL/min) with t_r (major): 17.2 min, t_r (minor): 20.1 min.

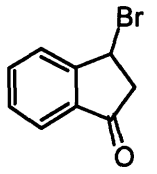
$[\alpha]^{23}_{D} = -19$ ($c = 0.60$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13-7.11 (m, 1H), 6.75-6.70 (m, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 3.12-3.05 (m, 1H), 2.89-2.73 (m, 2H), 2.42-2.26 (m, 3H), 1.90-1.65 (m, 4H), 1.48-1.39 (m, 1H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.1, 158.6, 148.7, 135.9, 124.8, 111.9, 109.3, 55.4, 51.5, 44.7, 34.4, 34.2, 32.5, 30.5, 23.0;

IR (film) 2948, 2846, 1738, 1608, 1583, 1490, 1436, 1246, 1169, 1034, 808 cm^{-1};

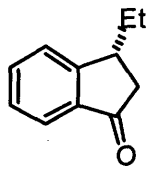
EIMS (70 eV) *m/z*: M^+ 248, 160, 147, 115, 91.



3-Bromo-1-indanone [40774-41-2]. A dry 500-mL round-bottomed flask was charged with 1-indanone (11.0 g, 83.2 mmol), *N*-bromosuccinimide (17.8 g, 100 mmol), and benzoyl peroxide (1.0 g, 4.1 mmol), and then it was equipped with a reflux condenser and placed under a nitrogen atmosphere. Dry benzene (200 mL) was added, and the solution was brought to reflux. After 2 h at reflux, the heterogeneous red mixture was allowed to cool to room temperature, and then it was concentrated under vacuum, and passed through Florisil (eluent: benzene). The resulting orange solution was concentrated and stirred under high vacuum for 2 h. Then, hexanes (100 mL) were added, and the resulting mixture was stirred (~3 rotations per min) at 0 °C, leading to the formation of small, dark-orange, granular crystals. The crystals were separated from the brown, gummy residue and resubmitted to the same crystallization conditions. After the second crystallization, pure product was obtained as yellow, granular crystals (4.7 g, 27%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.78-7.71 (m, 3H), 7.52-7.47 (m, 1H), 5.62 (dd, J = 2.7, 7.2 Hz, 1H), 3.38 (dd, J = 7.2, 19.8 Hz, 1H), 3.07 (dd, J = 2.7, 19.8 Hz, 1H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.5, 154.2, 136.0, 135.6, 129.6, 127.5, 123.4, 48.1, 40.6.



(–)-(*R*)-3-Ethylindan-1-one (eq 1.9) [16460-88-1]. This compound was prepared according to the General Procedure using (±)-3-bromo-1-indanone (211 mg, 1.00 mmol) and EtZnBr (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After purification by column chromatography (1 → 2% EtOAc in hexanes), the title compound was isolated as a clear, colorless oil.

1st run: 93 mg (58%; 92% ee); 2nd run: 88 mg (55%; 93% ee).

The ee's were determined by chiral GC: CP Chirasil-Dex CB, t_r (major) 22.0 min, t_r (minor) 21.5 min; heating program: 75 °C → 175 °C @ 3 °C/min; flow: 1.0 mL/min.

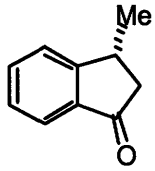
$[\alpha]^{23}_D$ = –27 (*c* = 2.8, $CHCl_3$) {lit.[34] $[\alpha]^{25}_D$ = –15.5 (*c* = 0.67, EtOH); I};

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75-7.73 (m, 1H), 7.64-7.58 (m, 1H), 7.52-7.50 (m, 1H), 7.40-7.35 (m, 1H), 3.37-3.29 (m, 1H), 2.86 (dd, *J* = 7.5, 19.1 Hz, 1H), 2.37 (dd, *J* = 3.3, 19.1 Hz, 1H), 2.05-1.92 (m, 1H), 1.63-1.48 (m, 1H), 0.99 (t, *J* = 7.4 Hz, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ 206.5, 158.7, 136.9, 134.6, 127.4, 125.6, 123.5, 42.6, 39.6, 28.7, 11.6;

IR (film) 2969, 2936, 1703, 1600, 1464, 1331, 1292, 1245, 765 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 160, 145, 132, 115, 103, 91, 77.



(–)-(*R*)-3-Methylindan-1-one (Scheme 1.2, 1st step) [769-14-2]. In the air (no special precautions are necessary), a dry 50-mL Schlenck tube was charged with $NiBr_2$·diglyme (705 mg, 2.00 mmol), I-(*i*-Pr)-Pybox (784 mg, 2.60 mmol), and (±)-3-bromo-1-indanone (4.22 g, 20.0 mmol). The tube was fitted with a septum cap and purged with argon for 15 min. DMA (25 mL) was then added, and the resulting heterogeneous orange mixture was allowed to equilibrate for 15 min under argon in an isopropanol bath cooled to 0 °C. The MeZnI solution (1.6 M in DMA; 20 mL, 32 mmol) was then added in a single

[34] Mani, N. S.; Wu, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4687–4691.

portion to the heterogeneous mixture, which rapidly became a clear, brown solution. The reaction mixture was allowed to stir for 48 h at –15 °C. Then, the excess organozinc reagent was quenched by the addition of ethanol (6.0 mL), and the resulting brown-orange liquid was passed through a large pad of silica gel (5% EtOAc in hexanes) to remove the inorganic salts and much of the DMA. The clear, bright-yellow washings were concentrated and further purified by flash chromatography (1% → 2% EtOAc in hexanes), which afforded the title compound as a clear, colorless oil.

1st run: 1.87 g (64%; 90% ee); 2nd run: 2.04 g (70%; 90% ee).

The ee's were determined by chiral GC: CP Chirasil-Dex CB, t_r (major) 18.7 min, t_r (minor) 18.0 min; heating program: 75 °C → 175 °C @ 3 °C/min; flow: 1.0 mL/min.

The second run was conducted with (*S*)-(*i*-Pr)-Pybox.

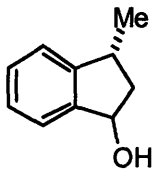
$[\alpha]^{23}_D = -7.6$ ($c = 0.63$, EtOH) {lit.[35] $[\alpha]_D = -6.67$ ($c = 1.05$, EtOH); I};

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75-7.73 (m, 1H), 7.65-7.59 (m, 1H), 7.53-7.51 (m, 1H), 7.41-7.36 (m, 1H), 3.51-3.40 (m, 1H), 2.95 (dd, $J = 7.5$, 19.1 Hz, 1H), 2.29 (dd, $J = 3.5$, 19.1 Hz, 1H), 1.42 (d, $J = 7.1$ Hz, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ 206.5, 159.9, 136.4, 134.7, 127.4, 125.3, 123.4, 45.3, 32.8, 21.3;

IR (film) 2961, 1713, 1606, 1464, 1464, 1326, 1281, 1239, 1041, 760 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 146, 131, 117, 103, 91, 77, 63, 51.



(3*R*)-*cis,trans*-3-Methyl-1-indanol (Scheme 1.2, 2nd step) [1006-18-4]. This compound was reduced according to the Reduction Procedure using I-3-methyl-1-indanone (1.85 g, 12.7 mmol) and $NaBH_4$ (960 mg, 25.4 mmol). The product was obtained as a white

[35] Yun, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 767–774.

solid (1.82 g, 97%) as a mixture of cis and trans isomers (~20:1). A second run was performed with (*S*)-3-methyl-1-indanone, and the product was obtained as a white solid (1.80 g, 96%) as a mixture of cis and trans isomers (~20:1).

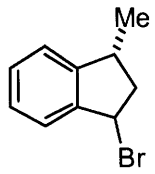
^{1}H NMR ($CDCl_3$, 500 MHz; cis isomer): δ 7.42-7.39 (m, 1H), 7.33-7.22 (m, 3H), 5.22-5.14 (m, 1H), 3.10-3.03 (m, 1H), 2.81-2.73 (m, 1H), 1.91 (d, J = 13.0 Hz, 1H), 1.53-1.43 (m, 1H), 1.37 (d, J = 11 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz; cis isomer): δ 147.3, 145.0, 128.1, 126.8, 123.6, 123.3, 75.1, 45.7, 36.2, 20.1;

IR (film) 3340, 2958, 2924, 2870, 1645, 1442, 1342, 1211, 1089, 1056, 759 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 148, 129, 105, 77, 51;

mp 74–76 °C.



(3*R*)-*cis,trans*-1-Bromo-3-methylindane (Scheme 1.2, 3rd step). This compound was prepared according to the Halogenation Procedure using (3*R*)-*cis,trans*-3-methyl-1-indanol (20:1 mixture; 1.76 g, 11.9 mmol), PBr_3 (1.61 g, 5.95 mmol), and dry pyridine (0.1 mL). The product was obtained as a clear, colorless oil (2.34 g, 93%) as a mixture of trans and cis isomers (~2:1).

A second run was conducted, and the product was obtained as a clear, colorless oil (2.41 g, 96%) as a mixture of trans and cis isomers (~2:1).

^{1}H NMR ($CDCl_3$, 400 MHz; trans isomer): δ 7.41-7.39 (m, 1H), 7.32-7.20 (m, 3H), 5.56 (d, J = 6.1 Hz, 1H), 3.54-3.45 (m, 1H), 2.69 (dd, J = 6.4, 14.2 Hz, 1H), 2.10 (ddd, J = 6.2, 8.9, 14.2 Hz, 1H), 1.35 (d, J = 6.9 Hz, 3H);

cis isomer: δ 7.41-7.39 (m, 1H), 7.32-7.20 (m, 3H), 5.46 (dd, J = 6.2, 6.7 Hz, 1H), 3.33-3.24 (m, 1H), 3.04-2.97 (m, 1H), 2.24-2.18 (m, 1H), 1.42 (d, J = 7.0 Hz, 3H);

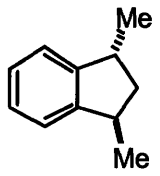
^{13}C NMR ($CDCl_3$, 100 MHz; trans isomer): δ 148.4, 143.6, 129.1, 127.1, 124.9, 123.4,

53.8, 46.8, 36.9, 17.8;

cis isomer: δ 147.3, 143.0, 128.7, 127.2, 125.6, 123.5, 51.2, 45.5, 38.5, 20.4;

IR (film) 2958, 2919, 2868, 2364, 2331, 1650, 1634, 1454, 753 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 210, 208, 193, 129, 115, 103, 77.



(+)-(*R,R*)-*trans*-1,3-Dimethylindane (Scheme 1.2, 4th step) [4175-53-5]. In the air (no special precautions are necessary), a dry 50-mL Schlenk tube was charged with $NiBr_2$·diglyme (368 mg, 1.04 mmol), I-(*i*-Pr)-Pybox (409 mg, 1.36 mmol), and (3*R*)-1-bromo-3-methylindane (2.20 g, 10.4 mmol). The tube was fitted with a septum cap and purged with argon for 15 min. DMA (15 mL) was then added, and the resulting heterogeneous orange mixture was allowed to equilibrate for 15 min under argon in an isopropanol bath cooled to 0 °C. The MeZnI solution (1.6 M in DMA; 10.4 mL, 16.6 mmol) was then added in a single portion, and the resulting homogeneous brown solution was allowed to stir for 48 h at –15 °C. Then, the excess organozinc reagent was quenched by the addition of ethanol (6.0 mL), and the resulting brown-orange liquid was passed through a large pad of silica gel (pentanes) to remove the inorganic salts and much of the DMA. The solution was then concentrated and further purified by flash chromatography (pentanes), which afforded the title compound as a clear, colorless oil.

1st run: 1.27 g (83%; 93% ee); 2nd run: 1.32 g (87%; 94% ee).

The ee's were determined by chiral GC: CP Chirasil-Dex CB, t_r (major) 45.7 min, t_r (minor) 45.1 min; heating program: 70 °C ; flow: 0.9 mL/min.

The second run was conducted with (*S*)-(*i*-Pr)-Pybox.

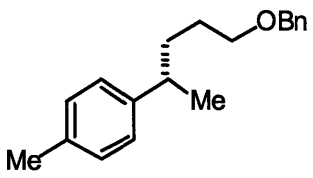
$[\alpha]^{23}_D$ = +2.75 (*c* = 1.92, $CHCl_3$);

^1H NMR ($CDCl_3$, 500 MHz): δ 7.20 (s, 4H), 3.31-3.27 (m, 2H), 1.93-1.90 (m, 2H), 1.26 (d, *J* = 7.0 Hz, 6H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.3, 126.3, 123.4, 42.9, 37.6, 20.5;

IR (film) 3068, 3019, 2956, 2925, 2866, 1476, 1453, 1373, 1330, 1019, 750 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 146, 131, 115, 91.



***(S)-O*-Benzyl-4-(*p*-tolyl)pentan-1-ol (eq 1.11) [85758-06-1].** This compound was prepared according to the General Procedure using (±)-1-(1-bromoethyl)-4-methylbenzene (199 mg, 1.00 mmol) and the appropriate organozinc reagent (~1.6 M in DMA; 1.0 mL, 1.6 mmol). After careful purification by column chromatography (0% → 2% EtOAc in hexanes), the title compound was isolated as a clear, colorless oil.

1st run: 170 mg (63%; 76% ee); 2nd run: 166 mg (62%; 74% ee).

The ee's were determined via HPLC on an OJ-H column (eluent: 1.0% isopropanol in hexanes; flow rate: 1.0 mL/min) with t_r (major): 15.7 min, t_r (minor): 22.6 min.

$[\alpha]^{23}_D$ = +12 (*c* = 0.59, EtOH) {lit.[36] $[\alpha]^{25}_D$ = +12.3 (*c* = 0.91, EtOH); (*S*)};

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.28 (m, 5H), 7.12-7.06 (m, 4H), 4.47 (s, 2H), 3.45-3.42 (m, 2H), 2.70-2.62 (m, 1H), 2.33 (s, 3H), 1.70-1.44 (m, 4H), 1.24 (d, *J* = 6.9 Hz, 3H);

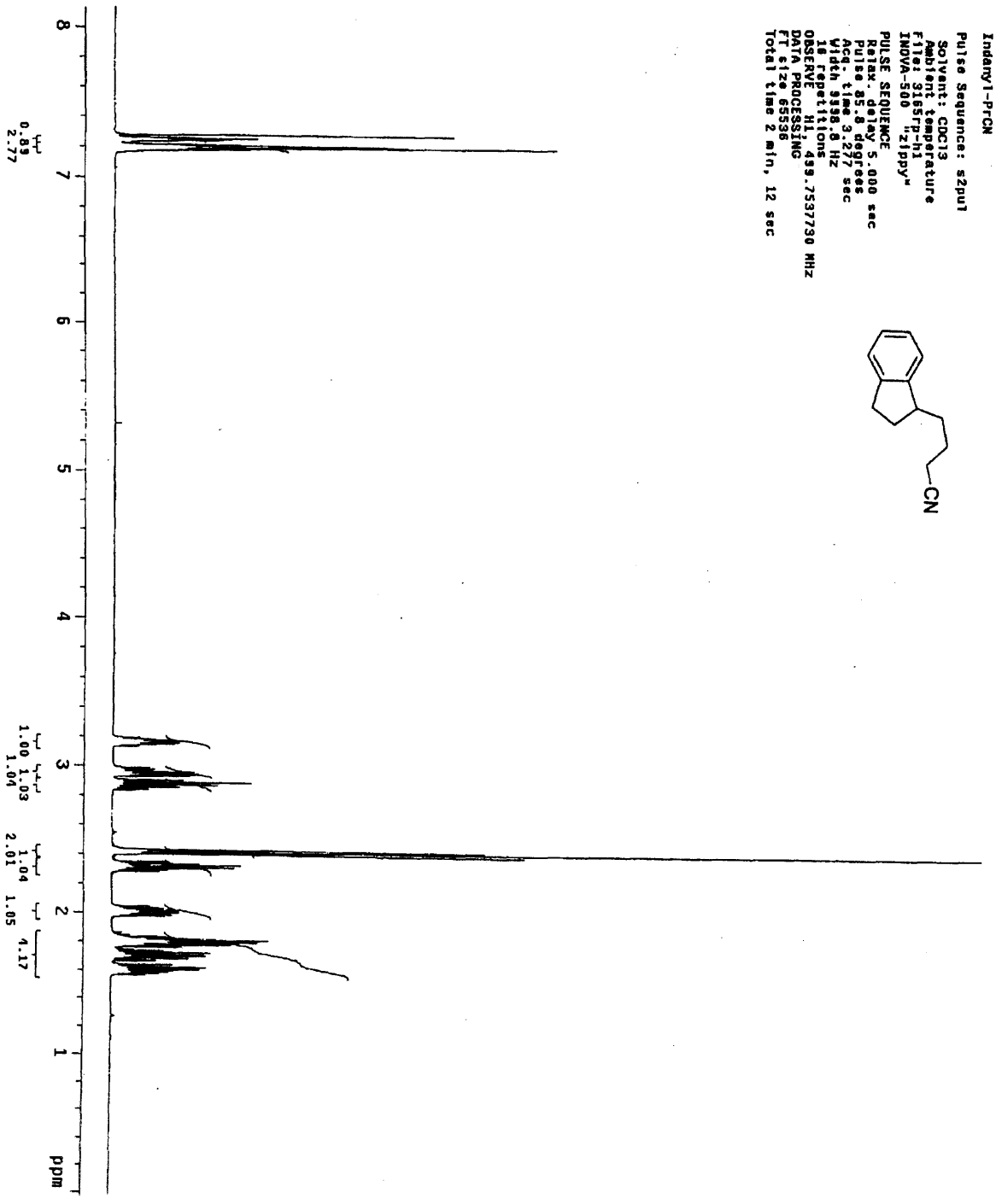
^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.4, 138.6, 135.3, 129.0, 128.3, 127.6, 127.4, 126.8, 72.8, 70.5, 39.3, 34.8, 28.0, 22.4, 21.0;

IR (film) 3025, 2924, 2854, 1510, 1491, 1454, 1362, 1101, 816, 733, 697 cm^{-1};

EIMS (70 eV) *m/z*: M^+ 268, 177, 159, 119, 91.

[36] Takano, S.; Sugihara, T.; Samizu, K.; Akiyama, M.; Ogasawara, K. *Chem. Lett.* **1989**, 1781–1784.

^{1}H NMR Spectra of Coupling Products



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Solvent: CDCl3
Ambient temperature
File: 3202rp-h1
INOVA-500 "zippy"

PULSE SEQUENCE
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Width 9998.8 Hz
16 repetitions
OBSERVE H1, 499.7446543 MHz
DATA PROCESSING
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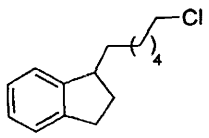
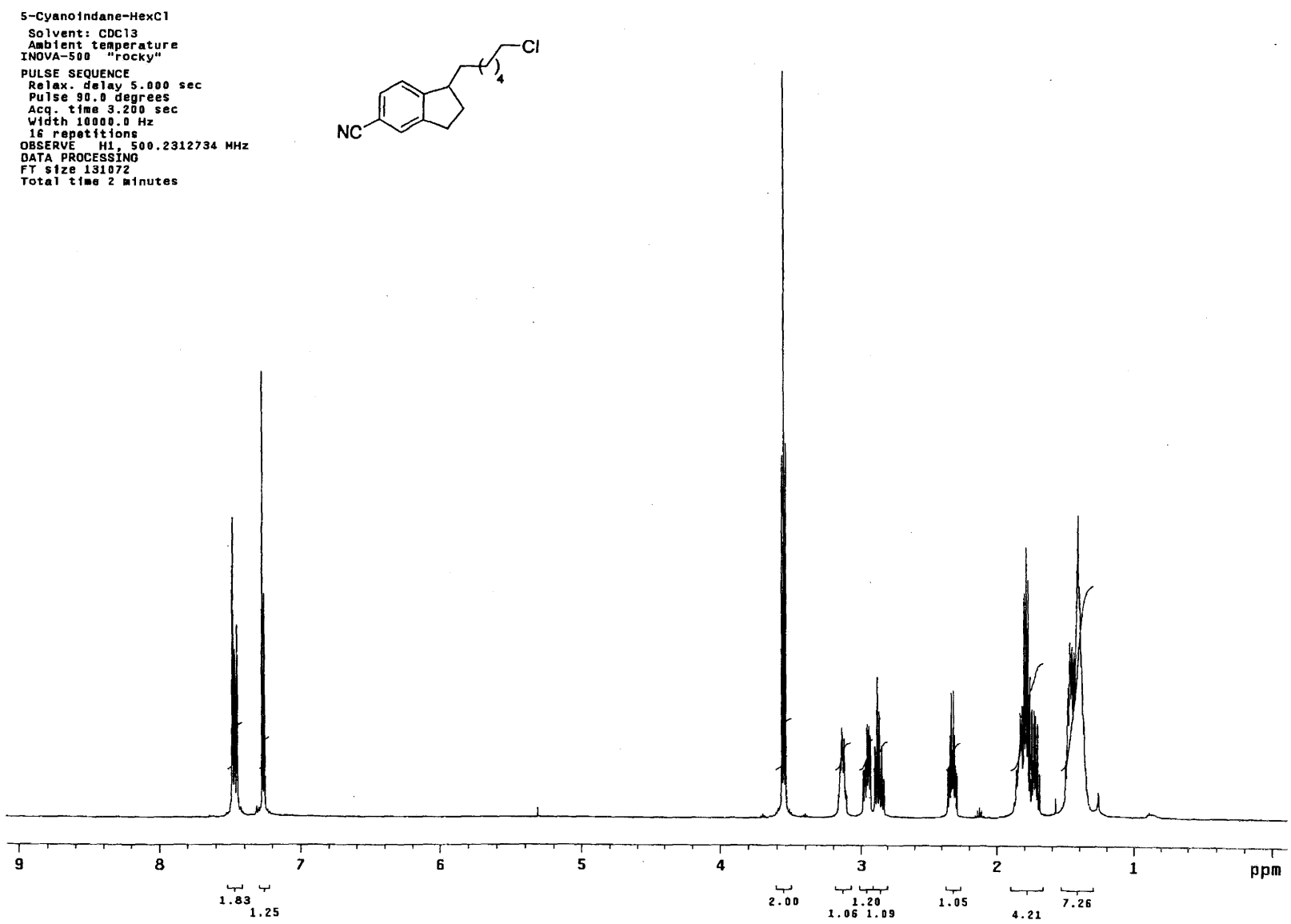
Total time 0 min, 52 sec




5-Cyanoindane-HexCl
Solvent: CDCl3
Ambient temperature
INOVA-500 "rocky"
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Relax. delay 5.000 sec
Pulse 90.0 degrees
Acq. time 3.200 sec
Width 10000.0 Hz
16 repetitions
OBSERVE H1, 500.2312734 MHz
DATA PROCESSING
FT size 131072
Total time 2 minutes
NC
Cl
4
9
8
7
6
5
4
3
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ppm
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1.20
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1.05
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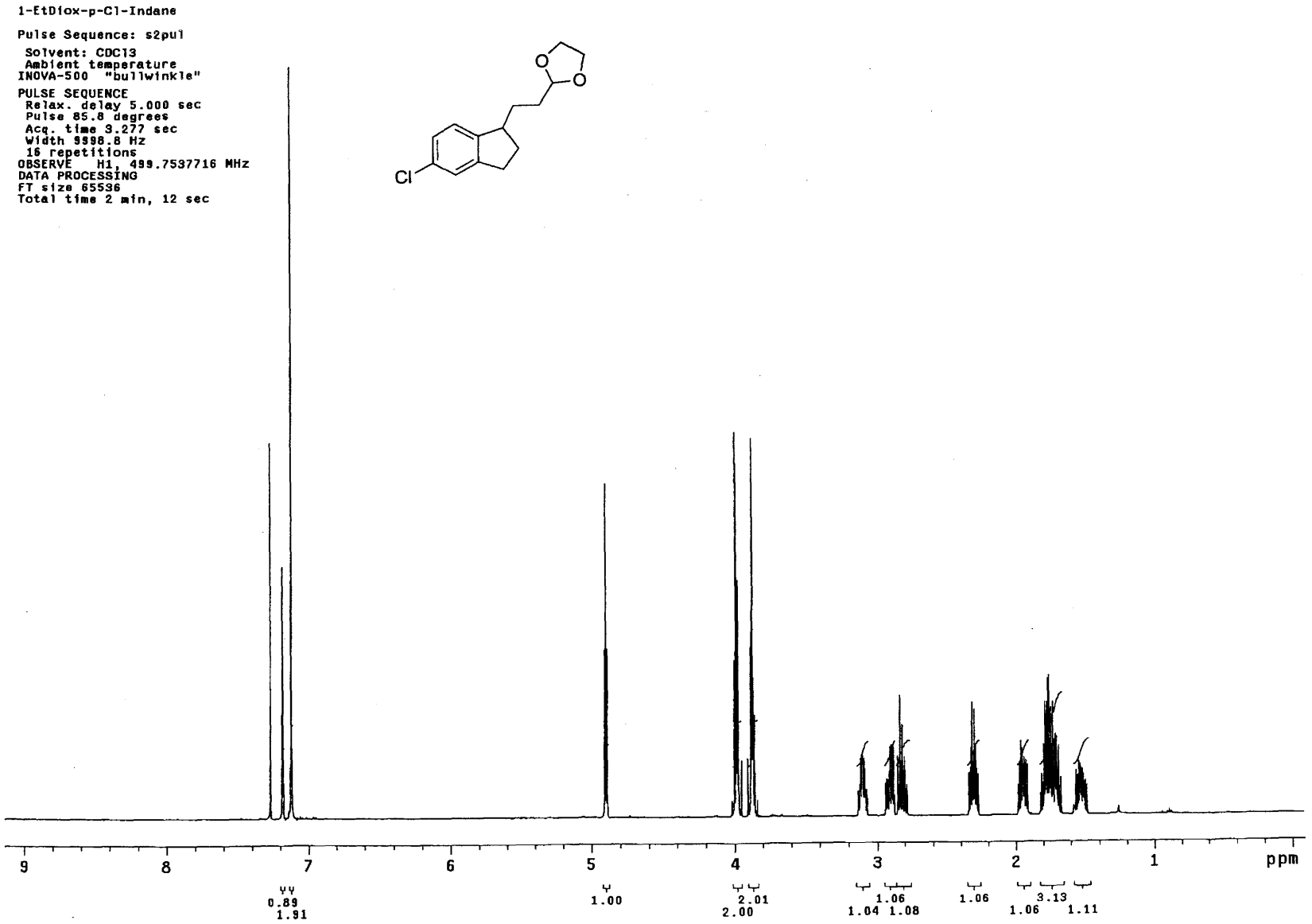
7.26


1-EtDiox-p-Cl-Indane
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "bullwinkle"
PULSE SEQUENCE
Relax. delay 5.000 sec
Pulse 85.8 degrees
Acq. time 3.277 sec
Width 9998.8 Hz
16 repetitions
OBSERVE H1, 499.7537716 MHz
DATA PROCESSING
FT size 65536
Total time 2 min, 12 sec
Cl
O
O
9
8
7
6
5
4
3
2
1
ppm
0.89
1.91
1.00
2.01
2.00
1.04
1.06
1.08
1.06
3.13
1.06
1.11

Current Data Parameters
NAME 6-Me-1-hexInd
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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Time 12.43
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PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 4
SWH 8278.146 Hz
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AQ 3.9584243 sec
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DE 6.00 usec
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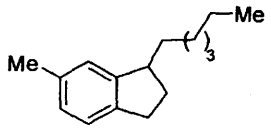
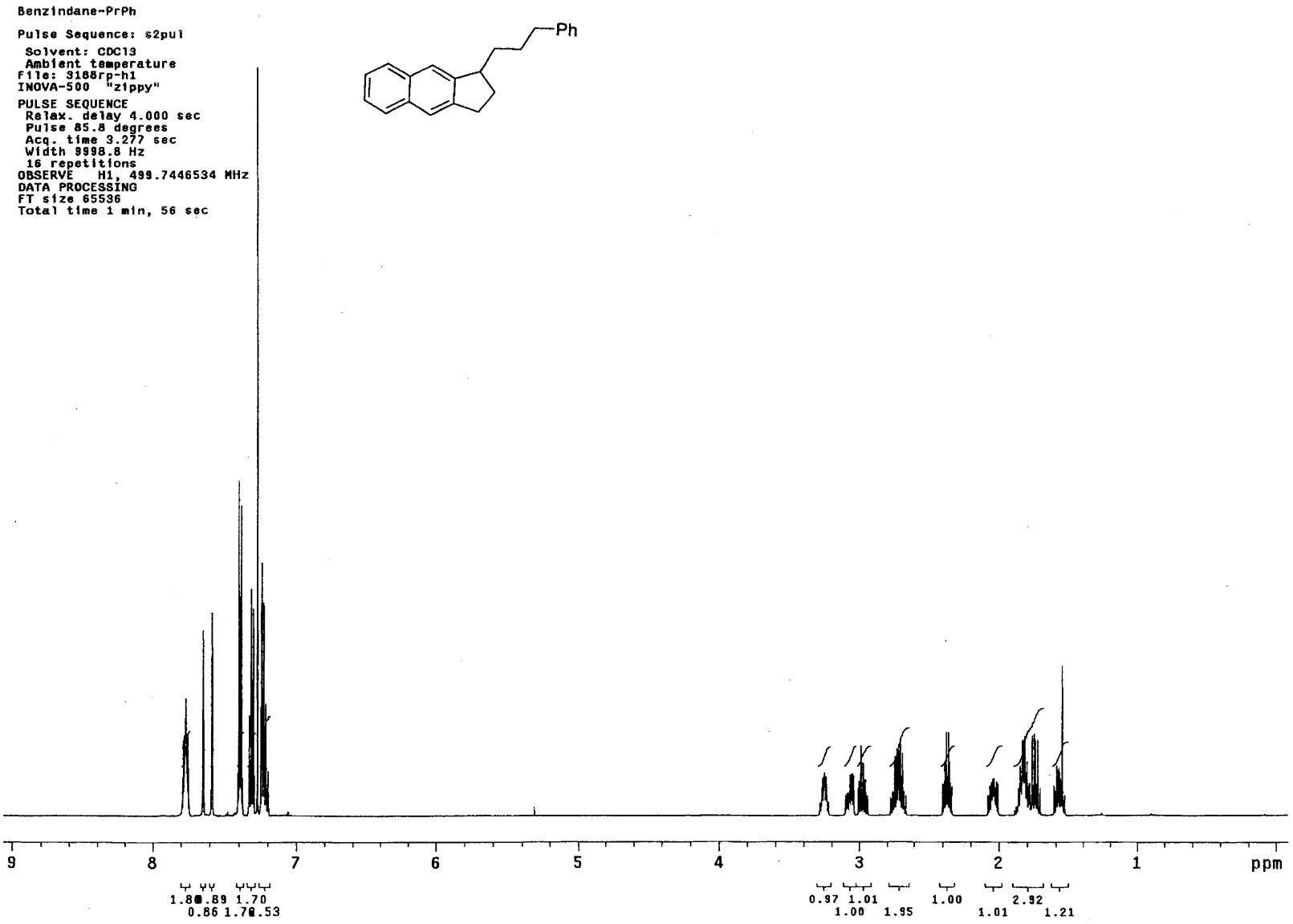
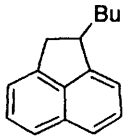


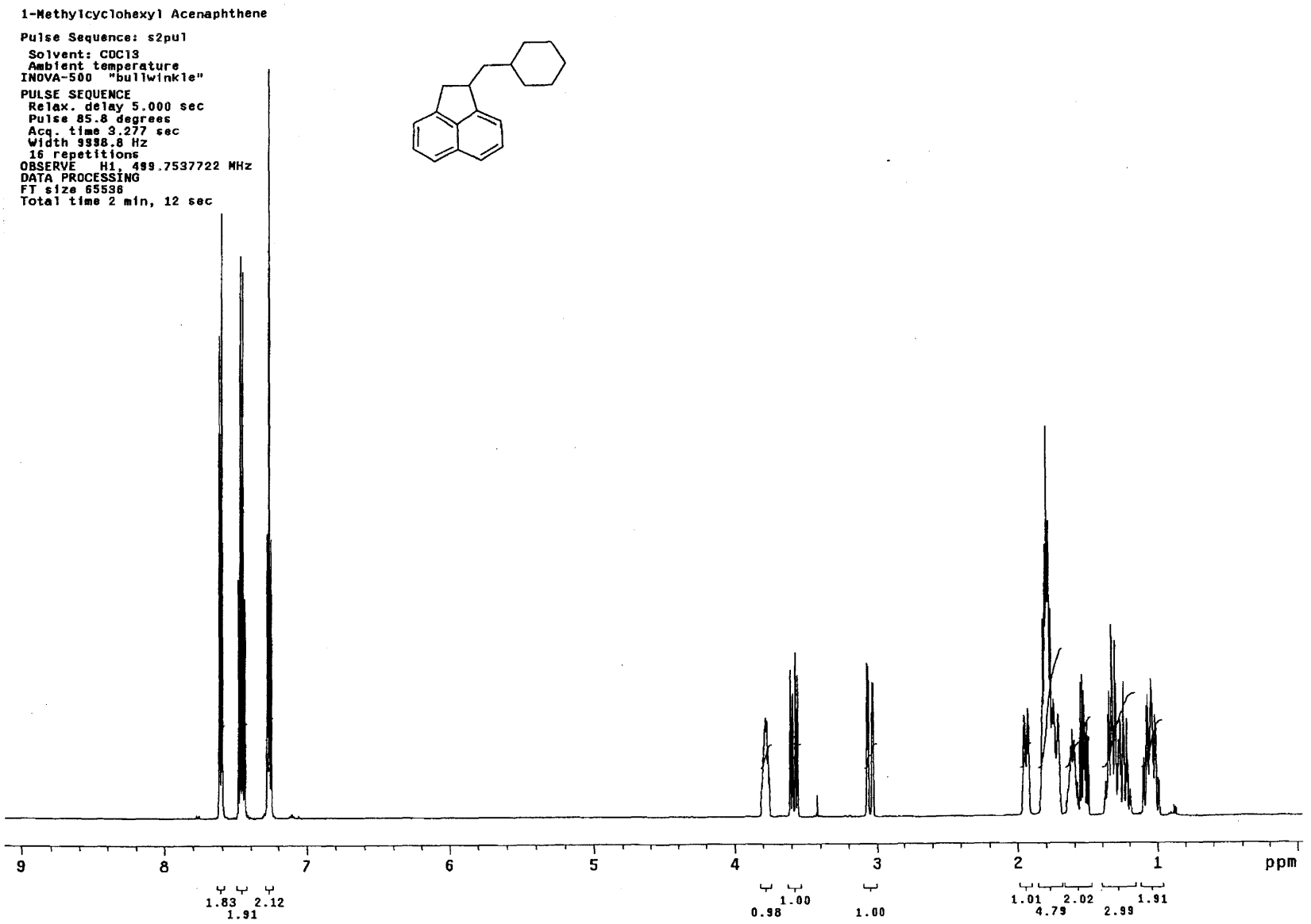

Benzindane-PrPh
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: 3188rp-h1
INOVA-500 "zippy"
PULSE SEQUENCE
Relax. delay 4.000 sec
Pulse 85.8 degrees
Acq. time 3.277 sec
Width 9998.8 Hz
16 repetitions
OBSERVE H1, 499.7446534 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 56 sec
Ph
9
8
7
6
5
4
3
2
1
ppm
1.80 0.89 1.70
0.86 1.78 0.53
0.97 1.01
1.00 1.95
1.00
2.92
1.01 1.21

1-Bu-Acenaphthene

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "bullwinkle"

PULSE SEQUENCE
Relax. delay 5.000 sec
Pulse 85.8 degrees
Acq. time 3.277 sec
Width 9998.8 Hz
16 repetitions
OBSERVE H1, 499.7537716 MHz
DATA PROCESSING
FT size 65536
Total time 2 min, 12 sec




1-Methylcyclohexyl Acenaphthene
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
INOVA-500 "bullwinkle"
PULSE SEQUENCE
Relax. delay 5.000 sec
Pulse 85.8 degrees
Acq. time 3.277 sec
Width 9998.8 Hz
16 repetitions
OBSERVE H1, 499.7537722 MHz
DATA PROCESSING
FT size 65536
Total time 2 min, 12 sec
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8
7
6
5
4
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2
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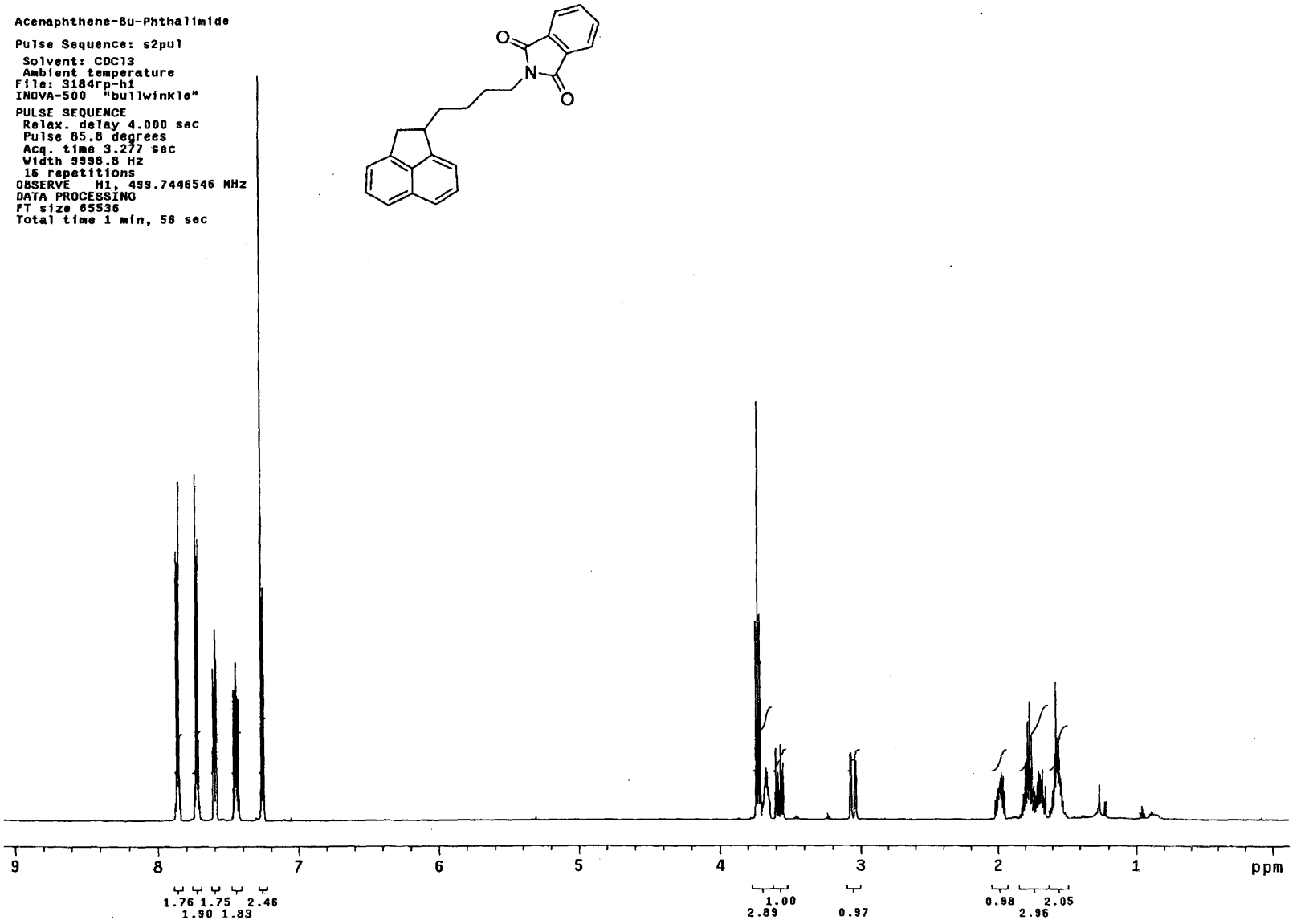
1.91


Acenaphthene-Bu-Phthalimide
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: 3184rp-h1
INOVA-500 "bullwinkle"
PULSE SEQUENCE
Relax. delay 4.000 sec
Pulse 85.8 degrees
Acq. time 3.277 sec
Width 9998.8 Hz
16 repetitions
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O
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8
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1
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1.90 1.83
1.00
2.89
0.97
0.98 2.05
2.96

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PROCNO 1

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INSTRUM spect
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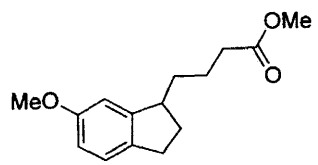

3-Ethyl-1-Indanone, RP

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Solvent: CDCl3
Ambient temperature
Mercury-300 "mrhat"

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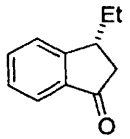

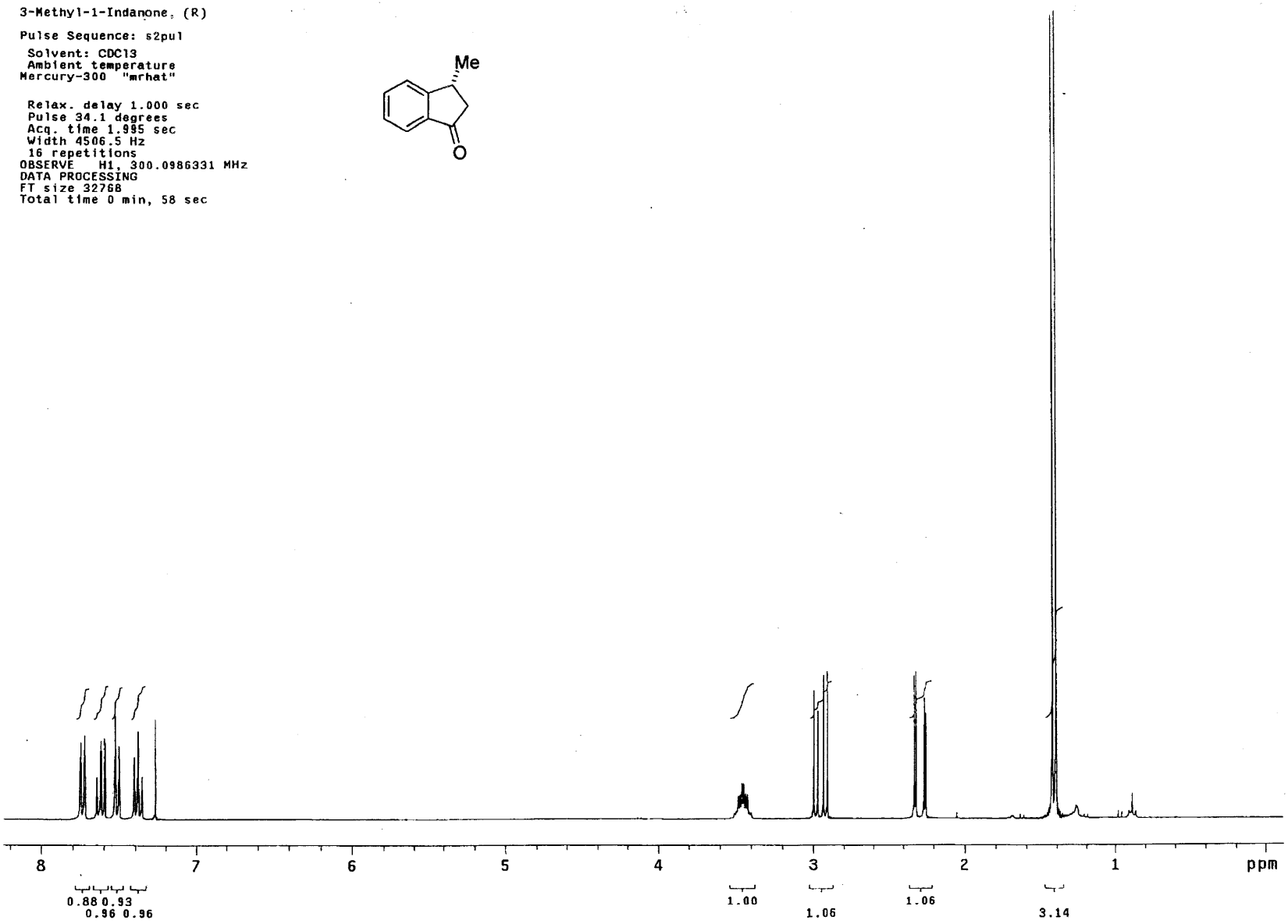
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Mercury-300 "mrhat"
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Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.0986331 MHz
DATA PROCESSING
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Me
O
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5
4
3
2
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0.96 0.96
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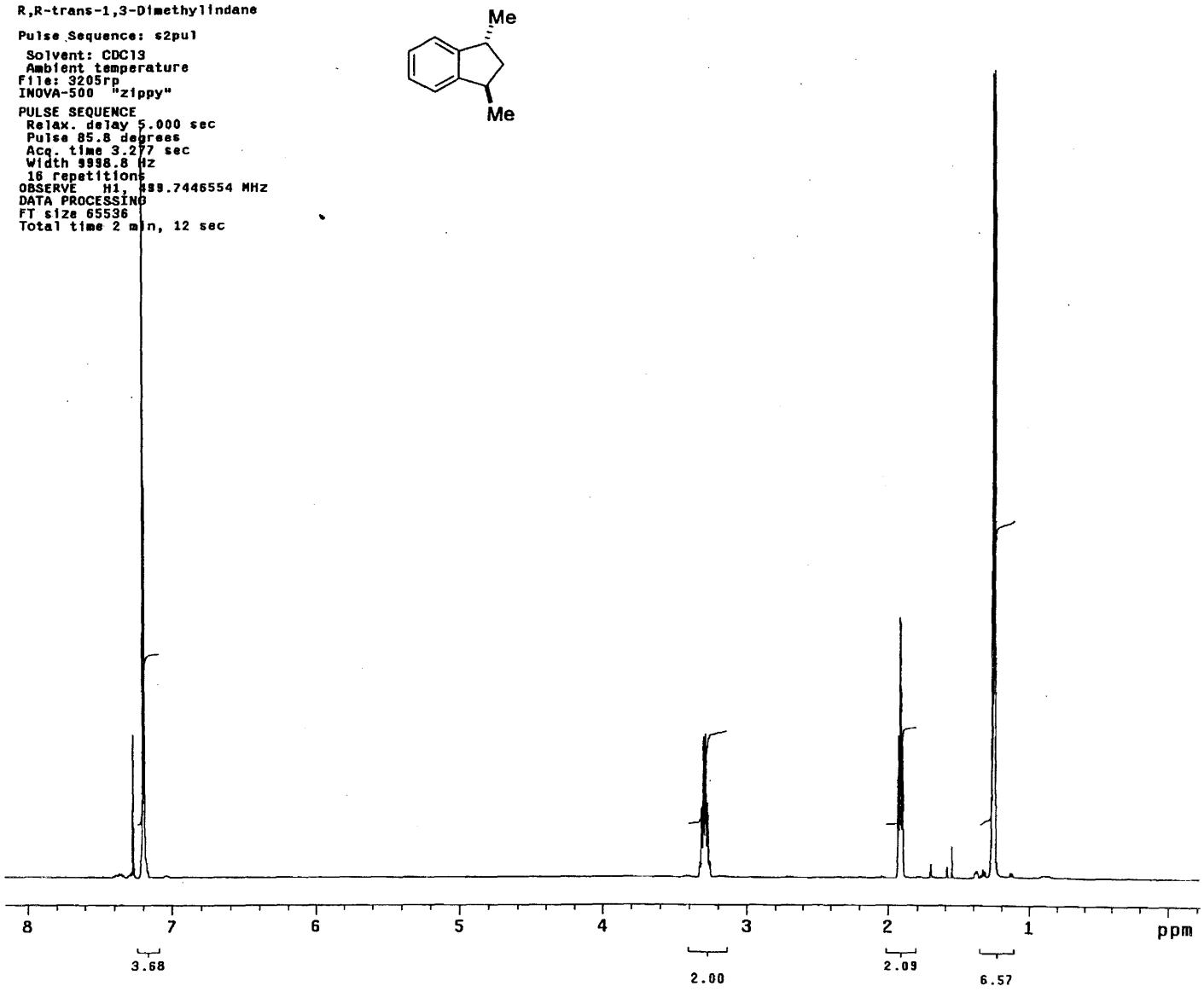
1.06
1.06
3.14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Solvent: CDCl3
Ambient temperature
File: 3205rp
INOVA-500 "zippy"
PULSE SEQUENCE
Relax. delay 5.000 sec
Pulse 85.8 degrees
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16 repetitions
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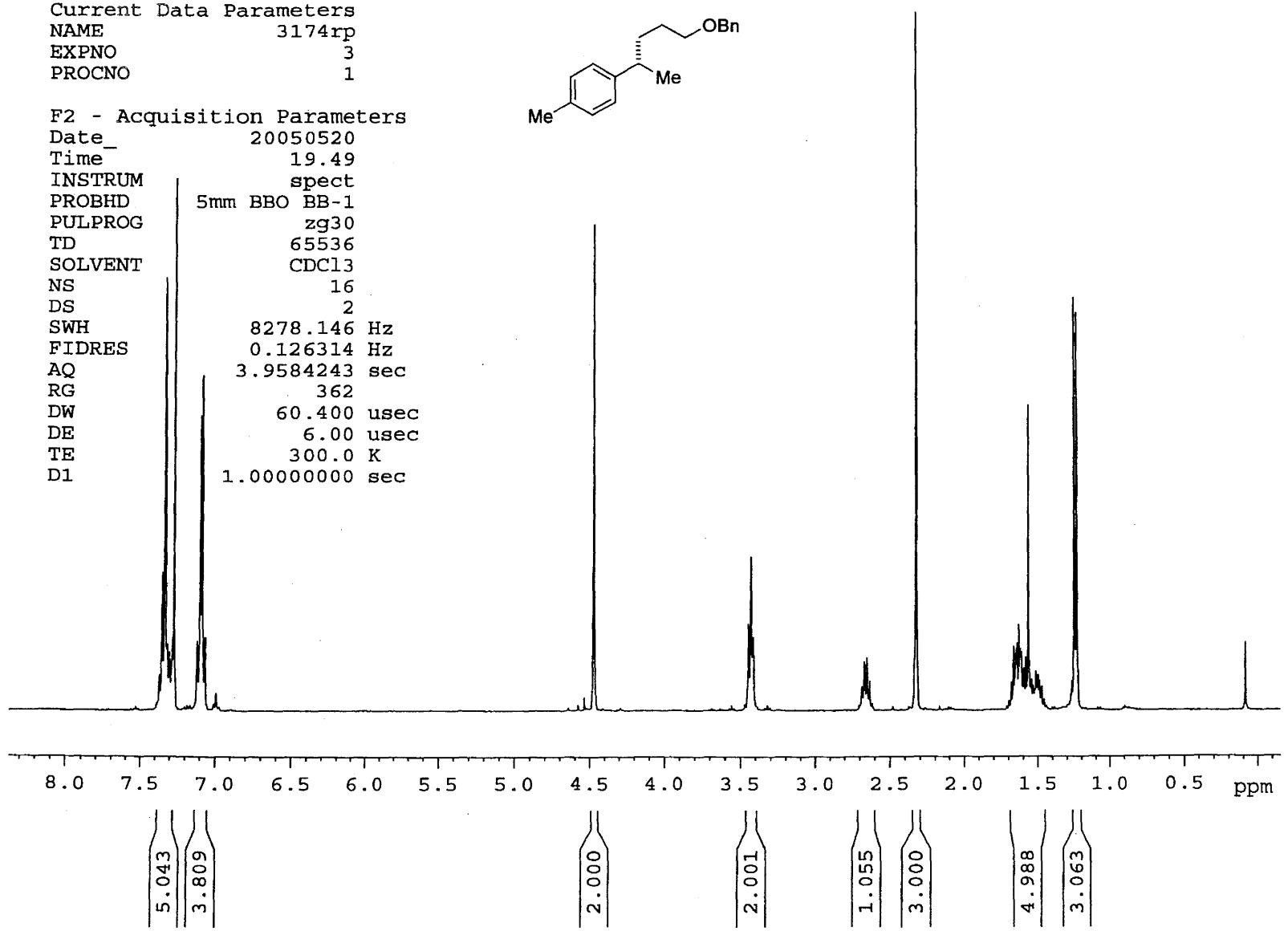
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FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
OBn
Me
Me
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.043
3.809
2.000
2.001
1.055
3.000
4.988
3.063

Chapter 2

Kinetic Resolution of Indolines with a Ferrocene-based Acylation Catalyst

2.1 Background

A kinetic resolution is a process in which a racemic mixture of material undergoes a process of enantioenrichment (i.e., becomes resolved) by means of reaction with another enantioenriched substance.[37] It is based on the principle that a given enantiomer of substrate (e.g., (*S*)-SM; Figure 2.1) could have a lower kinetic barrier to reaction with a chiral substance than the barrier of the antipode of substrate ((*R*)-SM, where $\Delta G^{\ddagger}_{S} < \Delta G^{\ddagger}_{R}$). Therefore, given a half-equivalent of the chiral reactant, the faster-reacting enantiomer of substrate could be preferentially "funneled out" of the mixture, leaving the remaining mixture enriched in the slower-reacting enantiomer (enriched in (*R*)-SM).

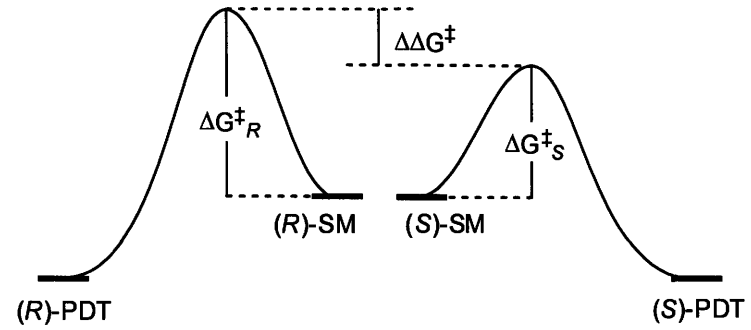


Figure 2.1. Comparative energies of starting materials and products in an example kinetic resolution.

The above definition can include processes in which a chiral catalyst performs an operation preferentially on one enantiomer of a racemic mixture. As a practical matter, in both stoichiometric and catalytic cases, the final mixture of enantioenriched starting material and product is often easier to separate (e.g., by chromatography) than the initial racemic mixture of starting material.

One commonly accepted metric for evaluating the efficiency of kinetic resolutions is to discuss them in terms of their selectivity factor (denoted: **s**). The selectivity factor is the

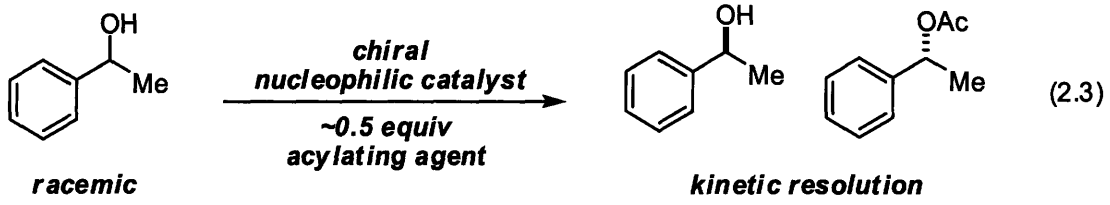
[37] Reviews on kinetic resolution: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *1*, 5–26. (c) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407–1446. (d) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974–4001.

ratio of the two rate constants of reaction, with the higher rate constant over the lower (**s** = $k_{rel} = k_R/k_S$ or k_S/k_R). Selectivity factors and reaction conversion (c) can be calculated from the enantiomeric excesses of product (ee_{pdt}) and recovered starting material (ee_{sm}), through eqs 2.1 and 2.2, as described by Kagan.[37a]

$$c = \left(\frac{ee_{sm}}{ee_{sm} + ee_{pdt}} \right) \qquad (2.1)$$

$$\mathbf{s} = \frac{\ln[1 - c(1 + ee_{pdt})]}{\ln[1 - c(1 - ee_{pdt})]} \qquad (2.2)$$

In the current literature, enantioselective acylations of chiral alcohols by nucleophilic catalysts represent a frequently explored example of catalyzed kinetic resolution (eq 2.3). Although the field of enzyme-based catalysts is well developed,[38] significant effort has also been directed toward the development of synthetic (i.e., non-enzymatic) catalysts.[39] Synthetic catalysts are often preparable in both enantiomeric forms, and can undergo more rational or systematic modification of their structure as compared with enzyme-based catalysts.



(2.3)

A simplified catalytic cycle for alcohol resolution is shown in Figure 2.2. The chiral nucleophilic catalyst (denoted Nuc*) obtains an acyl group from the acylating agent, and transfers it preferentially to one enantiomer of alcohol, thus regenerating free catalyst.

[38] Enzyme-based kinetic resolutions of amine: van Rantwijk, F.; Sheldon, R. A. *Tetrahedron* **2004**, *60*, 501–519.
[39] Kinetic resolutions of alcohols: Jarvo, E. R.; Miller, S. J. In *Comprehensive Asymmetric Catalysis, Supplement 1*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.: Springer-Verlag: Berlin, 2004; Chapter 43.

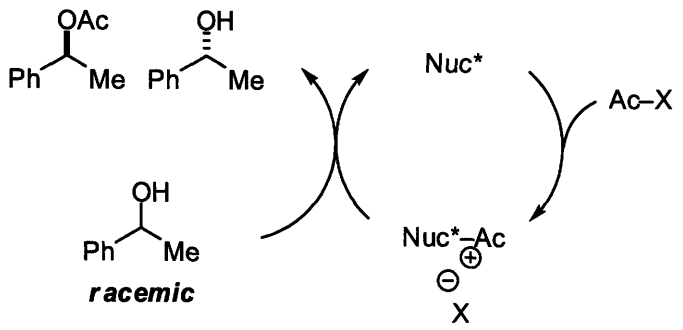


Figure 2.2. Cycle for Nuc*-catalyzed alcohol resolutions.

Several chiral variants of the DMAP nucleophile have been successfully employed in alcohol resolutions (Figure 2.3).[40] In many cases, the molecules do not bear alkyl-substitution at the 2-position of the pyridine ring, due to a general observation that hindrance at this position significantly diminishes catalyst reactivity.

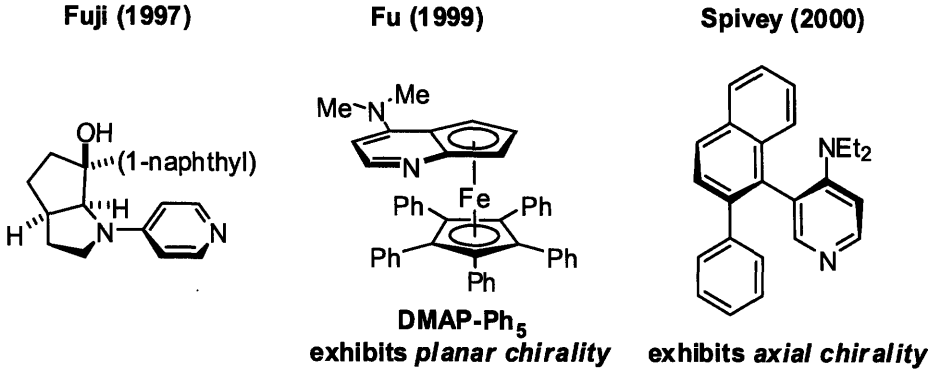


Figure 2.3. Chiral DMAP-variants used in catalytic kinetic resolutions of alcohols.

Literature pertaining to catalytic *amine* resolutions is far more scant. Before the present results, there were only two examples of catalyzed amine resolutions with synthetic catalysts, although the use of enzyme-based catalysts has also been reported.[41]

In 2001, our lab published a kinetic resolution of benzylamines using oxazole-based acylating agents (eq 2.4).[42] The system was based on a previous report from our lab, wherein

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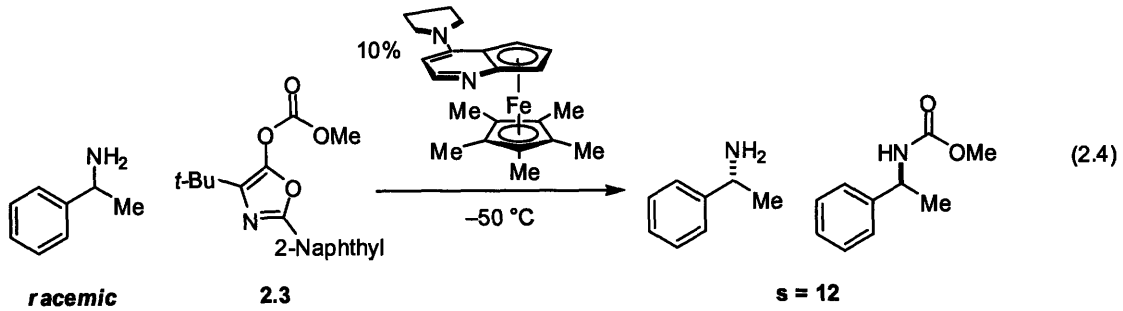
[40] Reviews of enantioselective catalysis, based on chiral DMAP derivatives: Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570–5595.

[41] Amine resolutions with enzyme-based catalysts: van Rantwijk, F.; Sheldon, R. A. *Tetrahedron* **2004**, *60*, 501–519

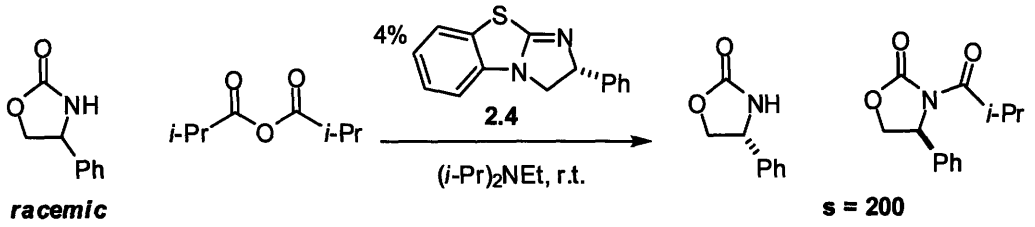
[42] Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234–236.

stoichiometric amounts of acylated-variants of DMAP-Ph_5 were shown to resolve benzylic amines.[43] In order to allow for catalyst-mediated acyl transfer, oxazole **2.3** was employed, which was adapted from those used in a previous series of rearrangement studies.[44]



(2.4)

In 2005, Vladamir Birman published a resolution of 2-aryl-oxazolidinones with outstanding selectivities (eq 2.5).[45] This system features a commercially available acylating agent and a heterocyclic catalyst, **2.4**, that is prepared in two steps from phenylglycinol.



(2.5)

The existing catalytic, enzyme-based systems are usually limited to resolutions of primary, benzylic amines.[40] In one notable case, Bäckvall demonstrated that the enzyme catalyst *Candida antarctica* lipase B (CALB or Novozyme 435) can mediate enantioselective acyl transfer onto benzylic amines in the presence of a dimeric Ru-based catalyst (**2.5**) which racemizes the chiral amine starting material.[46] Thus, they were able to demonstrate a very efficient dynamic kinetic resolution (eq 2.6), i.e., a kinetic resolution in which the enantiomers of starting material are interconverting, allowing for full conversion to product.

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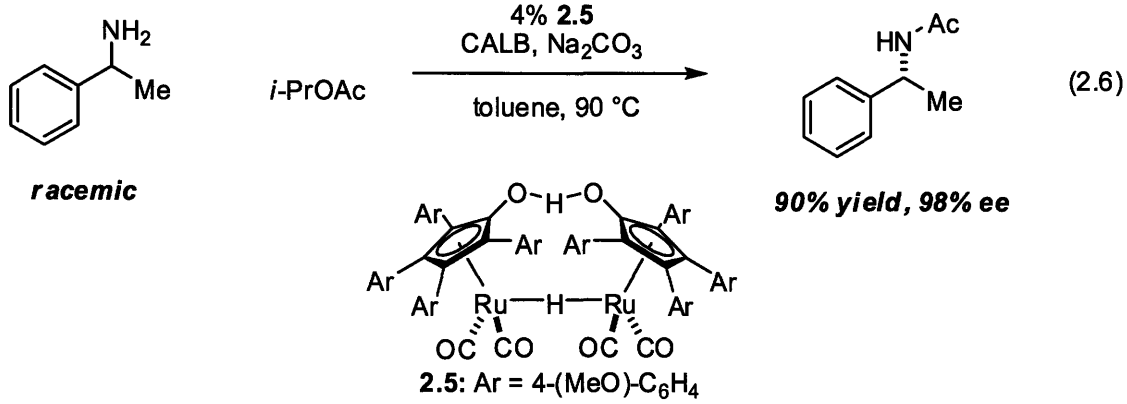
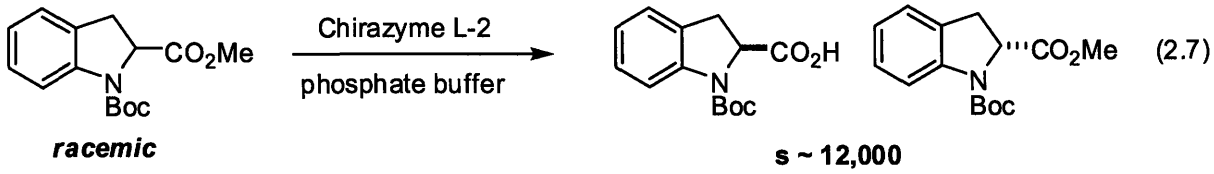
[43] Ie, Y.; Fu, G. C. *Chem. Comm.* **2000**, 119–120.
[44] Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.
[45] Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536–6537.
[46] Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621.



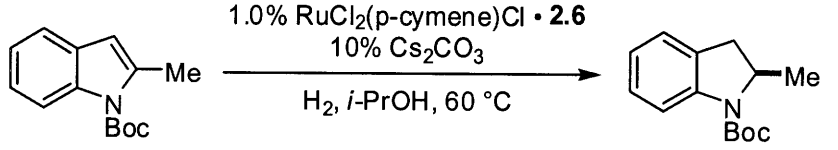
It is also notable, in the context of Section 2.3, that enzyme-based kinetic resolutions of indolines are currently not possible through *N*-acylation. However, enzyme-based hydrolysis of Boc-protected methyl indoline-2-carboxylate with immobilized *Candida antarctica* lipase (Chirazyme L-2) is extremely efficient (eq 2.7).[47]



Enantioenriched indolines may also be prepared by catalytic hydrogenation of the corresponding *N*-protected indole, using the bisferrocene ligand, **2.6** (eq 2.8).[48] The reaction proceeds in good enantioselectivities for 2-substituted indoles and 3-substituted indoles, but not 2,3-disubstituted indoles.

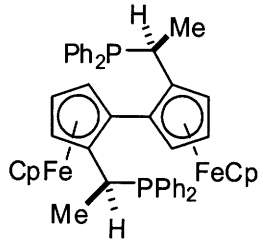
[47] Kurokawa, M.; Sugai, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1021–1022.

[48] Ru-catalyzed hydrogenation of N-protected indolines: (a) Kuwano, R.; Sato, K.; Kurokawa, T.; Karube, D.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614–7615. (b) Kuwano, R.; Kashiwabara, M.; Sato, K.; Ito, T.; Kaneda, K., Ito, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 521–535. (c) Kuwano, R.; Kashiwabara, M. *Org. Lett.* **2006**, *8*, 2653–2655.



(2.8)

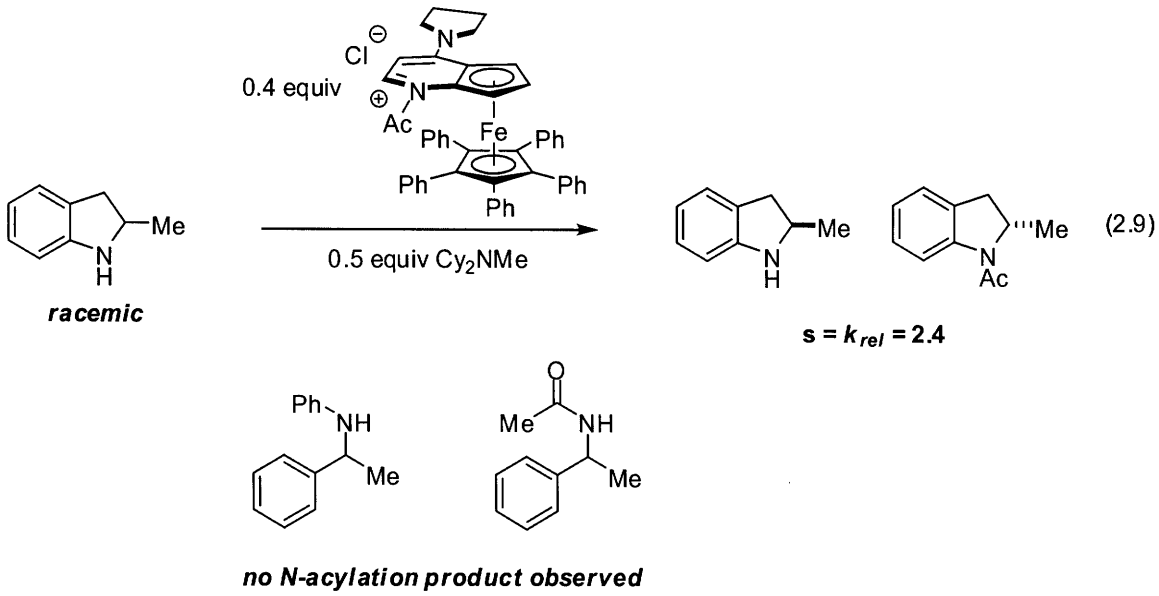
99% yield, 95% ee



2.6

2.2 Results and Discussion

We began our studies with the goal of expanding the scope of catalytic amine resolutions, to improve their efficiency in the resolution of secondary amines (i.e., disubstituted amines). To help meet that goal, we prepared a series of acylated DMAP-based catalysts, and tested their efficiencies as stoichiometric resolving agents. Although indolines were resolved in modest selectivity, open-chain aniline analogues were unreactive in the tested systems (eq 2.9).

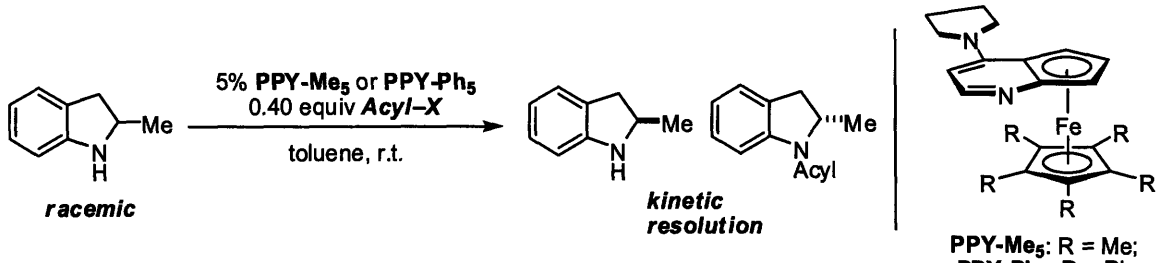


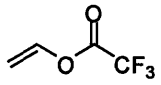
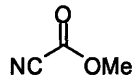
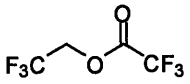
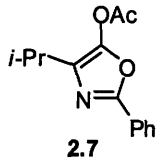
(2.9)

At the same time, we were pursuing a catalyzed version of the resolution. We anticipated that this would be a more difficult problem to solve because it introduced the possibility of a competitive, non-catalyzed background reaction between the amine and the acylating agent. Nevertheless, we screened several systems, both with oxazole-based acylating agents and other families of acylating agent.

The majority of prospective acyl-transfer reagents were either unreactive in catalytic systems, or showed fast reactions with the racemic amine in both catalyzed and non-catalyzed systems (all giving $s < 1.1$). However, four reagents were capable of undergoing fast, catalyzed acyl transfer, while limiting the extent of the undesired background reaction with the amine substrate (Table 2.1).

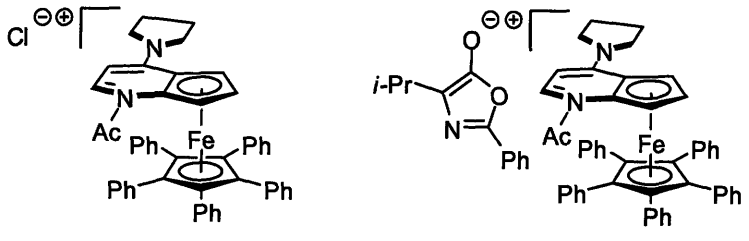
Table 2.1. Comparison of acylating agents that allow catalyzed acyl transfer to indolines.



entry	acylating agent	catalyst	$k_{cat}/k_{non\text{-}cat}$	*s*
1		**PPY-Me$_5$**	2.3	1.0
2[a]		**PPY-Me$_5$**	>11	1.9
3		**PPY-Me$_5$**	>25	2.1
4	 **2.7**	**PPY-Ph$_5$**	>35	1.1

[a] Reaction performed with 0.50 equiv $NMeCy_2$.

The low selectivities deriving from systems with acylating agent **2.7** struck us as interesting. Whereas in the stoichiometric reaction, the acyl pyridinium chloride **2.8** produced low selectivities, its catalytically active counterpart, **2.9**, gave essentially no selectivity (Figure 2.4).



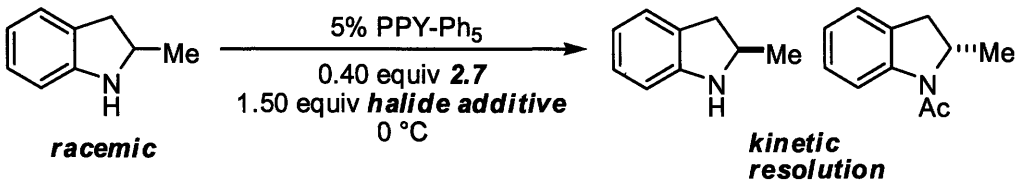
2.8
stoichiometric reagent
s = 2.4

2.9
catalytically active species
s = 1.1

Figure 2.4. Two distinct acylating species.

We reasoned that kinetic resolution systems involving oxazole **2.7** might therefore benefit from added chloride counteranion. Indeed, the addition of 1.5 equiv TBACl to catalyzed systems gave a small boost in resolution efficiency (Table 2.2).[49] Further screening would reveal that the use of lithium chloride and 18-crown-6, a traditionally "mismatched" crown ether, gave a larger boost to selectivities.[50] Lower temperatures and use of lithium bromide gave us our first double-digit selectivity factors.

Table 2.2. Effect of halide additives and temperature on resolution efficiency



entry	halide additive (1.5 equiv)	temp	s
1	NBu_4Cl	r.t.	1.7
2	LiCl · 18-crown-6	r.t.	4.4
3	LiCl · 18-crown-6	0 °C	8.2
4	LiBr · 18-crown-6	0 °C	10

Through further optimization, we found that systems using the 4-*tert*-butyl-oxazole, **2.10,** gave more efficient catalyzed acyl transfer to indolines than systems with **2.7** (eq 2.10).[51,52] Additionally, exploration showed several other Lewis acidic additives that improved selectivity of the resolution (Table 2.3). Although none of them were superior to the lithium/crown-ether systems, it is notable that all additives tested, which gave any degree of selectivity, also gave the same absolute *sense* of selectivity in the products.

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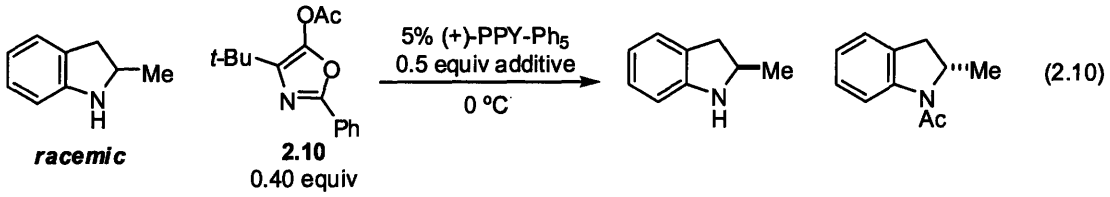
[49] Salt additives have previously been shown to improve selectivities of benzylamine resolution by stoichiometric resolving agents: Arseniyadis, S.; Subhash, P. V.; Valleix, A.; Mathew, S. P.; Blackmond, D. G.; Wagner, A.; Mioskowski, C. *J. Am. Chem. Soc.* **2005**, *127*, 6138–6139.

[50] Crystal structures have been obtained for LiCl • 18-crown-6 adducts, and show a coordinatively unsaturated lithium: Chang, T.-L.; Zhao, M.; Hu, N.-H.; Jin, Z.-S. *Rev. Chim. Min.* **1987**, *24*, 382–390.

[51] The 4-*iso*-propyl-bearing oxazole **2.7** underwent catalyzed acylation of its 4-carbon, to varying degrees (see ref 45).

[52] The analogous oxazoles transferring Ac = COEt or COPh gave a dramatic drop in the selectivity of resolution.

Table 2.3. Other salt-additives that improve resolution selectivities.

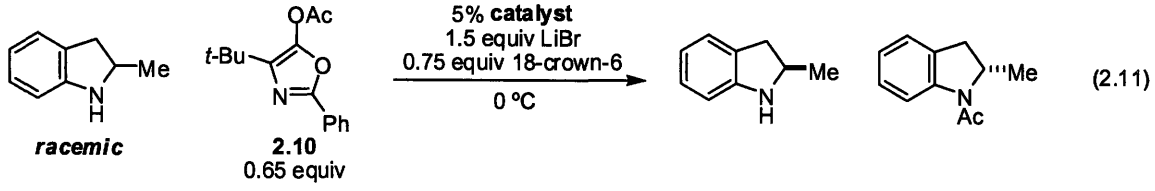


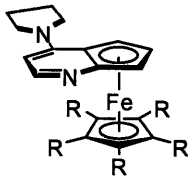
(2.10)

entry	additive	s
1	$MgCl_2$	2.4
2	$Mg(OTf)_2$	1.2
3	$Al(Ot\text{-}Bu)_3$	3.4
4	$CeCl_3$	1.9

We found that the selectivity could be increased by incorporating structurally modified catalysts (Table 2.4). On changing the aryl substitution of the cyclopentadiene fragment, we learned that 3,5-dimethyl-substitution on each aryl ring nearly doubled the selectivity of the system. Larger bottom rings did not provide a more efficient system, however. In terms of reaction rate, preliminary studies also showed that the 3,5-dialkyl substituted catalysts produced nearly identical reaction rates with one another over a 7-day period of time, but that rate is about half as fast as the parent pentaphenyl catalyst (catalyst reaction rates: 3,5–H > Me ~ Et ~ *i*-Pr).

Table 2.4. Screens of structurally modified catalysts.

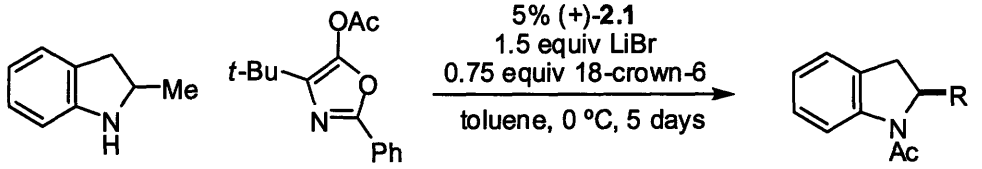




entry	R	s
1	phenyl	10
2	(+)-**2.1**: 3,5-dimethyl-phenyl	23
3	3,5-diethyl-phenyl	19
4	3,5-di(isopropyl)-phenyl	8.4
5	methyl	<2

The optimized system is shown in eq 2.12, and the effect of parameter changes are shown in Table 2.5. Systems with 15-crown-5 were comparably selective, but systems with 12-crown-4 gave very poor selectivities (entries 2 and 3). The exclusion of crown ether gives a system with very poor turnover rate and selectivity, whereas exclusion of lithium salt gives good turnover rate, with poor selectivity (entries 4 and 5). Other salt additives, such as TBABr, LiCl, or LiI, gave lower selectivity, as did lower temperature (entries 7–10).

Table 2.5. Effect of reaction parameters of the resolution efficiency.



(2.12)

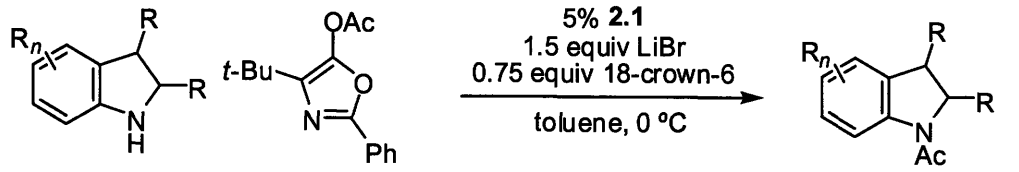
racemic **2.10** 0.65 equiv ***kinetic resolution***

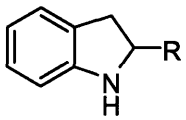
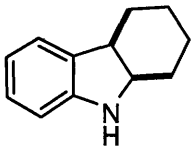
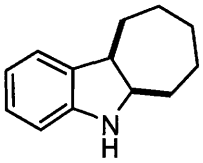
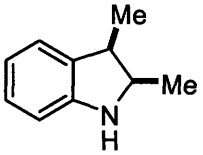
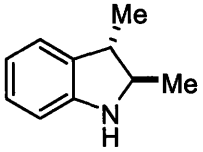
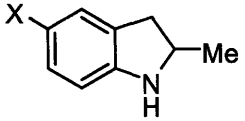
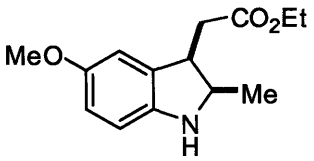
entry	racemic indoline	% conversion	s
1	none	54	23
2	15-crown-5 instead of 18-crown-6	54	20
3	12-crown-4 instead of 18-crown-6	43	3
4	no 18-crown-6	16	6
5	no LiBr	55	<2
6	no LiBr or 18-crown-6	43	<2
7	TBA–Br instead of LiBr/18-crown-6	49	2
8	LiCl instead of LiBr	43	14
9	LiI instead of LiBr	12	12
10	room temperature instead of 0 °C (2 days)	49	11

The indoline scope is shown in Table 2.6. As the size of the 2-substituent increases, the selectivities of the reaction steadily drop (entries 1–5). Tying back the alkyl side chain into a second 6-membered ring gives a selectivity factor of 9.8, whereas a 7-membered ring produces the highest selectivity encountered in the system (entries 6 and 7). 2,3-Disubstitution with a cis-configuration gives high selectivity, whereas trans-configuration gives low selectivity (entries 8 and 9).[53] Electronic perturbations are tolerated by the system (entries 10–12), although electron-poor aryl rings give a very slow rate of reaction.

[53] Notably, substrates without 2-alkyl substitution, but *with* 3-alkyl substitution, give selectivity factors of ca. 2–3 (cf. Figure 2.5, vide infra).

Table 2.6. Scope of Indoline Resolution.



entry	racemic indoline		s	ee of resolved indoline
1		R = Me	**25**	94% ee (55% conversion)
2		*n*-Pr	**26**	90% ee (53% conversion)
3		2-phenylethyl	**18**	98% ee (60% conversion)
4		CH_2OTBS	**14**	94% ee (56% conversion)
5		*i*-Pr	**8.2**	78% ee (58% conversion)
6			**9.8**	91% ee (64% conversion)
7			**31**	91% ee (51% conversion)
8			**18**	91% ee (55% conversion)
9			**9.5**	94% ee (64% conversion)
10		X = OMe	**13**	92% ee (60% conversion)
11		Br	**11**	90% ee (60% conversion)
12			**19**	95% ee (58% conversion)

Several aniline-based substrates were not suitable for resolution by this system (Figure 2.5). Low selectivities, with moderate rates of acylation, were observed for those

substrates with 3-substitution rather than 2-substitution, as well as substrates with 2-substitution containing sp^2-hybridization. Both slow conversion and poor selectivity were observed for substrates with 2-*tert*-butyl substitution, a tetrahydroisoquinoline framework, or for racemic BINAP-diamine, which primarily underwent mono-*N*-acylation in our final system.

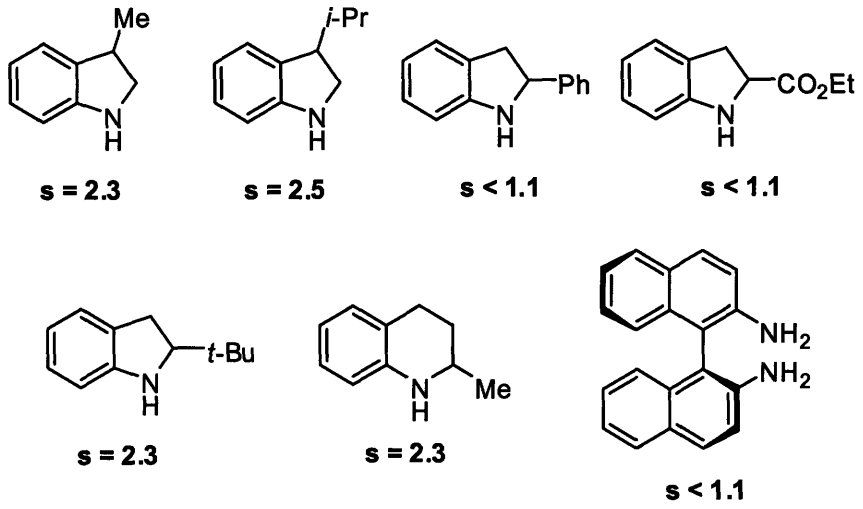
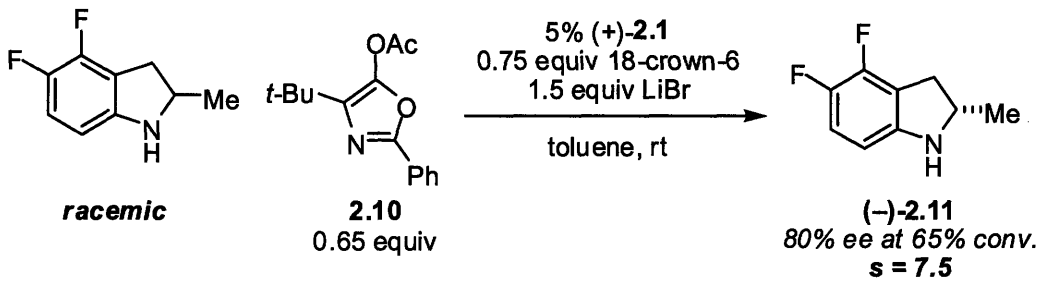


Figure 2.5. Racemic, aniline-based substrates that undergo inefficient resolution.

We were interested in applying the resolution to intermediates used en route to bioactive compounds. Thus, we resolved difluorinated indoline **2.11**, which had been used previously by Tsuji and Miyamoto in the synthesis of Floxin-based antibiotics (eq 2.13).[54,55] The racemic indoline is available through a one-step reduction from the commercially available indole, and it can be resolved with moderate levels of selectivity at room temperature.

[54] (a) Tsuji, K.; Ishikawa, H. *Synth. Comm.* **1994**, *24*, 2943–2953. (b) Tsuji, K.; Tsubouchi, H.; Ishikawa, H. *Chem. Pharm. Bull.* **1995**, *43*, 1678–1682.

[55] Ishikawa, H.; Uno, T.; Miyamoto, H.; Ueda, H.; Tamaoka, H.; Tominaga, M.; Nakagawa, K. *Chem. Pharm. Bull.* **1990**, *38*, 2459–2462.

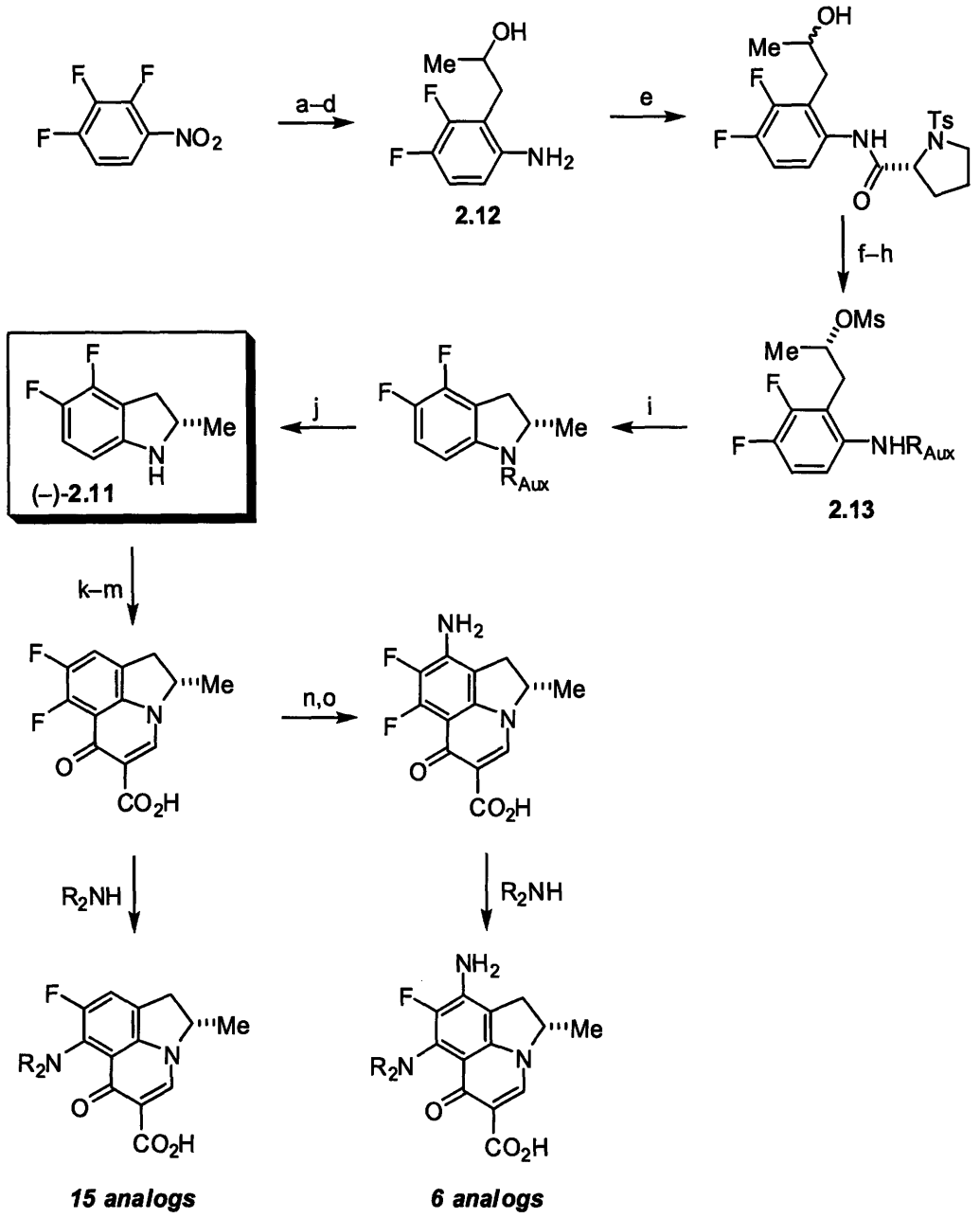


(2.13)

The synthesis of the Floxin analogues is outlined in Scheme 2.1. Onto amino alcohol **2.12**,[56] was installed a proline-based chiral auxiliary, and then through a reduction/oxidation sequence, preferentially generated mesylate **2.13**.[54] The core indoline ring was generated through base-mediated cyclization, which also set the 2-methyl stereocenter, and the chiral auxiliary was removed, affording free **(–)-2.11**. This indoline was further annulated with ethoxymethylenemalonate, producing the Floxin core structure, and nucleophilic aromatic substitutions then produced a range of bioactive analogs.[55]

[56] Parikh, V. D.; Fray, A. H.; Kleinman, E. F. *J. Heterocycl. Chem.* **1988**, *25*, 1567–1569.

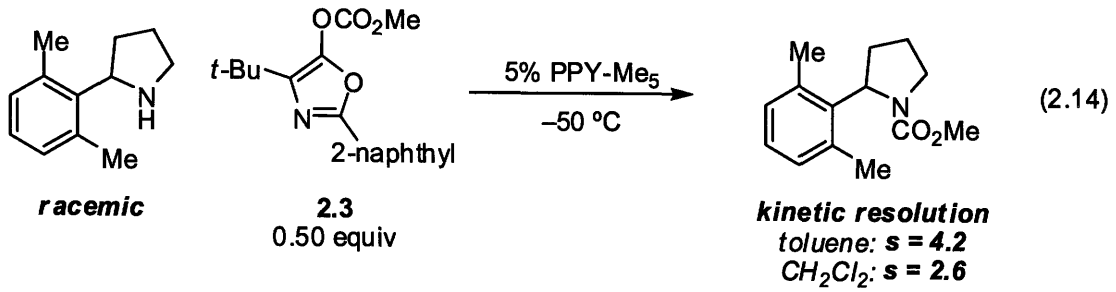
Scheme 2.1. Synthesis of Floxin analogs by Tsuji and Miyamoto.[a]



[a] Reagents and conditions: (a), ethyl acetoacetate, NaH; (b) HCl/HOAc; (c) $NaBH_4$; (d) H_2, Raney–Ni; (e) (*R*)-*N*-(*p*-tolylsulfonyl)prolinyl chloride, Py; (f) CrO_3, H_2SO_4; (g) $LiAlH_4$; (h) MsCl, TEA; (i) K_2CO_3, acetone; (j) KOH; (k) ethoxymethylenemalonate; (l) PPA; (m) HCl; (n) KNO_3; (o) H_2, Pd/C.

We also made some preliminary progress on pyrrolidine resolutions, using a similar system to that employed in the benzylamine resolutions (eq 2.14). This system did not benefit

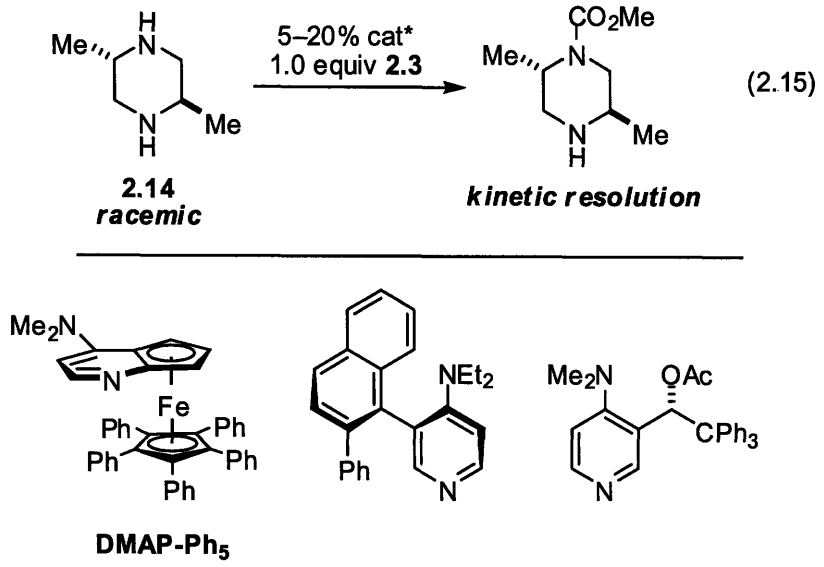
from the addition of lithium salt and crown ether, nor did the original benzylic amine resolution (from eq 2.4) during later control experiments.



(2.14)

Recent Work

Over the past two years, new reports of stoichiometric benzylamine resolving agents have surfaced,[57] as well as a catalyzed resolution of secondary diamine, **2.14**, employing oxazole **2.3** with various DMAP-based catalysts (**s** = ca. 2–3; eq 2.15).[58]



(2.15)

[57] For example: (a) Sabot, C.; Subhash, P. V.; Valleix, A.; Arseniyadis, S.; Mioskowski, C. *Synlett* **2008**, 268–272. (b) Karnik, A. V.; Kamath, S. S. *Tetrahedron: Asymmetry* **2008**, *19*, 45–48.

[58] Anstiss, M.; Nelson, A. *Org. Biomol. Chem.* **2006**, *4*, 4135–4143.

2.3 Mechanistic Discussion

The kinetic resolution of benzylic amines, reported in 2001, is believed to possess a reaction-coordinate diagram similar to that shown in Figure 2.6 (See eq 2.4; TLS = turnover-limiting step).[42] The resting state of the catalytic cycle is the acylated catalyst, and the reaction is zero order in acylating agent, and first order in catalyst and amine. In a simplified, two-step cycle the second step is believed to be both turnover-limiting, and, of course, stereochemistry-determining.

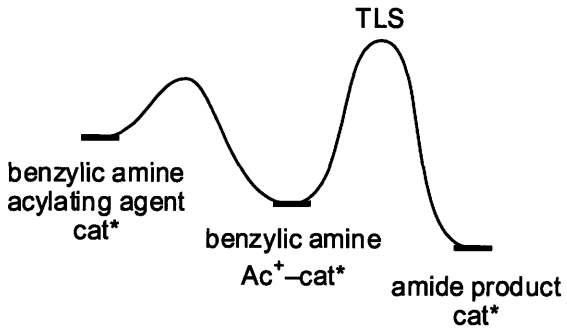


Figure 2.6. Simplified, two-transformation energy diagram for the catalyzed benzylic amine resolution (eq 2.4). Some components have not been listed, for clarity (e.g., base and solvent).

For the indoline resolution, NMR studies show that catalyst and acylating agent rest as separate species, under the finalized reaction conditions (eq 2.12). Additionally, we observe dramatically higher rates of product formation for electron-rich indolines versus electron-poor indolines. This seems to suggest that the indoline resolution also proceeds with the turnover-limiting and stereochemistry-determining step being the second one (in a simplified cycle), but that the corresponding energies of the pre-equilibrium are inverted compared to the benzylic amine resolution (Figure 2.7).

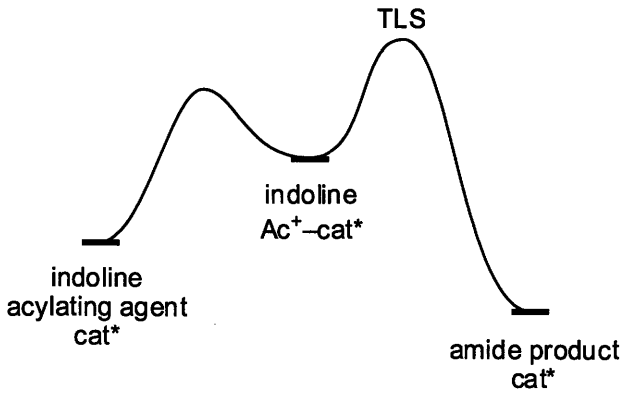


Figure 2.7. Simplified, two-step energy diagram for the catalyzed indoline resolution. Some components have not been listed, for clarity (e.g., additives and solvent).

Moving into an area of greater speculation, an expanded catalytic cycle for the additive-containing indoline resolution is proposed in Figure 2.8, which explicitly illustrates the orthoamidate intermediates.[59]

This cycle proceeds via an orthoamidate intermediate to the acylated catalyst (step 1). The turnover-limiting step (step 2, which may actually be a composite of several more-fundamental steps) is proposed to require indoline association with carbonyl center and deprotonation by the aryl-alkoxide, forming a high-order intermediate **2.15**. In step 3, the intermediate decomposes into a second orthoamidate, which is presumed to be the rate-limiting step for many types of DMAP-catalyzed alcohol acylations.[59] Finally, the second orthoamidate decomposes into amide product and regenerated catalyst.

[59] Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436–5441.

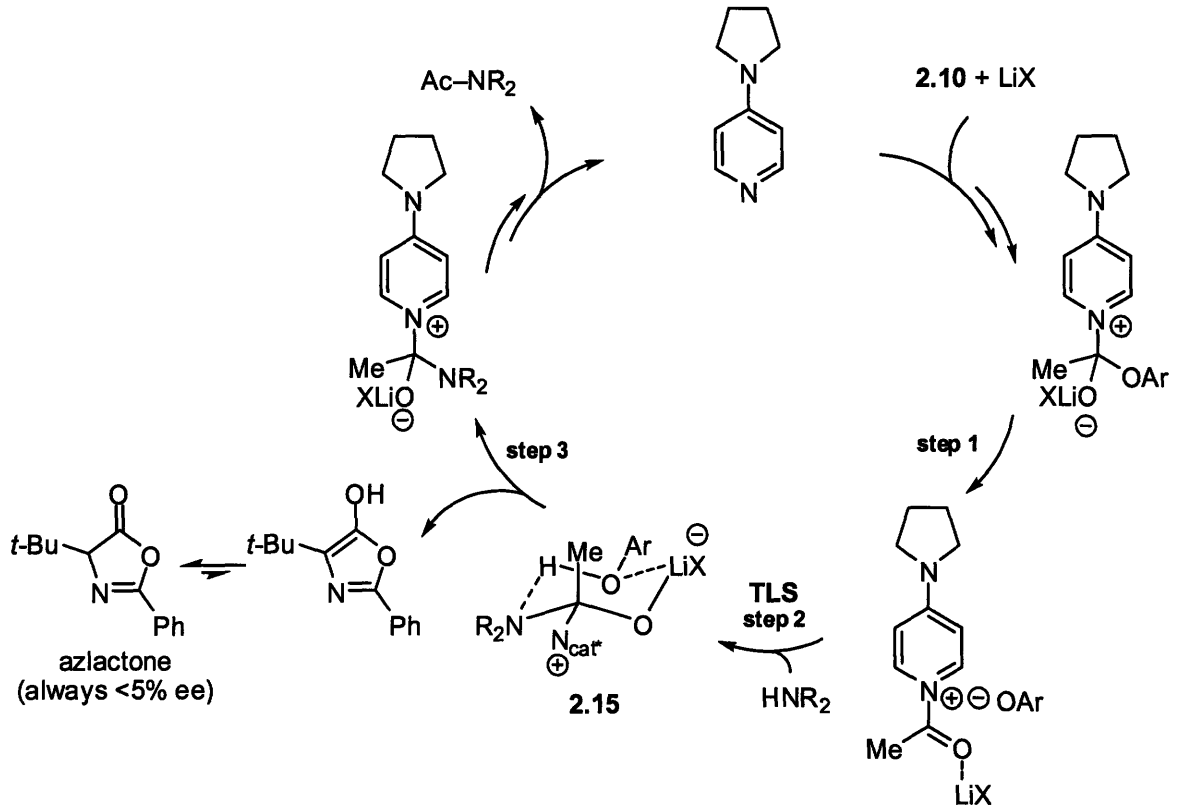


Figure 2.8. Expanded proposal for the catalytic cycle of the metal-containing indoline resolution.

Kinetically, this cycle could "short-circuit" the lithium-free cycle (e.g., the unselective cycle in Table 2.5, entry 6), and thus metal-containing and metal-free cycles may have little overlap with one another, despite the unremarkable difference in their reaction rates.

This speculative rate-limiting step also rationalizes the observation that electron-rich indolines produce product more quickly than electron-poor indolines, and the observation that substrates with hindered *N*-centers are slower reacting than those with small 2-substitution.

2.4 Conclusion

We have demonstrated the first method, enzymatic or non-enzymatic, for the kinetic resolution of indolines through *N*-acylation. The final system incorporates salt additives and a new planar-chiral catalyst, and it presents a rare example of non-enzymatic, catalytic amine resolution.[60]

[60] Arp, F. O.; Fu, G. G. *J. Am. Chem. Soc.* **2006**, *128*, 14264–14265.

2.5 Experimental Section

I. General

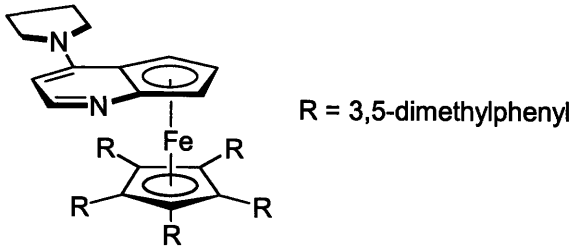
Lithium bromide (Alfa Aesar; ultra dry, 99.998%) was crushed into a fine powder under nitrogen, and 2-methylindoline (Aldrich) was purified by distillation from calcium hydride. Toluene was dried by passage through an activated alumina column. All other chemicals were reagent grade and used as received.

HPLC analyses were performed on an Agilent 1100 Series system with Daicel Chiralpak® columns in hexanes/isopropanol solvent mixtures.

All reactions were conducted under nitrogen, unless otherwise noted.

II. Preparation of Materials

The yields in this section have not been optimized.



Catalyst 2.1. *n*-Butyllithium (1.6 M in hexanes; 2.1 mL, 3.4 mmol) was added to a solution of penta(3,5-dimethylphenyl)cyclopentadiene (2.00 g, 3.41 mmol) in dry THF (20 mL).

A suspension of crushed $FeCl_2$ (433 mg, 3.42 mmol) in dry THF (250 mL) was prepared in a 500-mL round-bottomed flask. The flask was fitted with a rubber septum, equipped with a nitrogen-inlet needle, and then cooled to 0 °C in an ice bath. Next, the cyclopentadienyllithium solution was added by cannula into the $FeCl_2$ solution, and the resulting green mixture was stirred at 0 °C for 15 min.

In a separate flask, 4-dimethylaminopyridine[61] (0.529 g, 2.84 mmol) was dissolved in dry THF (15 mL) and then treated with *n*-butyllithium (1.6 M in hexanes; 1.8 mL, 2.9 mmol). The mixture was stirred at r.t. for 10 min, and then it was transferred by cannula into the cold mixture that contained the iron complex (previous paragraph). The resulting dark-yellow solution was placed into an oil bath preheated to 60 °C and stirred for 3 h. During that time, the solution turned dark red.

The solvents were removed by rotary evaporation, and the residue was purified by flash chromatography (CH_2Cl_2 and then ethyl acetate). The dark-purple fractions were concentrated to provide the product as a glassy, dark-purple solid (1.68 g, 72%).

Catalyst **1** is air-stable (for months).

---

[61] Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532–11533.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, J = 5.4 Hz, 1H), 6.72 (s, 5H), 6.57 (s, 10H), 5.73 (d, J = 5.4 Hz, 1H), 4.97-4.91 (m, 2H), 4.16 (t, J = 2.8 Hz, 1H), 3.53-3.42 (br, 4H), 2.09 (s, 30H), 1.94-1.88 (br, 4H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 156.5, 152.6, 149.6, 135.3, 135.1, 130.3, 127.2, 96.5, 85.2, 77.9, 77.0, 69.0, 65.1, 49.7, 25.3, 21.2;

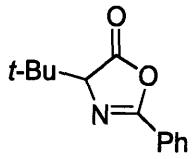
IR (film) 3434, 2918, 1642, 1600, 1536, 1485, 1462, 1401, 1339, 1025, 904, 848, 759, 706 cm^{-1};

HRMS calculated for $C_{57}H_{58}FeN_2$ 826.3949, found 826.3945;

mp 154-157 °C.

The enantiomers of catalyst **2.1** were separated by semi-preparative chiral HPLC: Regis (*R*,*R*)-Whelk-O 2 10/100, 25 cm × 10 mm; diethylamine/CH_2Cl_2/hexanes, 0.4:20:80; 2.50 mL/min flow rate; 25.0 mg catalyst in 0.5 mL per injection. Enantiomer (+)-**2.1** ($[\alpha]^{23}_D$ = +1100 (c = 0.021, $CHCl_3$)) was collected from 8.8 min to 11.1 min, and (–)-**2.1** was collected from 11.8 min to 16.0 min.

The absolute configuration of (+)-**2.1** was assigned by X-ray crystallography (see Section IV).

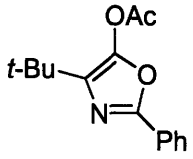


4-*tert*-Butyl-2-phenyloxazol-5(4H)-one [71953-55-4]. NaOH (3.4 g, 85 mmol) and then benzoyl chloride (4.9 mL, 42 mmol) were added to a solution of *tert*-leucine (5.03 g, 38.3 mmol) in water (200 mL) in a large Erlenmeyer flask. This heterogeneous mixture was stirred overnight, during which time it became homogeneous. The product amide was then precipitated by the slow addition of aqueous HCl (2 M), isolated by filtration, and dried thoroughly under high vacuum. This chalky white solid was dissolved in CH_2Cl_2 (50 mL), and then 1,3-dicyclohexylcarbodiimide (8.05 g, 39.0 mmol) was added. The resulting heterogeneous mixture was stirred open to air at r.t. overnight. The solution was filtered, and then the filtrate was washed with aqueous HCl (2 M; 100 mL), dried (Na_2SO_4), and concentrated. The desired product was purified by flash chromatography through a short pad

of silica gel (5% ethyl acetate in hexanes), which afforded a white solid (6.95 g, 84%, two steps).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.03-8.01 (m, 2H), 7.59-7.55 (m, 1H), 7.50-7.47 (m, 2H), 4.09 (s, 1H), 1.15 (s, 9H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.9, 161.2, 132.6, 128.7, 127.8, 125.9, 74.0, 35.9, 26.1.



4-*tert*-Butyl-2-phenyloxazol-5-yl acetate. A 500-mL round-bottomed flask was capped with a rubber septum, flushed with nitrogen, and charged with sodium hydride (845 mg, 35.2 mmol) and 4-*tert*-butyl-2-phenyloxazol-5(4H)-one (6.95 g, 32.0 mmol). Dry THF (250 mL) was added, and the resulting heterogeneous mixture was cooled to –15 °C. 15-Crown-5 (7.75 g, 35.2 mmol) was added, and the resulting canary yellow, bubbling solution was stirred at –15 °C for 15 min. Then, acetyl chloride (2.76 g, 35.2 mmol) was added, and the resulting colorless solution was stirred for 20 min. The reaction mixture was then concentrated and purified by flash chromatography (5% ethyl acetate in hexanes) to remove most of the crown ether and sodium salts. The residue was further purified by flash chromatography (2.5% ethyl acetate in hexanes) to afford the product as a white solid (6.74 g, 81%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97-7.95 (m, 2H), 7.43-7.41 (m, 3H), 2.35 (s, 3H), 1.33 (s, 9H);

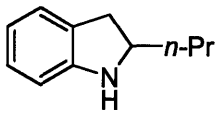
^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.1, 154.4, 143.4, 132.1, 129.9, 128.5, 127.5, 125.8, 31.0, 28.9, 20.3;

IR (film) 2959, 2870, 1798, 1636, 1556, 1486, 1450, 1371, 1322, 1170, 1093, 1075, 1007, 873, 776, 724, 691 cm^{-1};

EIMS (70 eV) *m/z*: M^+ (calculated for $C_{15}H_{17}NO_3$: 259) 259, 218, 203, 174, 156, 133, 106, 84, 51;

mp 76-78 °C.

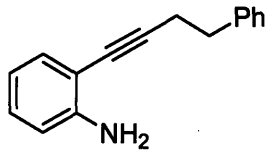
Reduction by Sodium Cyanoborohydride: General Procedure.[62] Sodium cyanoborohydride (3.0 equiv) was carefully dissolved in glacial acetic acid, and the resulting bubbling clear solution was added by pipette to a stirred solution of the indole in glacial acetic acid. This clear, colorless mixture was allowed to stir open to air for 12 h at r.t. Then, the mixture was transferred to an Erlenmeyer flask, and a saturated aqueous K_2CO_3 solution was added until the solution had become basic. The resulting mixture was extracted with diethyl ether (2 × 100 mL), and the combined organic phases were dried (K_2CO_3), concentrated, and purified by flash chromatography.



2-Propylindoline [76916-57-9]. This indoline was prepared from 2-propylindole[4] (906 mg, 5.69 mmol) and sodium cyanoborohydride (1.1 g, 18 mmol) via the general reduction procedure. After flash chromatography (5% ethyl acetate in hexanes), the product was obtained as a clear, colorless oil (508 mg, 55%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.10-6.99 (m, 2H), 6.72-6.60 (m, 2H), 3.92-3.82 (m, 2H), 3.14 (dd, J = 8.6, 15.5 Hz, 1H), 2.69 (dd, J = 8.5, 15.5 Hz, 1H), 1.66-1.57 (m, 2H), 1.49-1.35 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.0, 128.9, 127.2, 124.6, 118.4, 109.0, 59.8, 39.0, 36.1, 19.7, 14.1.



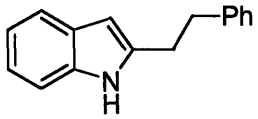
2-(4-Phenylbut-1-ynyl)benzenamine [736184-66-0]. A 100-mL round-bottomed flask was charged with 2-iodoaniline (2.30 g, 10.5 mmol), *trans*-

[62] Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, 859-860.

dichlorobis(triphenylphosphine)palladium (73.7 mg, 0.105 mmol), and CuI (100 mg, 0.53 mmol).[63] The flask was fitted with a rubber septum and purged with nitrogen for 5 min. Triethylamine (20 mL) and then but-3-ynylbenzene (2.39 g, 18.4 mmol) were added by syringe, and the resulting reaction mixture was stirred at r.t. for 24 h. Then, the triethylamine was removed in vacuo, and the resulting brown residue was purified by flash chromatography (5% ethyl acetate in hexanes), which afforded the product as an orange oil (2.25 g, 97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37-7.30 (m, 4H), 7.28-7.23 (m, 2H), 7.11-7.07 (m, 1H), 6.69-6.65 (m, 2H), 3.99 (br s, 2H), 2.96 (t, J = 7.3 Hz, 2H), 2.82 (t, J = 7.1 Hz, 2H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.7, 140.6, 131.9, 128.9, 128.6, 128.4, 126.3, 117.7, 114.0, 108.5, 94.6, 77.9, 35.1, 21.7.



2-Phenethylindole [98055-06-2]. A 100-mL round-bottomed flask was charged with 2-(4-phenylbut-1-ynyl)benzenamine (2.25 g, 10.2 mmol), CuI (387 mg, 2.03 mmol), and DMF (10 mL).[xx (ref below)] The flask was fitted with a reflux condenser, and the system was purged with nitrogen for 5 min. The heterogeneous reaction mixture was stirred at reflux for 12 h. Then, most of the DMF was removed in vacuo, and the residue was purified by flash chromatography (5% ethyl acetate in hexanes), which furnished the product as an off-white crystalline solid (643 mg, 29%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (br s, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.36-7.32 (m, 2H), 7.29-7.24 (m, 4H), 7.16-7.08 (m, 2H), 6.31 (s, 1H), 3.14-3.05 (m, 4H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.2, 139.0, 135.8, 128.6, 128.5, 128.4, 126.3, 121.1, 119.8, 119.6, 110.3, 99.8, 35.6, 30.1.

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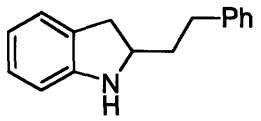
[63] Kuyper, L. F.; Baccanari, D. P.; Jones, M. L.; Hunter, R. N.; Tansik, R. L.; Joyner, S. S.; Boytos, C. M.; Rudolph, S. K.; Knick, V.; Wilson, H. R.; Caddell, J. M.; Friedman, H. S.; Comley, J. C. W.; Stables, J. N. *J. Med. Chem.* **1996**, *39*, 892–903.



2-Phenethylindoline. This indoline was prepared from 2-phenethylindole (643 mg, 2.91 mmol) and sodium cyanoborohydride (550 mg, 8.8 mmol) via the general reduction procedure. After flash chromatography (5% ethyl acetate in hexanes), the product was obtained as an off-white solid (643 mg, 84%).

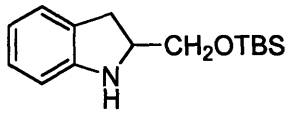
^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.33-7.29 (m, 2H), 7.23-7.19 (m, 3H), 7.09 (d, J = 7.2 Hz, 1H), 7.02 (t, J = 7.4 Hz, 1H), 6.70 (t, J = 7.4 Hz, 1H), 6.61 (d, J = 7.7 Hz, 1H), 3.93-3.86 (m, 1H), 3.17 (dd, J = 8.7, 15.5 Hz, 1H), 2.79-2.68 (m, 3H), 2.00-1.94 (m, 2H), 1.58 (br s, 1H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.8, 141.7, 128.7, 128.4, 128.3, 127.2, 125.9, 124.6, 118.5, 109.1, 59.5, 38.4, 36.1, 32.9;

IR (film) 3368, 3022, 2922, 2848, 1607, 1484, 1466, 1454, 1319, 1246, 1017, 745 cm^{-1};

EIMS (70 eV) *m/z*: M^+ (calculated for $C_{16}H_{17}N$: 223) 223, 207, 130, 118, 91, 65;

mp 39-41 °C.



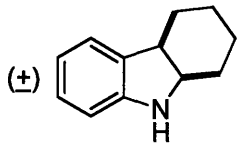
2-((*tert*-Butyldimethylsilyloxy)methyl)indoline [321744-15-4]. Lithium aluminum hydride (1.0 M in THF; 37 mL, 37 mmol) was carefully added to a solution of (±)-indoline-2-carboxylic acid (2.0 g, 12.3 mmol) in dry THF (100 mL). The mixture was stirred for 1 h at r.t., and then the reaction was carefully quenched by the addition of aqueous sodium potassium tartrate (10% by weight; 100 mL). The resulting mixture was stirred for an additional hour, and then it was filtered. The filtrate was concentrated to a yellow oil, which was purified by flash chromatography (CH_2Cl_2) to afford the aminoalcohol.

The aminoalcohol (1.00 g, 6.70 mmol) was dissolved in CH_2Cl_2 (100 mL), and then imidazole (500 mg, 7.4 mmol) and *tert*-butyldimethylsilyl chloride (1.1 g, 7.4 mmol) were added. The resulting mixture was stirred at r.t. for 2 h, and then it was filtered. The filtrate

was concentrated and then purified by flash chromatography (5% ethyl acetate in hexanes), which afforded the product as a clear yellow oil (1.50 g, 46%, two steps).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09-7.00 (m, 2H), 6.71-6.63 (m, 2H), 4.23 (br s, 1H), 3.98-3.91 (m, 1H), 3.62-3.52 (m, 2H), 3.11 (dd, J = 9.0, 15.7 Hz, 1H), 2.65 (dd, J = 5.7, 15.8 Hz, 1H), 0.92 (s, 9H), 0.07 (s, 6H);

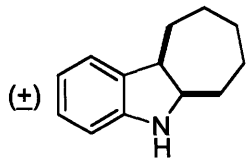
^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.5, 128.1, 127.3, 124.7, 118.4, 109.4, 66.6, 60.4, 32.0, 25.9, 18.3, –5.3.



***cis*-5,6,7,8,8a,9-Hexahydro-4bH-carbazole [4828-96-0].** This indoline was prepared from 6,7,8,9-tetrahydrocarbazole (1.00 g, 5.84 mmol) and sodium cyanoborohydride (1.1 g, 18 mmol) via the general reduction procedure. After flash chromatography (5% ethyl acetate in hexanes), the product was obtained as a white solid (779 mg, 78%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.13-7.03 (m, 2H), 6.80-6.69 (m, 2H), 3.78-3.72 (m, 1H), 3.68 (br s, 1H), 3.13 (app q, J = 6.6 Hz, 1H), 1.83-1.77 (m, 2H), 1.83-1.53 (m, 3H), 1.47-1.35 (m, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.7, 133.5, 126.9, 123.1, 118.7, 110.1, 59.6, 40.8, 29.1, 26.9, 22.5, 21.6.



***cis*-5,5a,6,7,8,9,10,10a-Octahydrocyclohepta[b]indole [886024-65-3].** This indoline was prepared from 5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole (Ryan Scientific; 650 mg, 3.51 mmol) and sodium cyanoborohydride (660 mg, 10.5 mmol) via the general

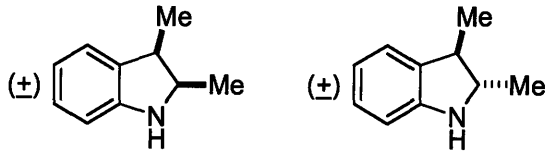
reduction procedure. After flash chromatography (5% ethyl acetate in hexanes), an inseparable mixture of the cis and trans isomers was obtained as a white solid (569 mg; ~9:1).

To facilitate isolation of the cis isomer, the mixture was acylated (diethyl ether (25 mL), triethylamine (515 μL, 1.3 equiv), and acetyl chloride (222 μL, 1.1 equiv); 15 min at r.t.) and purified by flash chromatography (10% → 15% ethyl acetate in hexanes), which furnished the isomerically pure *N*-acetylated cis diastereomer.

The title compound was then obtained by dissolving the *N*-acetylated cis isomer in dioxane (10 mL), adding concentrated aqueous HCl (5.0 mL), and refluxing the reaction mixture overnight. Then, the mixture was concentrated and purified by flash chromatography (5% ethyl acetate in hexanes), which afforded the desired product as a feathery white solid (482 mg, 73%, three steps).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.04-6.99 (m, 2H), 6.73-6.67 (m, 1H), 6.58-6.55 (m, 1H), 4.05 (dt, J = 5.5, 9.8 Hz, 1H), 3.65 (br s, 1H), 3.48 (dt, J = 3.8, 10.6 Hz, 1H), 2.03-1.68 (m, 7H), 1.47-1.29 (m, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.1, 133.5, 127.3, 124.1, 118.1, 108.4, 63.4, 46.7, 33.5, 31.31, 31.34, 28.7, 26.0.



***cis*-2,3-Dimethylindoline [10276-90-1] and *trans*-2,3-dimethylindoline [7356-42-5].** These indolines were prepared from 2,3-dimethylindole (2.28 g, 15.7 mmol) and sodium cyanoborohydride (3.0 g, 48 mmol) via the general reduction procedure. After flash chromatography (3% → 5% ethyl acetate in hexanes), *cis*-2,3-dimethylindoline (221 mg, 10%) and *trans*-2,3-dimethylindoline (1.09 g, 47%) were obtained as yellow oils.

***cis*-2,3-Dimethylindoline:**

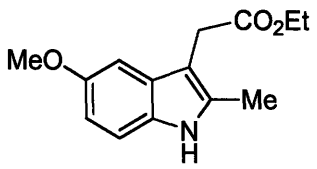
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09-7.01 (m, 2H), 6.76-6.72 (m, 1H), 6.63-6.62 (m, 1H), 3.99-3.93 (m, 1H), 3.65 (br s, 1H), 3.31-3.25 (m, 1H), 1.19 (d, J = 7.2 Hz, 3H), 1.15 (d, J = 6.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.1, 134.2, 127.2, 123.8, 118.7, 109.3, 58.3, 39.4, 16.3, 13.6.

***trans*-2,3-Dimethylindoline:**

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24-7.21 (m, 2H), 6.95-6.91 (m, 1H), 6.77-6.76 (m, 1H), 3.96 (br s, 1H), 3.61-3.56 (m, 1H), 3.02-2.96 (m, 1H), 1.50-1.47 (m, 6H);

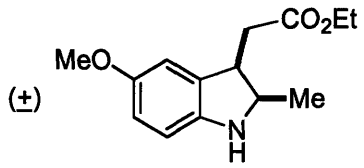
^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.3, 134.0, 127.0, 122.9, 118.2, 108.8, 63.6, 44.0, 20.2, 16.9.



Ethyl 2-(5-methoxy-2-methyl-1H-indol-3-yl)acetate [17536-38-8]. A 50-mL round-bottomed flask was charged with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (1.38 g, 5.42 mmol) and 2-(5-methoxy-2-methyl-1H-indol-3-yl)acetic acid (Aldrich; 1.08 g, 4.93 mmol) and then flushed with nitrogen. Dry CH_2Cl_2 (15 mL) and triethylamine (1.51 mL, 10.8 mmol) were added, and the solution was stirred at r.t. for 5 min. Then, dry ethanol (1.0 mL, 17 mmol) was added, and the mixture was stirred overnight. The solution was then extracted with water (2 × 50 mL), and the organic layer was dried (Na_2SO_4), concentrated, and purified by flash chromatography through a short pad of silica gel (33% ethyl acetate in hexanes), which afforded the desired product as a viscous yellow oil (0.97 g, 86%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (br s, 1H), 7.14 (d, J = 8.5 Hz, 1H), 7.02-7.01 (m, 1H), 6.79-6.77 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.65 (s, 2H), 2.39 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2, 153.9, 133.5, 130.1, 128.8, 110.9, 110.8, 104.3, 100.3, 60.6, 55.8, 30.5, 14.2, 11.6.



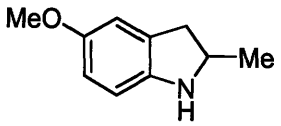
***cis*-Ethyl 2-(5-methoxy-2-methylindolin-3-yl)acetate.** A 25-mL round-bottomed flask was charged with ethyl 2-(5-methoxy-2-methyl-1H-indol-3-yl)acetate (657 mg, 2.66 mmol), trifluoroacetic acid (8.0 mL), and triethylsilane (2.12 mL, 13.3 mmol).[64] The flask was fitted with a reflux condenser, heated to 70 °C, and stirred for 48 h. Then, additional triethylsilane (2.12 mL, 13.3 mmol) was added, and the reaction was stirred for another 48 h. Next, the mixture was carefully transferred by pipette into an aqueous K_2CO_3 solution (5% by weight; 150 mL) and extracted with diethyl ether (2 × 100 mL). The combined organic layers were dried (K_2CO_3), concentrated, and purified by flash chromatography (15% → 20% ethyl acetate in hexanes), which afforded the desired product as a yellow oil (401 mg, 60%; cis isomer), along with recovered starting material (43 mg, 7%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.70 (s, 1H), 6.63-6.61 (m, 1H), 6.61-6.56 (m, 1H), 4.19 (q, J = 7.1 Hz, 2H), 4.06 (dq, J = 6.7, 6.5 Hz, 1H), 3.75 (s, 3H), 3.68-3.62 (m, 1H), 3.40 (br s, 1H), 2.65-2.53 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.5 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.6, 153.4, 144.0, 133.0, 112.6, 111.0, 110.0, 60.5, 58.2, 55.8, 41.6, 33.7, 16.2, 14.1;

IR (film) 3435, 2981, 2832, 2099, 1727, 1639, 1491, 1232, 1156, 1033 cm^{-1};

EIMS (70 eV) *m/z*: M^+ (calculated for $C_{14}H_{19}NO_3$: 249) 249, 234, 222, 204, 178, 160, 142, 117.



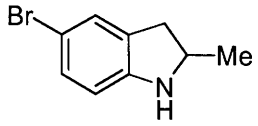
5-Methoxy-2-methylindoline [41568-27-8]. This indoline was prepared from 5-methoxy-2-methylindole (500 mg, 3.10 mmol) and sodium cyanoborohydride (580 mg, 9.2

[64] Lanzilotti, A. E.; Littell, R.; Fanshawe, W. J.; McKenzie, T. C.; Lovell, F. M. *J. Org. Chem.* **1979**, *44*, 4809-4813.

mmol) via the general reduction procedure. After flash chromatography (15% ethyl acetate in hexanes), the product was obtained as a yellow oil (445 mg, 88%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.73 (s, 1H), 6.61-6.54 (m, 2H), 4.01-3.95 (m, 1H), 3.75 (s, 3H), 3.59 (br s, 1H), 3.12 (dd, J = 8.4, 15.5 Hz, 1H), 2.63 (dd, J = 7.9, 15.5 Hz, 1H), 1.30 (d, J = 6.2 Hz, 3H);

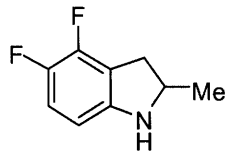
^{13}C NMR ($CDCl_3$, 125 MHz): δ 144.7, 130.7, 130.5, 112.0, 111.6, 109.8, 55.9, 55.7, 38.2, 22.2.



5-Bromo-2-methylindoline [99847-70-8]. This indoline was prepared from 5-bromo-2-methylindole (500 mg, 3.11 mmol) and sodium cyanoborohydride (450 mg, 7.2 mmol) via the general reduction procedure. After flash chromatography (15% ethyl acetate in hexanes), the product was obtained as a clear, colorless oil (454 mg, 90%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.17 (s, 1H), 7.10 (d, J = 8.2 Hz, 1H), 6.46 (d, J = 8.2 Hz, 1H), 4.05-3.96 (m, 1H), 3.78 (br s, 1H), 3.13 (dd, J = 8.6, 15.6 Hz, 1H), 2.63 (dd, J = 7.6, 15.7 Hz, 1H), 1.28 (d, J = 6.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.7, 131.3, 129.8, 127.6, 110.4, 110.1, 55.6, 37.5, 22.1.



2.11

4,5-Difluoro-2-methylindoline [85730-59-2]. This indoline was prepared according to the reduction procedure from 4,5-difluoro-2-methylindole (832.1 mg; Astatech, Inc.) and sodium cyanoborohydride (940 mg, 3.0 equiv). After silica chromatography (7% ethyl acetate in hexanes) the product was obtained as a clear, colorless oil (438.0 mg, 52%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.84-6.75 (m, 1H), 6.26-6.22 (m, 1H), 4.07 (ddq, J = 6.2, 7.6, 8.6 Hz, 1H), 3.75 (br s, 1H), 3.22 (dd, J = 8.6, 15.9 Hz, 1H), 2.72-2.63 (m, 1H), 1.30 (d, J = 6.2 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 148.5 (dd, J_{CF} = 7.2, 1.3 Hz), 147.2 (dd, J_{CF} = 246, 14.9 Hz), 144.1 (dd, J_{CF} = 236, 12.8 Hz), 116.5 (d, J_{CF} = 17.4 Hz), 115.1 (d, J_{CF} = 18.9 Hz), 103.3 (dd, J_{CF} = 6.3, 3.4 Hz), 56.1, 34.1 (d, J_{CF} = 1.8 Hz), 21.8.

III. Kinetic Resolutions

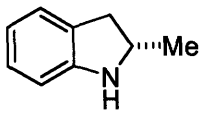
General Procedure. In a nitrogen-filled glovebox, an oven-dried 40-mL vial was charged with catalyst (+)-**1** (41 mg, 0.050 mmol), powdered LiBr (130 mg, 1.50 mmol), and the indoline (1.00 mmol). Toluene (8.5 mL) was added, resulting in a light purple, heterogeneous mixture. A solution of 18-crown-6 (0.375 M in toluene; 2.0 mL, 0.75 mmol) was added slowly to the stirred suspension over the course of 1 min, during which time the mixture turned darker. A solution of the acylating agent (0.325 M in toluene; 2.0 mL, 0.65 mmol) was then added. The vial was capped with a rubber septum, removed from the glovebox, and placed into a cold bath. After the indicated time had elapsed, the remaining acylating agent was quenched by the addition of propylamine (0.65 mmol), and the reaction mixture was concentrated and purified by flash chromatography.

The second runs were conducted with catalyst (–)-**1**.

The ee values were determined on Chirasil® Dex-CB or Daicel Chiralpak® columns. The catalyst can be recovered in good yield. For an example, see the kinetic resolution of 2-propylindoline (Table 2, entry 2).

The absolute stereochemistry of the indolines resolved in entries 1, 4, and 8 of Table 2 was assigned by comparison with compounds reported in the literature. All other assignments were made by analogy.

Note on reaction times: As indicated in Table 1 (entry 3 vs. entry 12), shorter reaction times can be employed, at the expense of lower selectivity.



(–)-(*S*)-2-Methylindoline (Table 2.6, entry 1). This compound was resolved according to the General Procedure using 133 mg (1.00 mmol) of racemic indoline (0 °C for 5 days). After quenching, the reaction mixture was passed through a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and LiBr. Purification by flash chromatography (5% → 20% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 56.8 mg (43% yield; 94% ee); $[\alpha]^{23}_D = -11$ ($c = 0.11$, benzene) {lit.[65] $[\alpha]^{20}_D = +11$ ($c = 2.0$, benzene); (*R*)}. The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 11.1 min (major) and 9.6 min (minor).

Acylated product: 88.5 mg (51% yield; 76% ee; white, crystalline solid); $[\alpha]^{23}_D = -45$ ($c = 0.65$, benzene). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 23.7 min (major) and 19.2 min (minor).

Calculated conversion = 55%; **s = 25.**

Second run: conversion = 55%; **s = 24** (indoline: 53.5 mg, 40% yield, 92% ee; *N*-acyl indoline: 90.4 mg, 52% yield, 77% ee).

2-Propylindoline (Table 2.6, entry 2). This compound was resolved according to the General Procedure using 161 mg (1.00 mmol) of racemic indoline (0 °C for 10 days). After quenching, the reaction mixture was passed through a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and LiBr. Purification by flash chromatography (10% → 20% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Catalyst **1** was recovered by flushing the initial short pad of silica gel with a solution of diethylamine/isopropanol/hexanes (10:10:80) and recovering the purple fractions, which contain the catalyst. Purification by flash chromatography (3 column volumes of CH_2Cl_2, then diethylamine/methyl *tert*-butyl ether/hexanes, 2.5:10:87.5) furnished the catalyst in ~80% yield (Run 1: 33.5 mg, 81%; Run 2: 35.3 mg, 85%).

Recovered indoline: 76.0 mg (47% yield; 82% ee); $[\alpha]^{23}_D = +39$ ($c = 0.56$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OJ-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 10.8 min (major) and 17.7 min (minor).

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[65] Krasnov, V. P.; Levit, G. L.; Bukrina, I. M.; Andreeva, I. N.; Sadretdinova, L. S.; Korolyova, M. A.; Kodess, M. I.; Charushin, V. N.; Chupakhin, O. N. *Tetrahedron: Asymmetry* **2003**, *14*, 1985–1988.

Acylated product: 97.2 mg (48% yield; 82% ee; white, crystalline solid); $[\alpha]^{23}_{D} = -79$ ($c = 0.32$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 21.5 min (major) and 15.3 min (minor).

Calculated conversion = 50%; **s = 25.**

Second run: conversion = 53%; **s = 28** (indoline: 59.0 mg, 37% yield, 90% ee; *N*-acyl indoline: 109 mg, 53% yield, 81% ee).

2-Phenethylindoline (Table 2.6, entry 3). This compound was resolved according to the General Procedure using 223 mg (1.00 mmol) of racemic indoline (r.t. for 14 days). After quenching, the reaction mixture was passed through a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and LiBr. Purification by flash chromatography (5% → 20% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 67.7 mg (30% yield; 98% ee); $[\alpha]^{23}_{D} = +12$ ($c = 0.17$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 24.9 min (major) and 17.0 min (minor).

Acylated product: 148 mg (56% yield; 64% ee; clear, colorless oil); $[\alpha]^{23}_{D} = -46$ ($c = 0.38$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak AS-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 26.9 min (major) and 35.9 min (minor).

Calculated conversion = 60%; **s = 20.**

Second run: conversion = 54%; **s = 17** (indoline: 63.5 mg, 28% yield, 85% ee; *N*-acyl indoline: 135 mg, 51% yield, 73% ee).

2-((*tert*-Butyldimethylsilyloxy)methyl)indoline (Table 2.6, entry 4). This compound was resolved according to the General Procedure using 264 mg (1.00 mmol) of racemic indoline (10 °C for 19 days). After quenching, the reaction mixture was passed through a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and

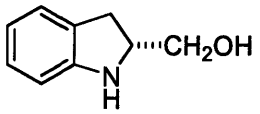
LiBr. Purification by flash chromatography (5% → 15% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 85.5 mg (32% yield; 84% ee); $[\alpha]^{23}_D = -43$ ($c = 0.20$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 0.5% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 12.0 min (major) and 11.0 min (minor).

Acylated product: 159 mg (52% yield; 62% ee; clear, colorless oil); $[\alpha]^{23}_D = -34$ ($c = 0.30$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 13.8 min (major) and 10.2 min (minor).

Calculated conversion = 57%; **s = 11.**

Second run: conversion = 56%; **s = 17** (indoline: 97.1 mg, 37% yield, 90% ee; *N*-acyl indoline: 160 mg, 52% yield, 71% ee).



(–)-(*R*)-2-Hydroxymethylindoline [77122-21-5]. This indoline was obtained by stirring resolved 2-((*tert*-butyldimethylsilyloxy)methyl)indoline (263 mg, 1.00 mmol) with tetrabutylammonium fluoride (1.0 M in THF; 0.65 mL, 0.65 mmol) in THF (5 mL) at r.t. for 30 min. The mixture was then concentrated and purified by flash chromatography (10% isopropanol in hexanes), which afforded the product as a clear, colorless oil (45.2 mg, 93%). $[\alpha]^{23}_D = -44$ ($c = 0.31$, ethanol) {lit.[66] $[\alpha]_D = +53.6$ ($c = 0.89$, ethanol); (*S*)}.

***cis*-5,6,7,8,8a,9-Hexahydro-4bH-carbazole (Table 2.6, entry 6).** This compound was resolved according to the General Procedure using 173 mg (1.00 mmol) of racemic indoline (0 °C for 6 days). After quenching, the reaction mixture was passed through a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and LiBr. Purification

[66] Pasquier, C.; Naili, S.; Mortreux, A.; Agbossou, F.; Pélinski, L.; Brocard, J.; Eilers, J.; Reiners, I.; Peper, V.; Martens, J. *Organometallics* **2000**, *19*, 5723–5732.

by flash chromatography (5% → 20% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 61.6 mg (36% yield; 84% ee); $[\alpha]^{23}_D = -20$ ($c = 0.25$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 10.3 min (major) and 9.5 min (minor).

Acylated product: 108 mg (49% yield; 53% ee; white, crystalline solid); $[\alpha]^{23}_D = -41$ ($c = 0.72$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 25.6 min (major) and 20.6 min (minor).

Calculated conversion = 58%; **s = 10.2**

Second run: conversion = 64%; **s = 9.3** (indoline: 53.6 mg, 31% yield, 91% ee; *N*-acyl indoline: 117 mg, 54% yield, 52% ee).

***cis*-5,5a,6,7,8,9,10,10a-Octahydrocyclohepta[b]indole (Table 2.6, entry 7).** This compound was resolved according to the General Procedure using 187 mg (1.00 mmol) of racemic indoline (0 °C for 10 days). After quenching, the reaction mixture was passed through a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and LiBr. Purification by flash chromatography (10% → 20% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 89.3 mg (48% yield; 86% ee); $[\alpha]^{23}_D = -30$ ($c = 0.52$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 13.0 min (major) and 10.2 min (minor).

Acylated product: 110 mg (48% yield; 80% ee; white, crystalline solid); $[\alpha]^{23}_D = -93$ ($c = 0.48$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 28.2 min (major) and 18.0 min (minor).

Calculated conversion = 52%; **s = 24.**

Second run: conversion = 51%; **s = 39** (indoline: 85.6 mg, 46% yield, 91% ee; *N*-acyl indoline: 104 mg, 45% yield, 85% ee).

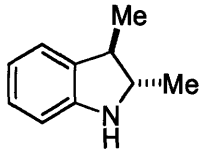
***cis*-2,3-Dimethylindoline (Table 2.6, entry 8).** This compound was resolved according to the General Procedure using 147 mg (1.00 mmol) of racemic indoline (0 °C for 7 days). After quenching, the reaction mixture was passed through a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and LiBr. Purification by flash chromatography (10% → 20% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 53.5 mg (36% yield; 91% ee); $[\alpha]^{23}_{D} = +41$ ($c = 0.060$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 0.5% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 34.6 min (major) and 30.5 min (minor).

Acylated product: 95.8 mg (51% yield; 74% ee; white, crystalline solid); $[\alpha]^{23}_{D} = -66$ ($c = 0.51$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 25.5 min (major) and 19.1 min (minor).

Calculated conversion = 55%; **s = 21.**

Second run: conversion = 55%; **s = 16** (indoline: 51.7 mg, 35% yield, 85% ee; *N*-acyl indoline: 87.3 mg, 46% yield, 71% ee).



(–)-(2*S*,3*R*)-*trans*-2,3-Dimethylindoline (Table 2.6, entry 9). This compound was resolved according to the General Procedure using 147 mg (1.00 mmol) of racemic indoline (r.t. for 20 days). After quenching, the reaction mixture was passed through a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and LiBr. Purification by flash chromatography (7% → 15% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 37.2 mg (25% yield; 94% ee); $[\alpha]^{23}_D = -41$ ($c = 0.13$, CCl_4) {lit.[67] $[\alpha]^{25}_D = -52.6$ ($c = 1.91$, CCl_4); (2*S*,3*R*)}. The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 0.5% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 19.3 min (major) and 17.8 min (minor).

Acylated product: 93.1 mg (49% yield; 53% ee; yellow oil); $[\alpha]^{23}_D = -2.0$ ($c = 0.26$, CCl_4). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 12.4 min (major) and 11.3 min (minor).

Calculated conversion = 64%; **s = 10.8.**

Second run: conversion = 65%; **s = 8.2** (indoline: 38.4 mg, 26% yield, 90% ee; *N*-acyl indoline: 95.3 mg, 50% yield, 48% ee).

5-Methoxy-2-methylindoline (Table 2.6, entry 10). This compound was resolved according to the General Procedure using 163 mg (1.00 mmol) of racemic indoline (–10 °C for 2.5 days). After quenching, the reaction mixture was passed through a short pad of silica gel (20% isopropanol in hexanes) to remove the catalyst and LiBr. Purification by flash chromatography (15% → 30% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 57.3 mg (35% yield; 92% ee); $[\alpha]^{23}_D = +16$ ($c = 0.17$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 7% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 15.6 min (major) and 8.3 min (minor).

Acylated product: 106 mg (52% yield; 60% ee; clear, colorless oil); $[\alpha]^{23}_D = -28$ (c = 0.70, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 7% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 19.0 min (major) and 17.0 min (minor).

Calculated conversion = 60%; **s = 12.**

Second run: conversion = 60%; **s = 14** (indoline: 53.7 mg, 33% yield, 92% ee; *N*-acyl indoline: 111 mg, 54% yield, 63% ee).

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[67] Scholl, B.; Hansen, H.-J. *Helv. Chim. Acta* **1980**, *63*, 1823–1832.

5-Bromo-2-methylindoline (Table 2.6, entry 11). This compound was resolved according to the General Procedure using 212 mg (1.00 mmol) of racemic indoline (r.t. for 23 days). After quenching, the reaction mixture was passed through a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and LiBr. Purification by flash chromatography (5% → 20% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 63.0 mg (30% yield; 83% ee); $[\alpha]^{23}_{D} = -11$ ($c = 0.18$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 16.4 min (major) and 9.6 min (minor).

Acylated product: 121 mg (47% yield; 64% ee; clear, colorless oil); $[\alpha]^{23}_{D} = +45$ ($c = 0.12$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 24.3 min (major) and 21.7 min (minor).

Calculated conversion = 57%; **s = 11.**

Second run: conversion = 60%; **s = 11** (indoline: 55.8 mg, 26% yield, 90% ee; *N*-acyl indoline: 120 mg, 47% yield, 59% ee).

***cis*-Ethyl 2-(5-methoxy-2-methylindolin-3-yl)acetate (Table 2.6, entry 12).** This compound was resolved according to the General Procedure using 249 mg (1.00 mmol) of racemic indoline (–10 °C for 4 days). After quenching, the reaction mixture was passed through a short pad of silica gel (20% isopropanol in hexanes) to remove the catalyst and LiBr. Purification by flash chromatography (15% → 40% ethyl acetate in hexanes) furnished the indoline and the N-acylated indoline.

Recovered indoline: 80.4 mg (32% yield; 85% ee); $[\alpha]^{23}_{D} = +9.6$ ($c = 0.27$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column (eluent: 10% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 17.1 min (major) and 13.5 min (minor).

Acylated product: 159 mg (55% yield; 75% ee; white, crystalline solid); $[\alpha]^{23}_{D} = -34$ ($c = 0.32$, $CHCl_3$). The ee was determined by HPLC using a Daicel Chiralpak OD-H column

(eluent: 10% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 23.6 min (major) and 17.5 min (minor).

Calculated conversion = 53%; **s = 18.**

Second run: conversion = 58%; **s = 19** (indoline: 97.8 mg, 39% yield, 95% ee; *N*-acyl indoline: 142 mg, 49% yield, 68% ee).

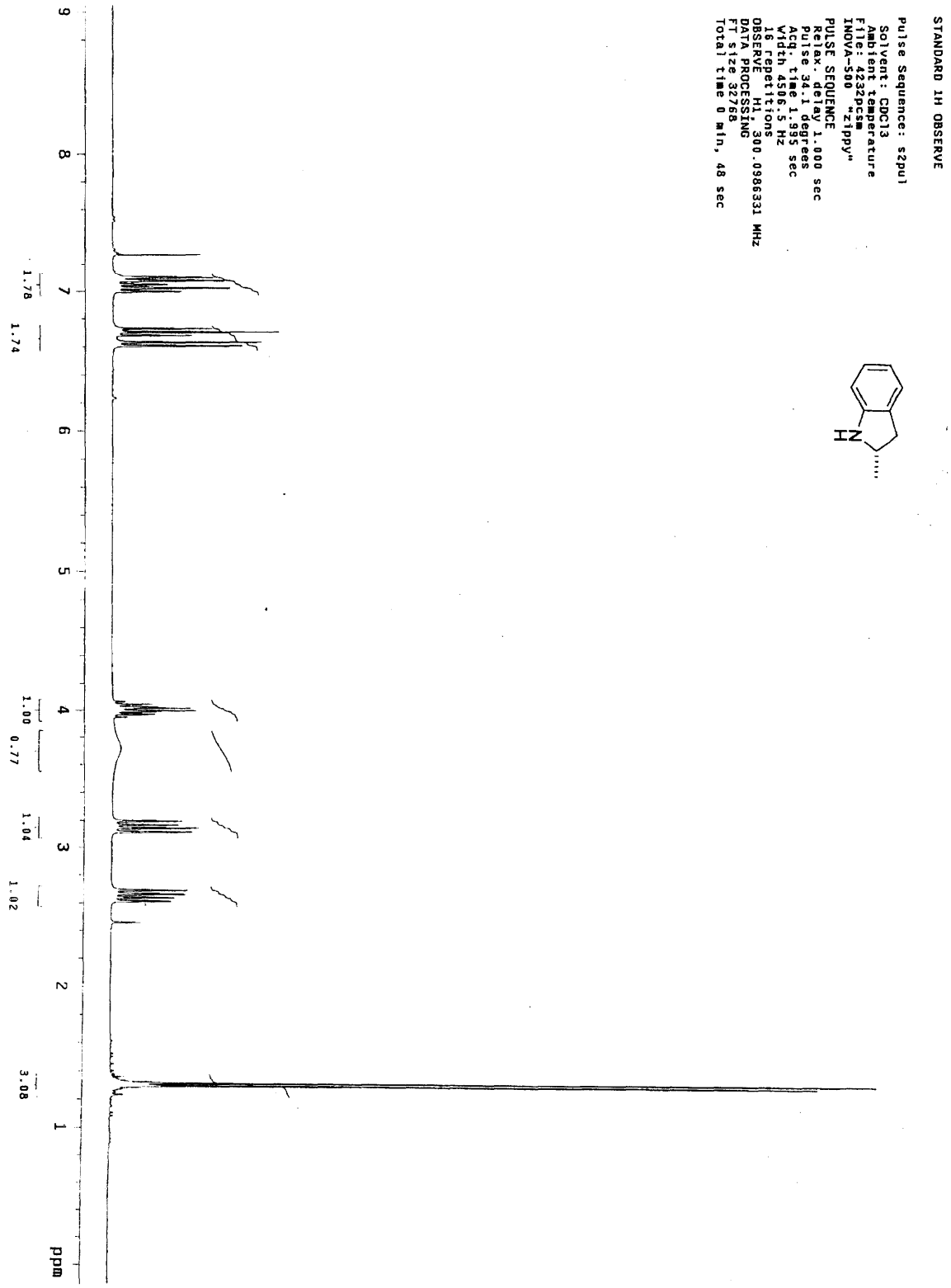
4,5-Difluoro-2-methylindoline (eq 2.13). This compound was resolved according to the General Procedure using 169.2 mg (1.00 mmole) of racemic indoline, reacted at room temperature for 23 days. After quenching, the reaction mixture was flashed across a short pad of silica gel (10% isopropanol in hexanes) to remove the catalyst and lithium salt. The solution was then concentrated and further purified by silica chromatography (15% → 30% ethyl acetate in hexanes) to separately afford the recovered indoline and acylated product.

Recovered indoline: 37.6 mg (22% yield; 79% ee); $[\alpha]^{23}_{D} = +10$ ($c = 0.26$, $CHCl_3$). The ee was determined by chiral GC, CP Chirasil Dex-CB; Heating program: 75 °C → 175 °C at 3 °C/min; flow: 1.0 mL/min. Retention times: 17.7 min (major) and 18.6 min (minor). Acylated product was obtained as a white, crystalline solid (113.6 mg, 54% yield; 58% ee); $[\alpha]^{23}_{D} = -23$ ($c = 0.67$, $CHCl_3$). Product ee was determined by chiral GC, CP Chirasil Dex-CB; Heating program: 75 °C → 175 °C at 3 °C/min; flow: 1.0 mL/min. Retention times: 28.0 min (major) and 27.0 min (minor).

Calculated conversion = 58%; **s = 8.6.**

Second run: conversion = 65%; **s = 5.9** (indoline: 40.0 mg, 24% yield, 80% ee; *N*-Acyl indoline: 125.2 mg, 59% yield, 44% ee).

^{1}H NMR Spectra of Resolved Indolines



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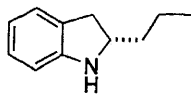

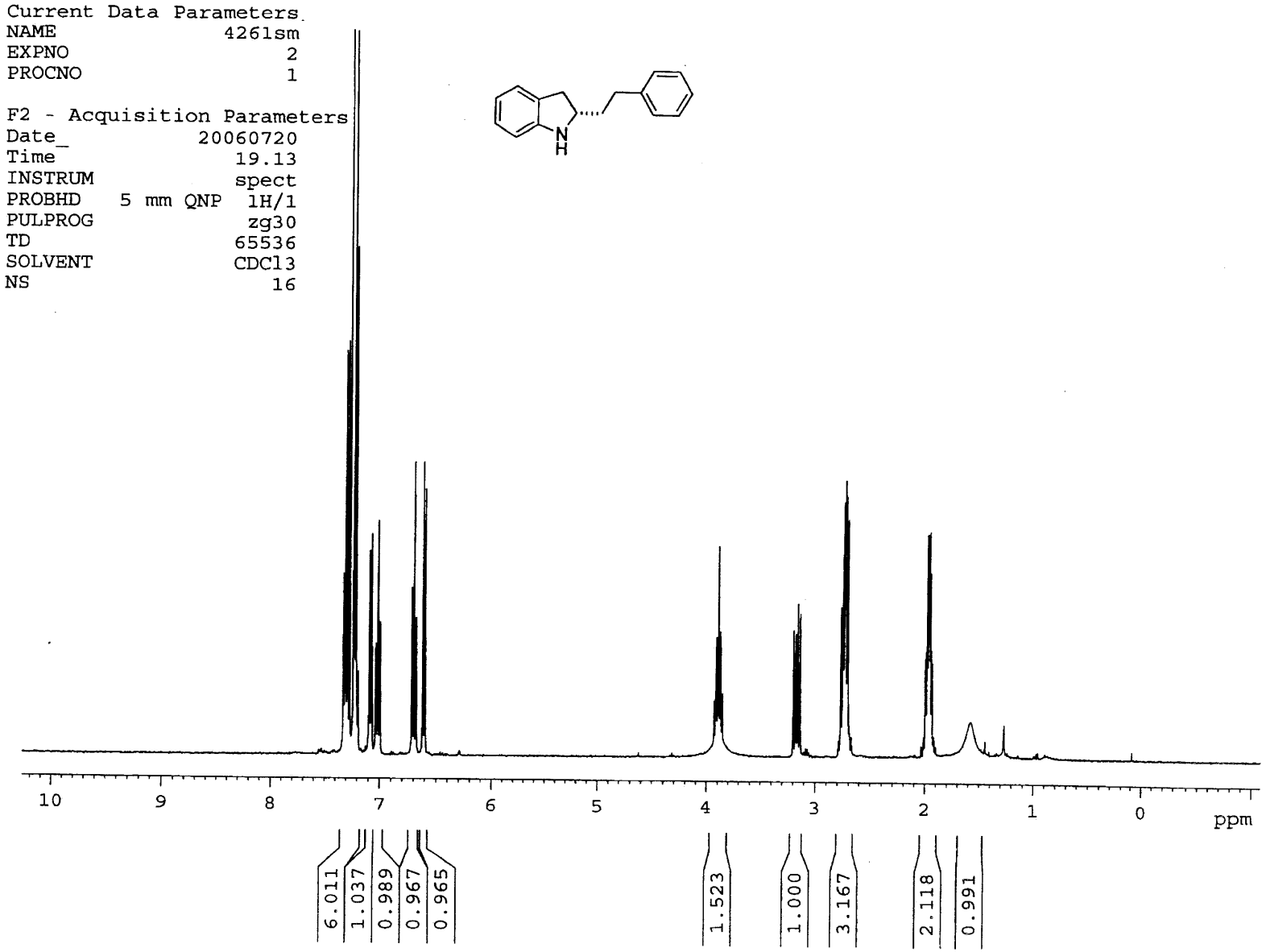
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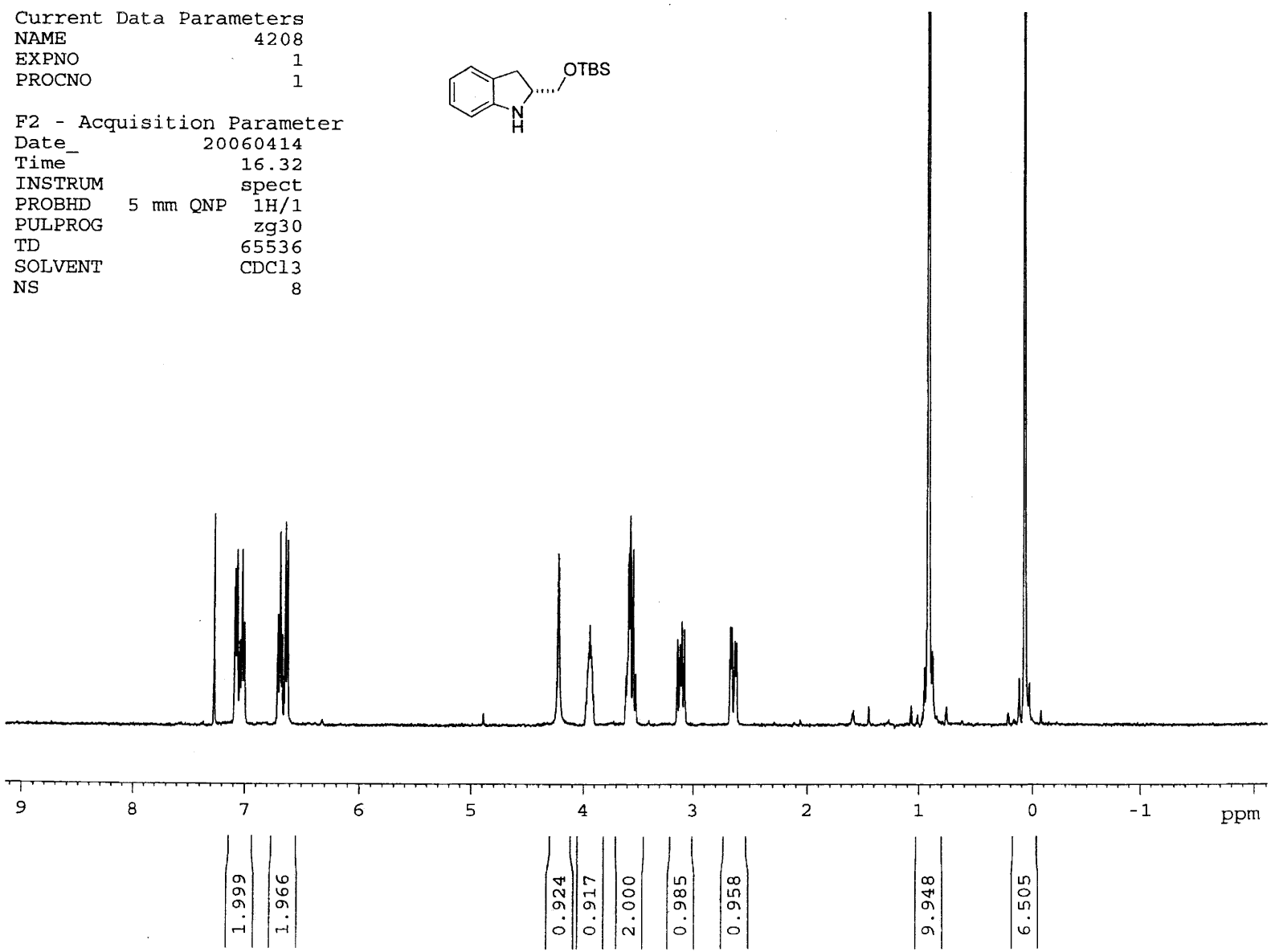
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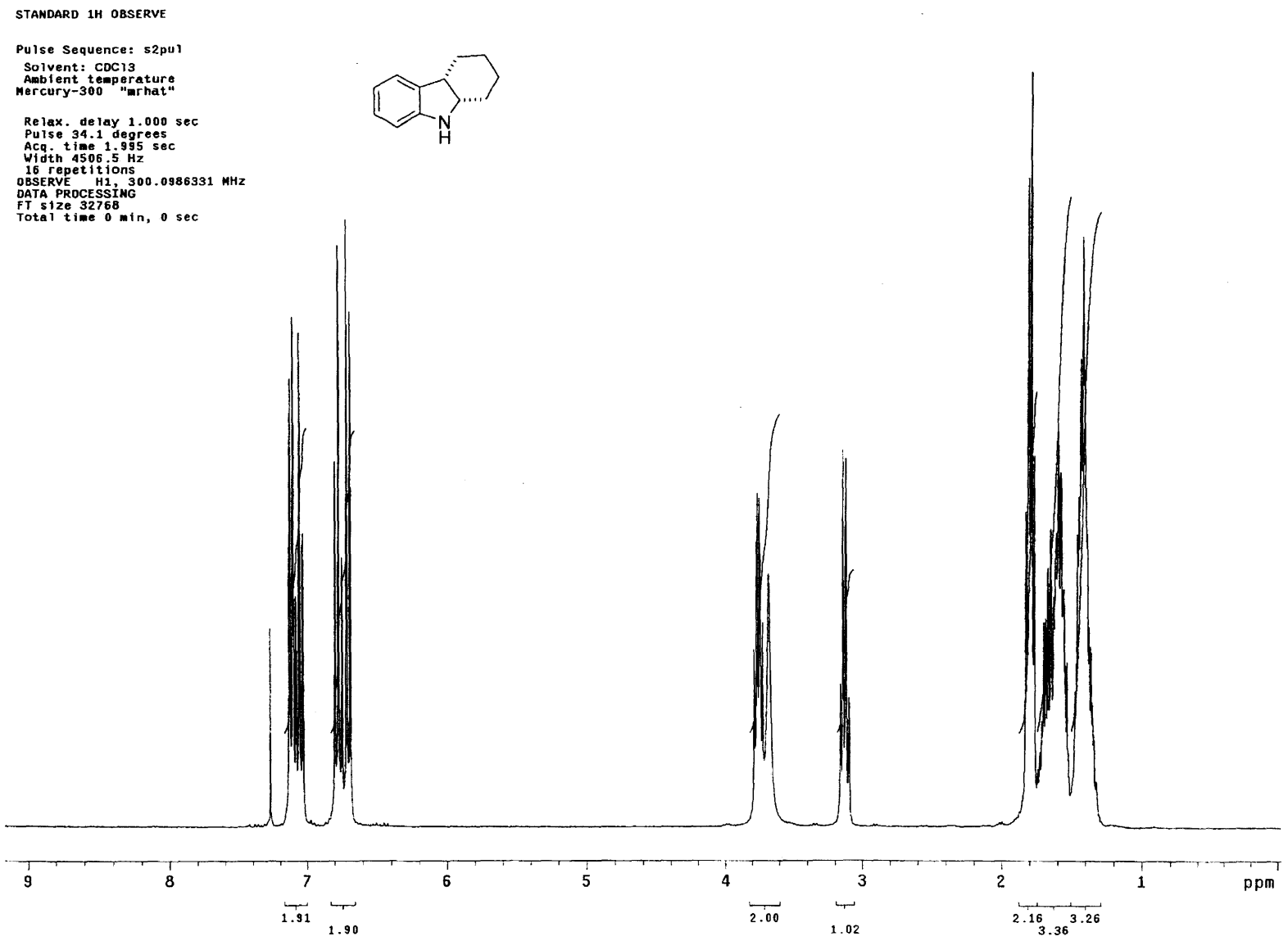
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16 repetitions
OBSERVE H1, 300.0986331 MHz
DATA PROCESSING
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STANDARD PROTON PARAMETERS

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INOVA-500 "zippy"

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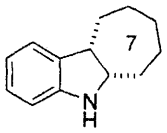

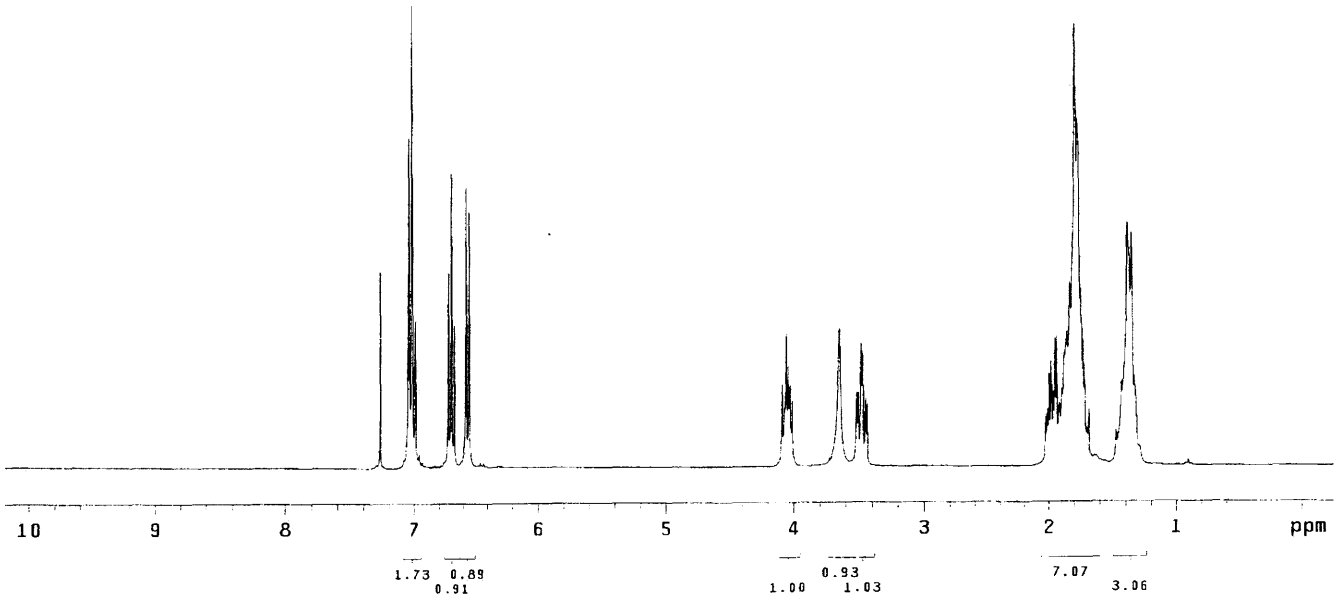

STANDARD PROTON PARAMETERS

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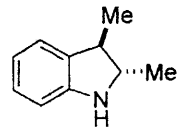

STANDARD PROTON PARAMETERS

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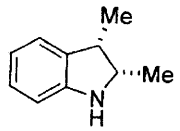

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PROCNO 1

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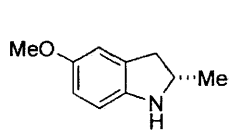
NS 8



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PROCNO 1

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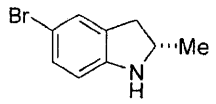
NS 8



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PROCNO 1

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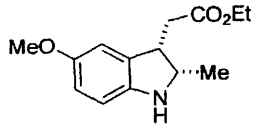
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16



STANDARD 1H OBSERVE

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Solvent: CDCl3
Ambient temperature
File: 4188pr
INOVA-500 "zippy"

Relax. delay 1.000 sec
Pulse 34.1 degrees
Acq. time 1.995 sec
Width 4506.5 Hz
16 repetitions
OBSERVE H1, 300.0986339 MHz
DATA PROCESSING
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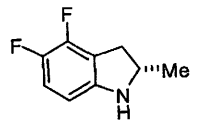
Total time 0 min, 48 sec



IV. Absolute Configuration of (+)-2.1

General. Low-temperature diffraction data were collected on a Siemens Platform three-circle diffractometer coupled to a Bruker-AXS Apex CCD detector with graphite monochromated Mo Kα radiation (λ = 0.71073Å), performing φ- and ω-scans. Raw data frames were integrated using the Bruker program SAINT+ for NT version 6.01. All structures were solved by direct methods using SHELXS and refined against F^2 on all data by full-matrix least squares with SHELXL-97 (Sheldrick, G. M. *SHELXL 97*, Universität Göttingen, Göttingen, Germany, 1997). SADABS absorption correction was performed. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were included in the model at geometrically calculated positions and refined using a riding model. The isotropic displacement parameters of the hydrogen atoms were fixed to 1.2 times the U value of the atoms they are linked to (1.5 times for methyl groups).

Experimental. A dark-purple needle (grown from a mixture of catalyst, acylating agent, 18-crown-6, and LiBr) of dimensions 0.25 x 0.20 x 0.10 mm^3 was mounted under STP and transferred to a Siemens Platform three-circle diffractometer equipped with a cold stream of N_2 gas. The data that were collected (185924 total reflections, 26781 unique, Rint = 0.058) had the following Miller index ranges: (–20 to 20 in h, –27 to 27 in k, and –46 to 46 in l). The structure was solved in the monoclinic space group *P2(1)2(1)2(1)*, a = 14.9080(4) Å, b = 19.7937(6) Å, c = 33.7362(10) Å, $\alpha = 90°$; $\beta = 90°$; $\gamma = 90°$, and refined using standard difference Fourier techniques. Final, full-matrix least squares refinement (26781 data for 1191 parameters) on F^2 yielded residuals of R1 and wR2 of 0.0624 and 0.1734 for data $I > 2\sigma(I)$, and 0.0822 and 0.1872, respectively, for all data. Residual electron density amounted to a maximum of 1.001 e/Å^3 and a minimum of –1.673 e/Å^3. The absolute structure (Flack) parameter for the correct enantiomer is 0.002(8), thus establishing the absolute stereochemistry.

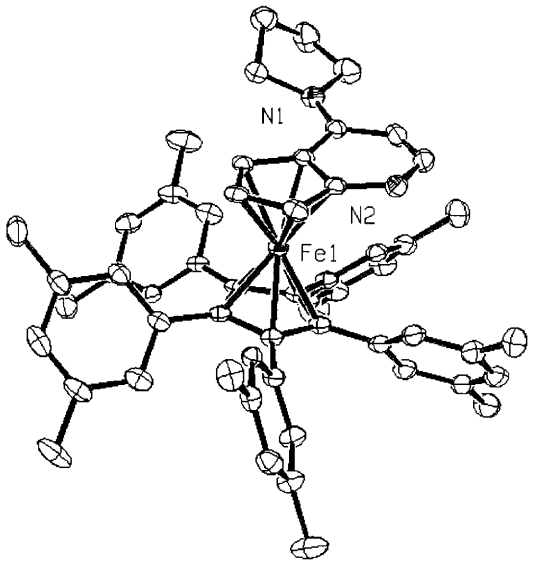


Figure 2.9. A portion of the unit cell, focusing on (+)-**2.1**.

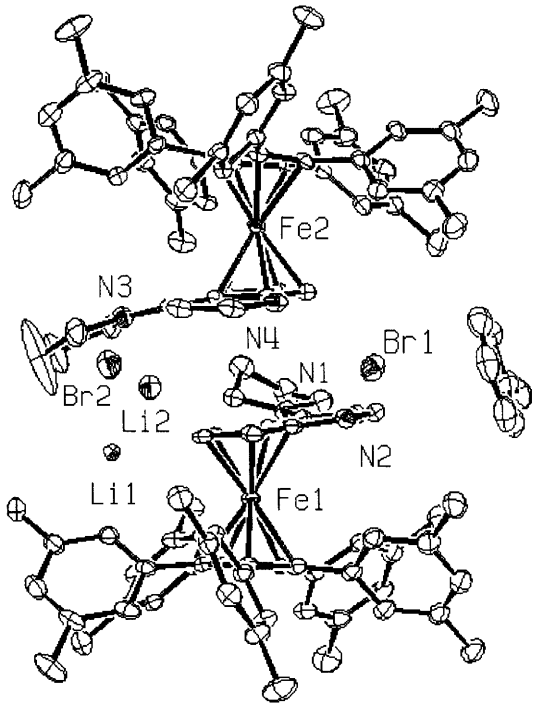


Figure 2.10. The entire unit cell: 2 × (+)-**2.1**, 2 × LiBr, toluene (identification code 06067).

Table 1. Crystal data and structure refinement for 06067.

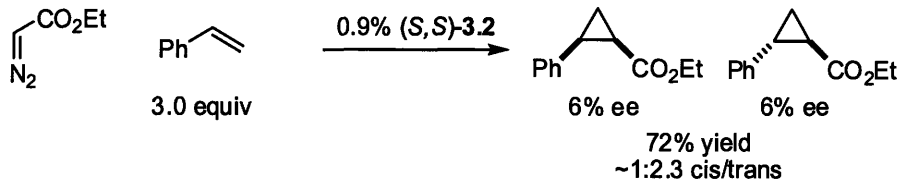
Identification code	06067	
Empirical formula	C121 H124 Br2 Fe2 Li2 N4	
Formula weight	1919.73	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 14.9080(4) Å	α= 90°.
	b = 19.7937(6) Å	β= 90°.
	c = 33.7362(10) Å	γ = 90°.
Volume	9955.0(5) Å^3	
Z	8	
Density (calculated)	2.476 Mg/m^3	
Absorption coefficient	2.290 mm^{-1}	
F(000)	7536	
Crystal size	0.25 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.19 to 29.13°.	
Index ranges	-20<=h<=20, -27<=k<=27, -46<=l<=46	
Reflections collected	185924	
Independent reflections	26781 [R(int) = 0.0578]	
Completeness to theta = 29.13°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8034 and 0.5983	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	26781 / 1362 / 1191	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I)]	R1 = 0.0624, wR2 = 0.1734	
R indices (all data)	R1 = 0.0822, wR2 = 0.1872	
Absolute structure parameter	0.002(8)	
Largest diff. peak and hole	1.001 and -1.673 e.Å^{-3}	

Chapter 3

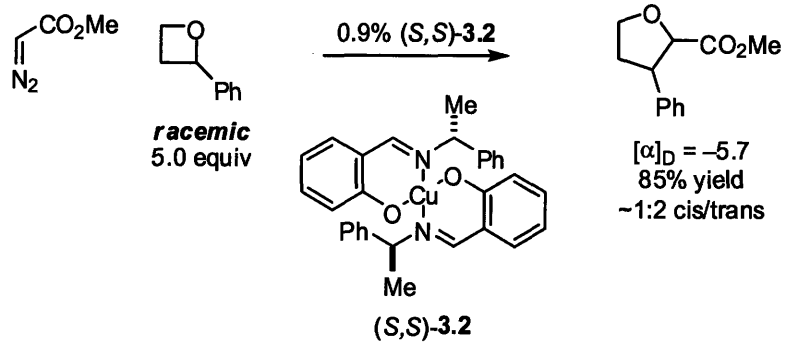
Catalytic Enantioselective C–N Insertion Reactions to Form 1,4-Benzoxazinones

3.1 Background

In 1966, Nozaki and Noyori reported the first examples of homogenous, transition metal-based enantioselective catalysis, as applied to small-molecule synthesis.[68,69] The report contained accounts of copper-catalyzed cyclopropanation of styrene with ethyl diazoacetate (eq 3.1) and a catalyzed methyl diazoacetate insertion into the C–O sigma bond of an oxetane, proceeding with undetermined levels of selectivity (eq 3.2).



(3.1)



(3.2)

The field of enantioselective organic synthesis through catalytic decomposition of diazo compounds has expanded greatly since that first report and currently spans a wide variety of processes.[70] However, significant effort is still being focused on the development of sigma-bond insertion processes, including literature on enantioselective C–X[71] and X–H[72] insertion reactions.

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[68] Nozaki, H.; Moruiti, S.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1966**, *22*, 5239–5244.

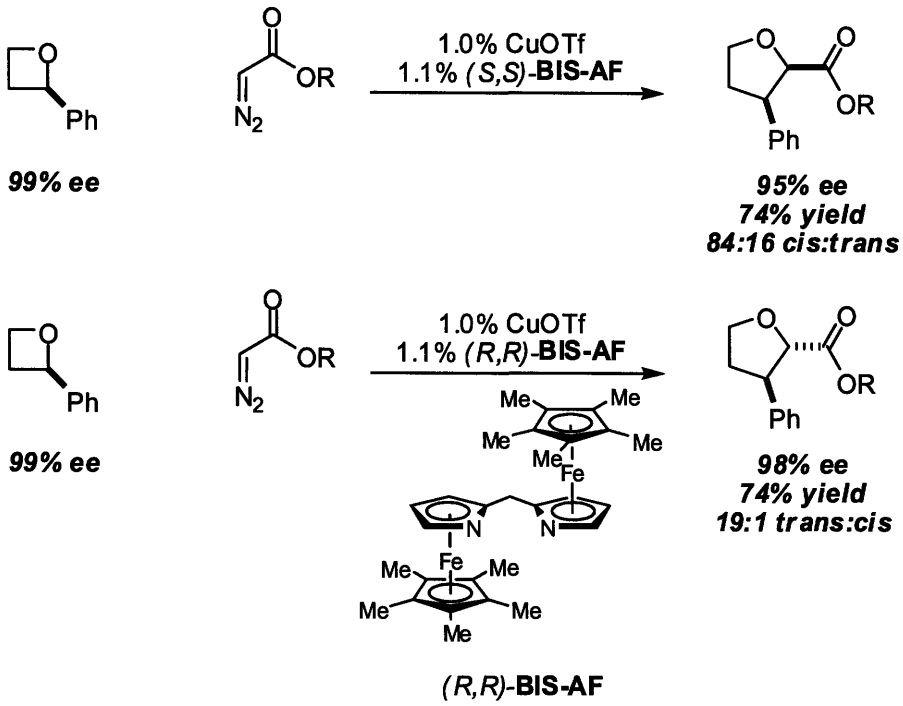
[69] For a leading discussion on the history of enantioselective catalysis, see: Kagan, H. B. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.: Springer-Verlag: Berlin, Heidelberg, 2004; Chapter 2.

[70] For an overview, see: Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley: New York, 1998.

[71] Catalytic, enantioselective C–X insertions: Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50–61.

[72] For recent examples of catalytic, enantioselective O–H insertions, see: (a) Maier, T. C.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 4594–4595. (b) Chen, C.; Zhu, S.-F., Liu, B.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem.*

On the basis of the first report by Nozaki and Noyori[68] as well as subsequent literature,[73] we also pursued oxetane expansions in the Fu lab. In 2001, Michael Lo reported an oxetane insertion using planar-chiral bisazaferrocene ligand, **BIS-AF**, which provides either *cis*- or *trans*-tetrahydrofurans with good preservation of enantiopurity (eqs 3.3 and 3.4; R = $CMeCy_2$).[74]



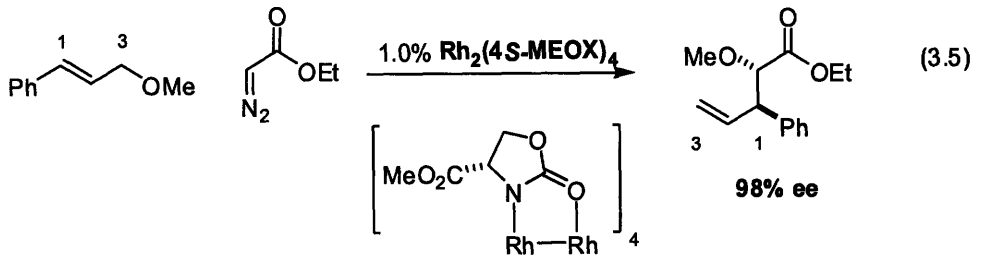
Carbenoid insertion into the C–O sigma bond of an achiral substrates has also been reported; Doyle used a dimeric rhodium species, **Rh_2(4S-MEOX)$_4$**, to catalyze the insertion of ethyl diazoacetate into allylic ethers for the formation of [2,3]-sigmatropic rearrangement products (eq 3.5).[75]

Soc. **2007**, *129*, 12616–12617. For recent N–H insertions, see: (c) Liu, B.; Zhu, S.-F.; Zhang, W.; Chen. C.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 5834–5835. (d) Lee, E. C.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 12066–12067.

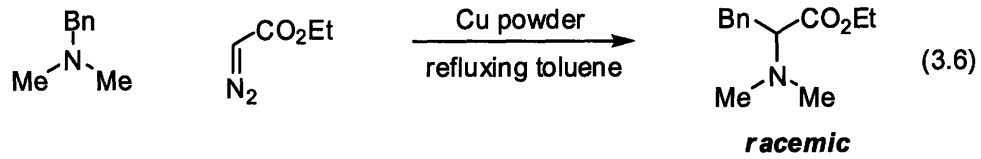
[73] Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. *Tetrahedron* **1968**, *24*, 3655–3669.

[74] Lo, M. M.-C.; Fu, G. C. *Tetrahedron* **2001**, *57*, 2621–2634.

[75] Doyle, M. P. Forbes, D. C.; Vasbinder, M. M.; Peterson, C. D. *J. Am. Chem. Soc.* **1998**, *120*, 7653–7654.



We are aware of no catalytic, enantioselective C–N insertion processes in the chemical literature. However, in several instances, non-enantioselective variants of these reactions have been used to prepare chiral organic fragments.[76] In 1993, West reported a system that prepares dialkylated amino ester products in a single step from commercially available starting materials (eq 3.6).[77]

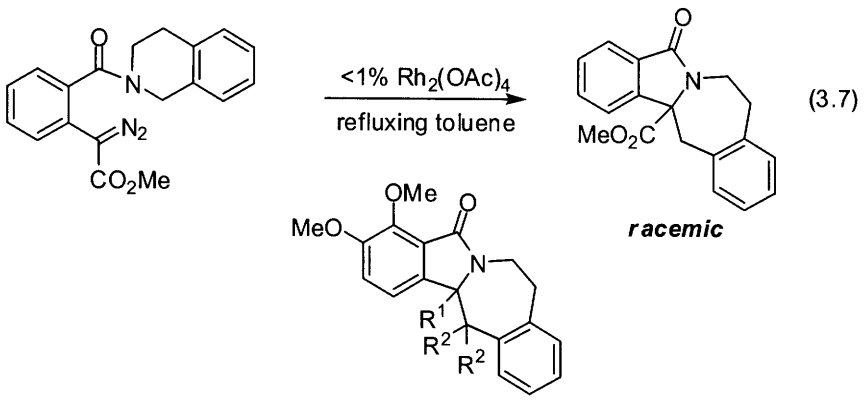


Padwa demonstrated that the process could be applied to natural-product-type scaffolds, such as those in eq 3.7.[78] These systems incorporated amide-based nitrogen substrates and low amounts of rhodium acetate catalyst. The authors argued that this transformation may ultimately be applicable in future syntheses of lennoxamine or chilenine.

[76] For reviews, see: (a) Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043–1062. (b) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis;* Elsevier Inc: Amsterdam, 2005; pp 434–435.

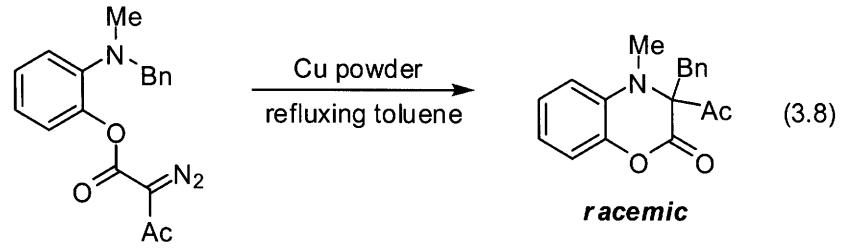
[77] West, F. G.; Glaeske, K. W.; Naidu, B. N. *Synthesis*, **1993**, 977–980.

[78] Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414–2421.



(3.7)

Additionally, West applied the Cu-powder systems to the preparation of 1,4-benzoxazinones (eq 3.8).[79] This system was capable of mediating reactions with arylamine, allylamine, or cyanomethylamine substrates.

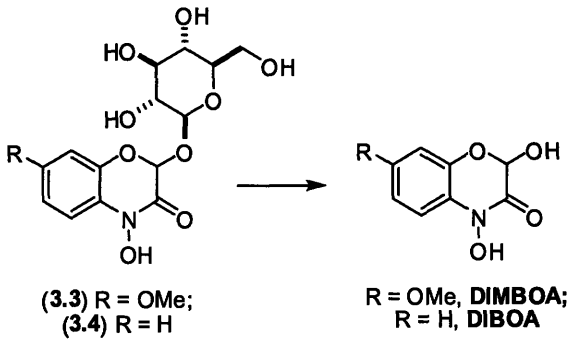


(3.8)

It is notable in the above context, and in Section 3.2, that the 1,4-benzoxazinone framework is common to some biologically active targets. Plants such as corn, wheat, rye, and maize produce allelochemicals[80] with a chiral 1,4-benzoxazinone subunit, such as glycosylated compounds **3.3** and **3.4**. These compounds can undergo enzymatic conversion to the corresponding aglycons, **DIMBOA** and **DIBOA** (eq 3.9), and other metabolites that possess antimicrobial, antifungal, anti-inflammatory, and mutagenic properties.[81] Achiral,

[79] West, F. G.; Naidu, B. N. *J. Org. Chem.* **1994**, *59*, 6051–6056.
[80] An allelochemical is a compound produced by an organism that goes on to induce some biological response in a separate species (e.g., a natural insecticide).
[81] For reviews on naturally occurring benzoxazinoids, see: (a) Hashimoto, Y.; Shudo, K. *Phytochemistry* **1996**, *43*, 551–559. (b) Fomsgaard, I. S.; Mortensen, A. G.; Carlsen, S. C. K. *Chemosphere* **2004**, *54*, 1025–1038. (c) Gierl, A.; Frey, M. *Planta* **2001**, *213*, 493–498.

synthetic variants of 1,4-benzoxazinones have also been prepared, and their biological activities surveyed.[82]

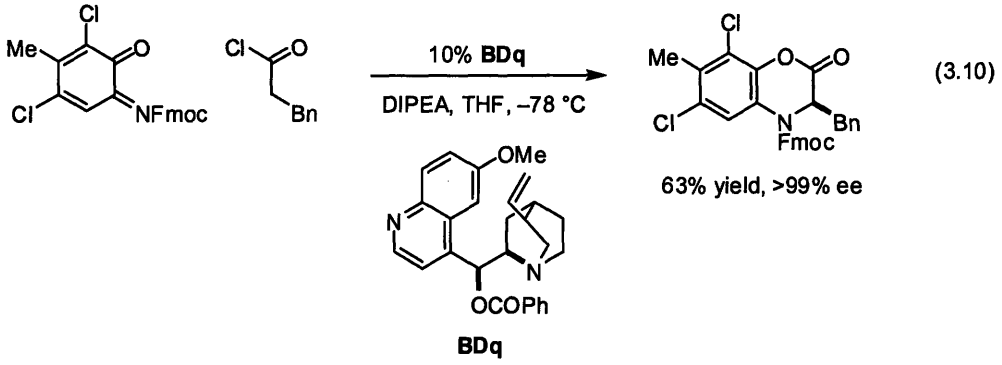


(3.3) R = OMe;
(3.4) R = H

R = OMe, **DIMBOA;**
R = H, **DIBOA**

(3.9)

The general utility of 1,4-benzoxazinones, in conjunction with their rigid 6,6-fused ring architecture, seems to render them promising targets for asymmetric catalysis. A few such methods have appeared in the literature. Lectka used a benzoylquinidine catalyst, **BDq**, to produce a series of *N*-protected products in good yields and excellent enantioselectivities (eq 3.10).[83] This report also demonstrated subsequent derivatization of those products, delivering the free amino acid derivatives.



BDq

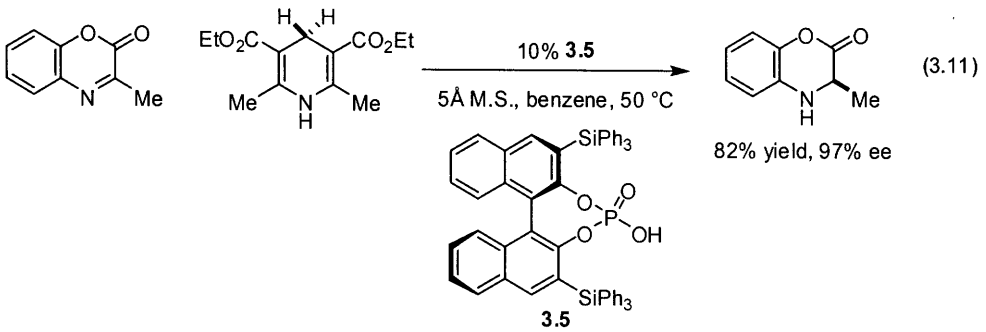
63% yield, >99% ee

(3.10)

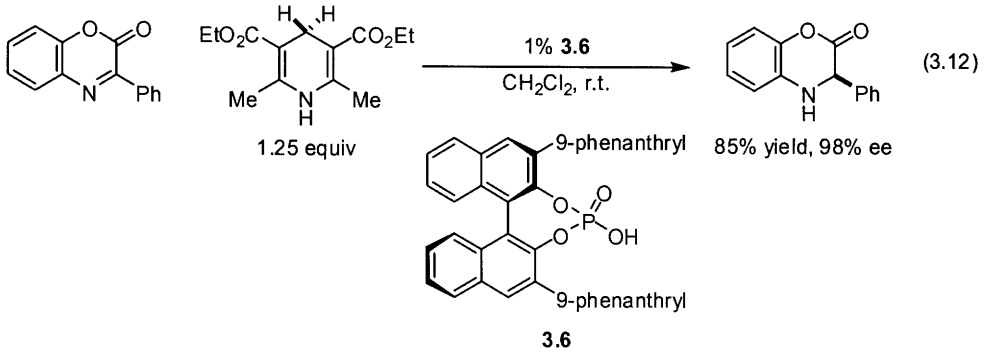
MacMillan and Rueping have individually accessed chiral 1,4-benzoxazinones through organocatalytic hydrogenation. MacMillan demonstrated that the chiral phosphoric acid catalyst **3.5** could be used in conjunction with a Hantzsch ester to yield these products

[82] For leading references, see: Wolfer, J.; Bekele, T.; Abraham, C. J., Dogo-Isonagie, C.; Leckta, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 7298–7400.

with high enantioselectivity (eq 3.11).[83] In the following year, Rueping used a related system to prepare several families of compounds with the 6,6-fused ring structure, including arylglycine derivatives (eq 3.12).[84] Both systems produced the same absolute sense of enantioselectivity with a given enantiomer of phosphoric acid catalyst.



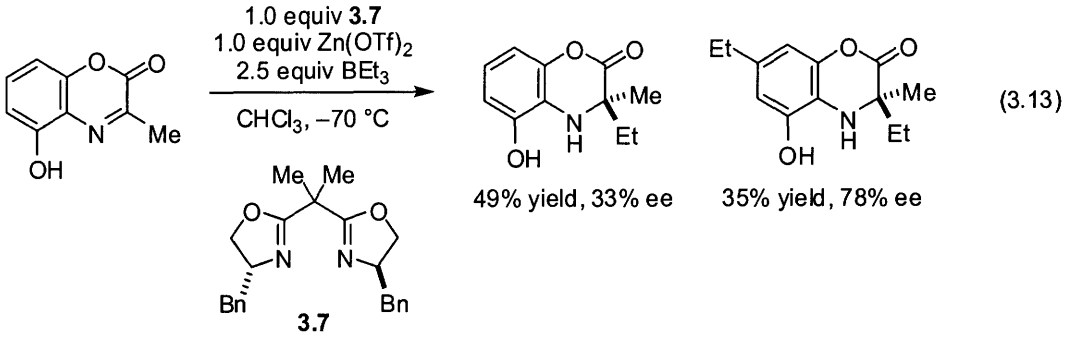
(3.11)



(3.12)

Finally, in a non-catalytic realm, Takemoto has prepared the corresponding *quaternary* stereocenters with chiral Lewis acid-mediated imine alkylations (eq 3.13).[85] These substrates required 5-hydroxy or 5-methoxy substitution and, in varying yields and enantioselectivities, underwent a concomitant aryl-alkylation process. The mechanistic pathways leading to these products were unclear, but the authors speculate that they may involve alkyl radical addition to a metal-coordinated imine.

[83] Storer, I. J.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84–86.
[84] Rueping, M.; Antonchik, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6751–6755. These ester products could be further derivatized into a corresponding amino acid derivative with pyrridin-2-ol and benzylamine.
[85] Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2006**, *71*, 2099–2106.

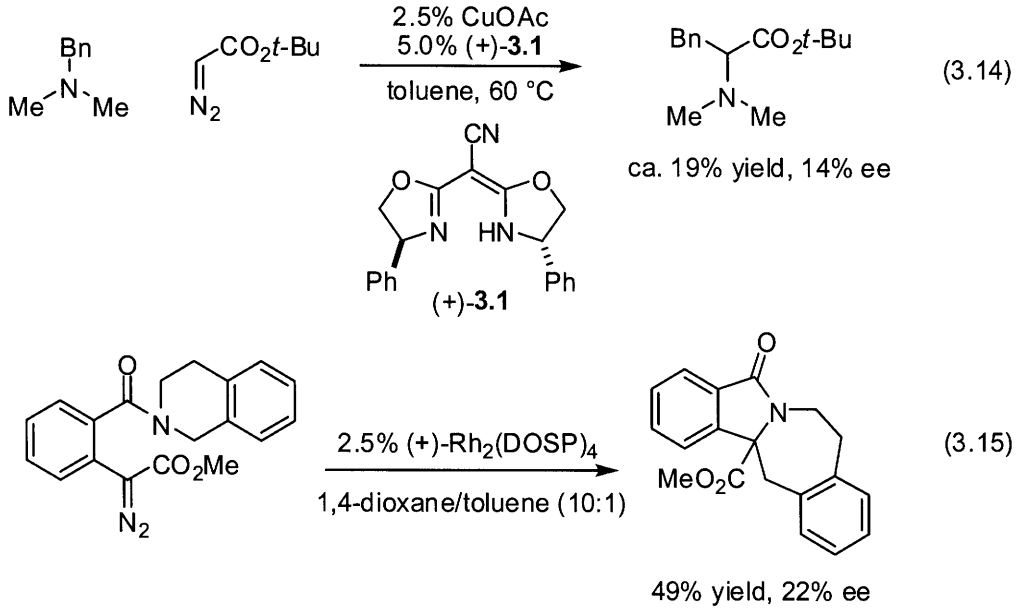

1.0 equiv 3.7
1.0 equiv Zn(OTf)2
2.5 equiv BEt3
CHCl3, –70 °C
Me Me
Bn Bn
3.7
49% yield, 33% ee
35% yield, 78% ee

(3.13)

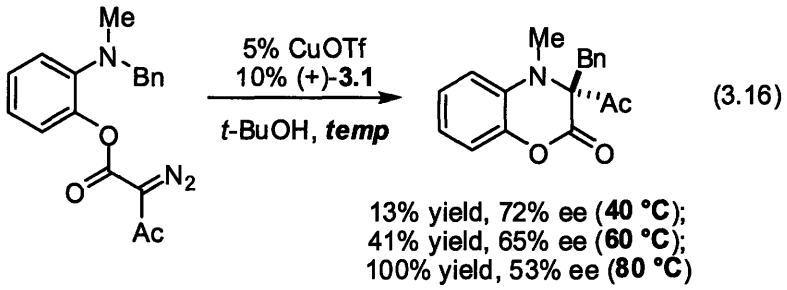
3.2 Results and Discussion

We began our studies in this area with the goal of reporting the first enantioselective C–N insertion reaction. Clearly, for the broadest interest to the synthetic community, we first pursued systems with the potential to produce useful products downstream.

Significant effort was spent attempting to locate a chiral variant of the amino ester synthesis by West (for example, eq 3.14). We also found a preliminary lead by screening the amide-based insertion method by Pawda, across chiral rhodium catalysts (eq 3.15).

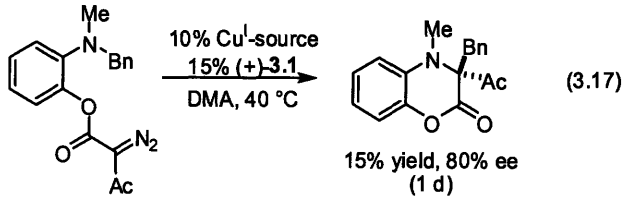


Our best preliminary results pertained to enantioselective variants of the 1,4-benzoxazinones system by West. For example, in eq 3.16, the use of systems with copper triflate and semicorrin ligand **3.1** gave promising levels of enantioselectivity in *tert*-butanol solvent. At increased temperature (80 °C), the system provided quantitative conversion to product, but at the cost of enantioselectivity.



(3.16)

We decided to further investigate this family of substrates. In Figure 3.1 are the results of some early studies that investigate the effects of modified substrate scaffolding, as well as solvent. Polar solvents tend to produce lower yields and rates of conversion in these systems, with higher enantioselectivity (eq 3.17). Reaction rates were always improved by incorporation of 7-methoxy- or thioether-substitution, whereas reaction rates were hampered by bulkier *N*-substitution. Interestingly, bulkier substitution at the arylamine 5-position, *ortho* to nitrogen, increased reaction rate.[86] In the case of a 2-naphthylamine-derived substrate, both reaction rates and enantioselectivities were improved (71% yield and 91% ee, after two days).



(3.17)

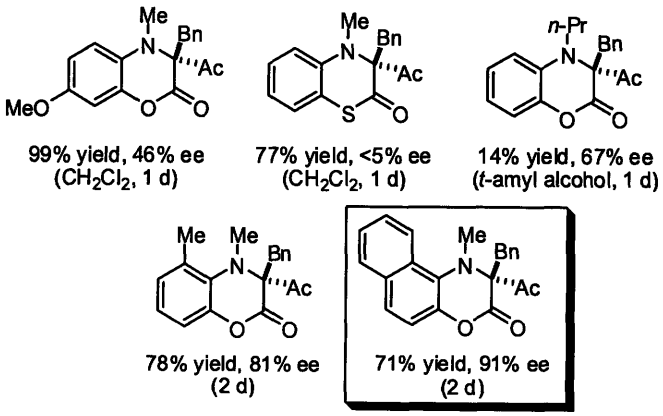
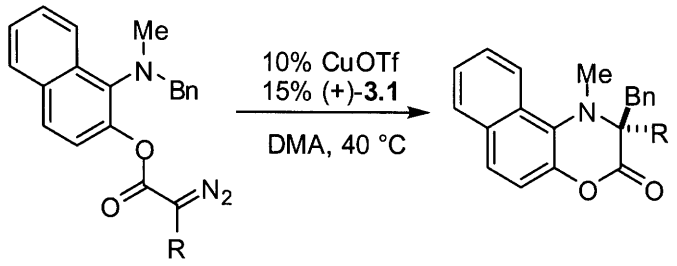


Figure 3.1. Variation of fused-ring scaffold and the N-alkyl substituent.

[86] This may be due to an increase in sp^3 character of the aryl nitrogen.

Exploration of 2-naphthylamine-derived substrates revealed some boundaries in reaction scope. The substitution on the α-position of the diazoester was critical to selectivity, as phenyl, cyano, or proton substitution all gave low ee's (entries 1–3; Table 3.1). A substrate with α-ethyl substitution did not convert to the desired product (entry 4), but produced the corresponding unsaturated aryl ester, presumably via C–H_{alkyl} insertion.

Table 3.1. Variation of the substrate's diazoester portion.



entry	R	yield (%)	ee (%)
1	Ph	77	26
2	CN	21	25
3	H	10	37
4	Et	<5	–

Other modifications on the substrate were unsuccessful (Figure 3.2). Inclusion of *N,N*-dibenzyl substitution on the substrate did not produce product in useful yields or selectivities. No product was observed for isopropyl or phenethyl migrating groups, nor from 1-naphthylamine-based substrates. Substrates with bisallylamine substitution formed cyclopropanation product, to the exclusion of desired C–N insertion product.

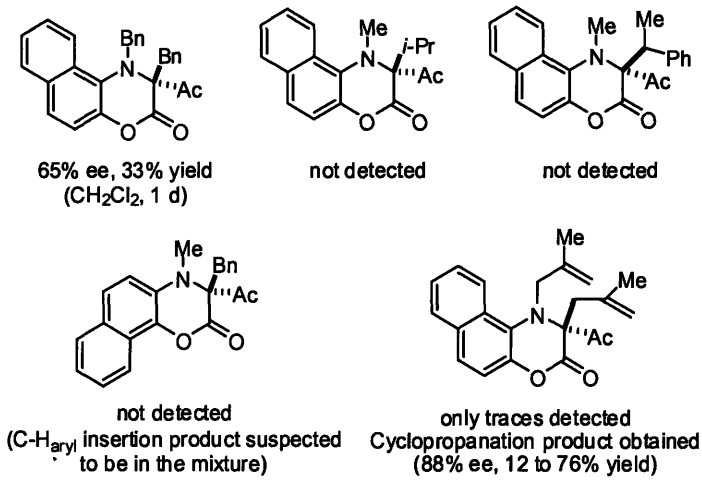
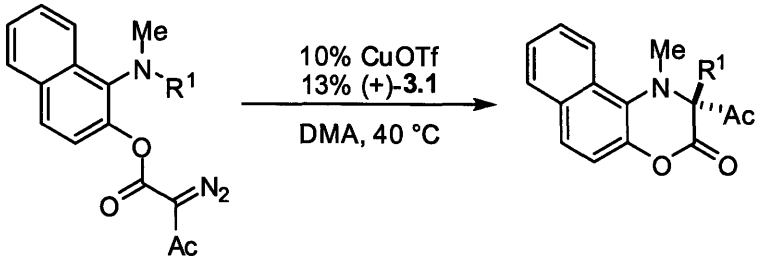


Figure 3.2. Further unsuccessful variation of naphthylamine-derived substrates.

We went on to finalize the reaction conditions (eq 3.18) and develop a set of working substrates (Tables 3.2 and 3.3). The C–N insertion proceeds with high levels of enantioselectivities for a range of benzylamine-derived substrates (entries 1-5; Table 3.2), including those with electronic perturbations (entries 2 and 3) and with increased steric demand at the ortho-position of the benzylic migrating group (entries 4 and 5).[87] Interestingly, we observed good enantioselectivity in reactions of a substrate with an α-aminoethylester fragment (entry 6).[77]

[87] Neither the 5-*endo* nor the 6-*exo* cyclization products were observed in the crude reaction mixture (formation of either ring would be Baldwin-favored).

Table 3.2. Catalytic Enantioselective C–N Insertion Reactions.[a]



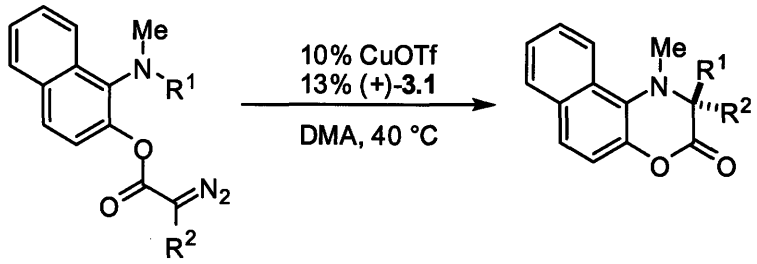
(3.18)

entry	R^1	yield (%)	ee (%)
1	Bn	81	91
2	4-(MeO)Bn	74	93
3	4-BrBn	56	90
4	2-MeBn	62	93
5	2-allylbenzyl	57	93
6	CH_2CO_2Et	72	93

[a] All data are the average of two experiments.

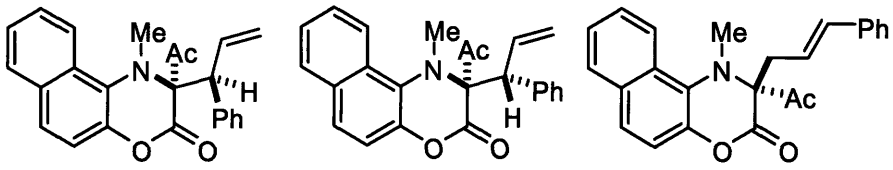
Allylamine-derived substrates, with branching at the 2-position, also converted to the desired products in good enantioselectivities (71–97% ee, entries 1–5; Table 3.3). With the straight-chain cinnamylamine-derived substrate in entry 6, several cyclization products were formed. The reaction gave high selectivity for the branched [2,3]-rearrangement products over the straight-chain [1,2] product (ca. 98:2, (*R,S*)-**3.8** and (*R,R*)-**3.8** vs. (*R*)-**3.9**).

Table 3.3. Insertion Reactions with Allylamine Substrates.[a]



entry	R^1	R^2	yield (%)[b]	ee (%)
1	2-methylallyl	Ac	84	97
2	2-methylallyl	COPh	63	90
3	2-methylallyl	CO_2Et	74	71
4	2-phenyallyl	Ac	73	97
5	2-(ethoxycarbonyl)allyl	Ac	57	95
6	1-cinnamyl	Ac	(*R,S*)-**3.8**: 51 (73)[c]	71
			(*R,R*)-**3.8**: – (25)[c]	–
			(*R*)-**3.9**: – (2)[c]	–

[a] All data are the average of two experiments. [b] Isolated yield.
[c] Percent isomer composition by ^{1}H NMR analysis of unpurified reaction mixture.

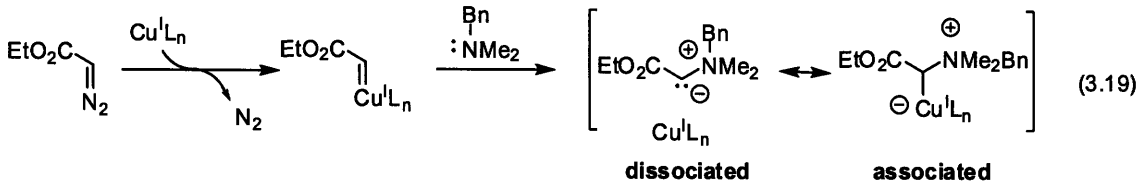


(*R,S*)-**3.8** (*R,R*)-**3.8** (*R*)-**3.9**

The remaining synthetic work for this project will likely focus on derivatization of the tricyclic products to access the free quaternary amino acid. Additionally, we plan to submit the final products for screening of their biological activities.

3.3 Mechanistic Discussion

The mechanism involved in these processes is an area of some dispute, and three limiting cases have been proposed.[76a] Each mechanism initiates first through metal carbenoid formation, and then amine association with the electrophilic carbenoid center, generating the C–N bond in the product (eq 3.19). The resulting metallocarbenoid complex can be represented in either the dissociated or associated form.



(3.19)

The mechanistic pathways diverge after formation of the metallocarbenoid intermediate (Figure 3.3). Pathway A, which is favored by West,[76a,77] proceeds from the metal-dissociated structure, and features a radical bond homolysis to cleave the C–N bond. Then, radical recombination produces the C–C bond of product.

Pathway B, which has also been suggested for oxetane expansions (e.g., eqs 3.2–3.4),[71] proceeds from the associated complex, through an S_N1-like dissociation of the benzyl cation from the ammonium, to cleave the C–N bond. The C–C bond is formed though heterolytic C–Cu cleavage and recombination with the benzyl cation.

Finally, Pathway C is a catalytic variant of a previous proposal by Woodward and Hoffmann for the mechanistic pathway of base-induced Stevens rearrangements of ammonium ylides.[88] In this pathway, the associated form of the metallocarbenoid intermediate undergoes a formal $[{}_{\sigma}2_a + {}_{\sigma}2_s]$ rearrangement to deliver the product in a single step. Schematically, this could be viewed as simultaneous $\sigma_{C-Cu} \rightarrow \sigma^*_{C-N}$ and $\sigma_{C-N} \rightarrow \sigma^*_{C-Cu}$ donation processes, wherein the C–Cu component is antarafacial, and the C–N component is suprafacial (a symmetry-allowed process).[89]

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[88] Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781–932.

[89] For a discussion on the generalized orbital symmetry rule, and for a discussion on suprafacial and antarafacial nomenclature as it pertains to sigma-bonds, see: Anslyn, E. V.; Dougherty, D. A. In *Modern Physical Organic Chemistry*; University Science Books: Sausalito, 2006; pp 890–892.

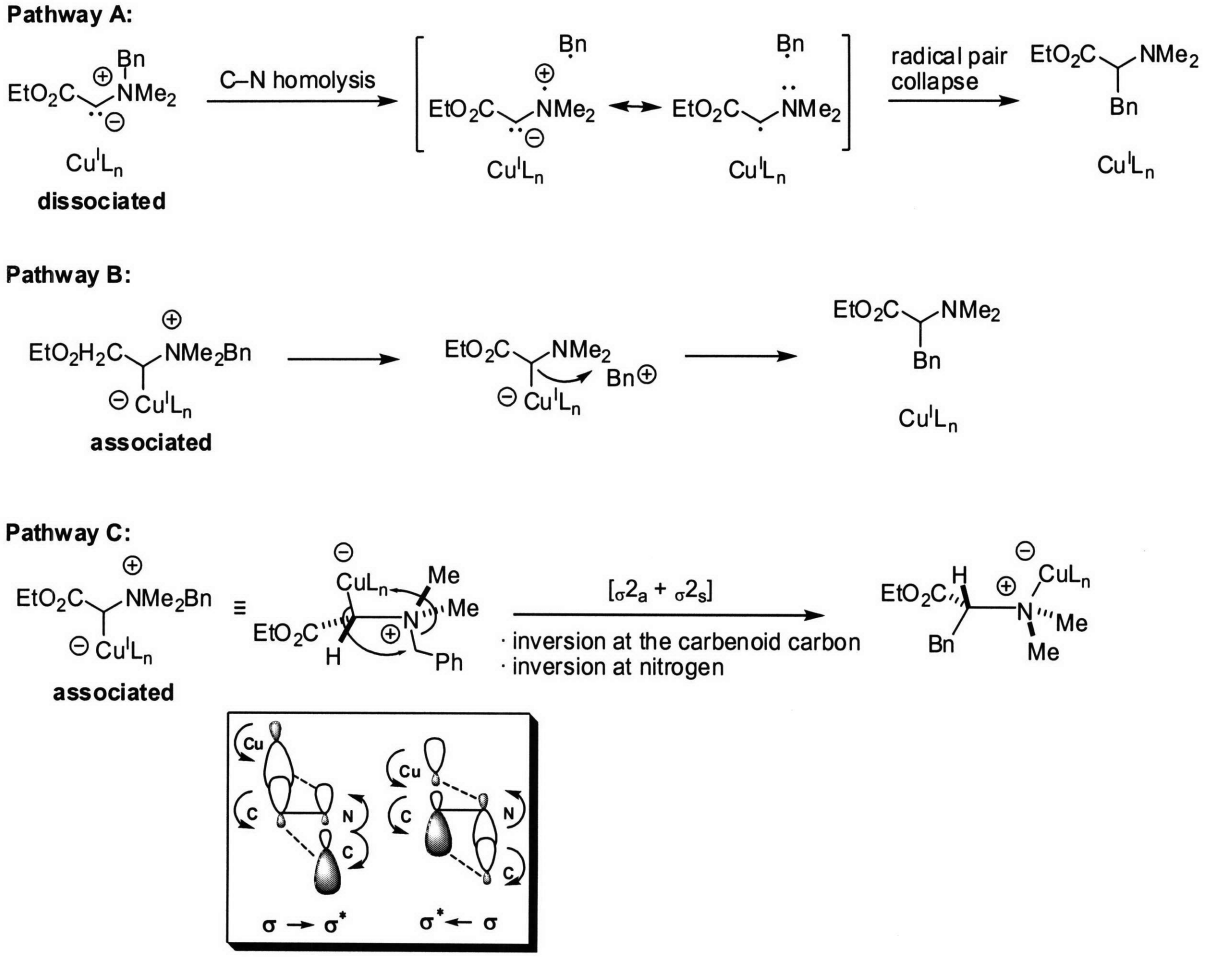


Figure 3.3. Divergent Mechanistic Pathways for the C–N Bond-Breaking Process.

Unfortunately, attempts to identify intermediates empirically through reaction monitoring by ^{1}H NMR were inconclusive, as the spectra of these heterogeneous reactions showed significant line-broadening[90] and baseline distortion[91] in all cases. Additionally, we were unable to obtain crystals of an intermediate suitable for X-ray crystallographic analysis despite significant experimentation.[92]

In light of the high enantioselectivities obtained in Tables 3.2 and 3.3, the dissociative Pathway A seems unlikely. Additionally, on the basis of reactivity difference between the 7-

[90] Line-broadening has been previously observed for other Cu(1)-based systems, presumably due to oligomeric, aggregate formation. See, for example: Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120–4121.

[91] Cu(I) complexes, having a d^{10} electronic configuration, are not usually expected to be paramagnetic. However, paramagnetic species could be present if decomposition occurs, forming Cu(0) or Cu(II) species.

[92] In one case we obtained a crystal structure of a decomposition product, $Cu(I)L_2$ (see Section 3.5, part V).

methoxy-derivative and the parent compound in Figure 3.1, it appears that the rate constant for the amine-metallocarbenoid association (eq 3.19) probably factors heavily into the observed rate constant.

3.4 Conclusion

We have demonstrated the first examples of catalytic, enantioselective C–N insertion reactions with high enantioselectivities for a variety of migrating groups. The reactions produce 1,4-benzoxazinone fused-ring cores, which are subunits in a series of pharmaceutical targets and chiral natural products.

3.5 Experimental Section

I. General

Copper (I) triflate benzene complex[93] (CuOTf • ½ benzene; Aldrich or Alfa Aesar) was recrystallized out of benzene/*n*-hexane under a nitrogen atmosphere prior to use. *N*,*N*-Dimethylacetamide (DMA; anhydrous in a Sure-Seal bottle; Fluka) and *N*,*N*-Dimethylformamide (DMF; anhydrous in a Sure-Seal bottle; Fluka) were used as received. Tetrahydrofuran (THF) was dried by passage through a neutral alumina column under argon pressure. Aqueous formaldehyde solution (ca. 37%) was purchased from Alfa Aesar, and 1-amino-2-naphthol hydrochloride was purchased from TCI. All other chemicals were reagent-grade and used as received.

HPLC analyses were performed on an Agilent 1100 Series system with Daicel Chiralpak columns in hexanes/isopropanol solvent mixtures. SFC analyses were performed on a Berger SFC MiniGram system with Daicel Chiralpak columns in carbon dioxide/methanol mixtures. Low-resolution mass spectrometric measurements were performed on an Agilent LC/MSC SL Multimode (ES/APCI) system with a Zorbax Eclipse (Agilent) XDB-C18 column in methanol solvent.

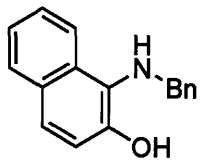
[93] Salomon, R. G.; Kochi, J. K. *J. Chem. Soc., Chem. Comm.* **1972**, 559–560.

II. Preparation of Substrates

The yields in this section have not been optimized. All reactions were conducted under a nitrogen atmosphere, unless otherwise noted.

General Procedure for Benzylation of Amines. In CH_2Cl_2, 1-amino-2-naphthol hydrochloride (TCI) and triethylamine were stirred for 30 min. Then, the aldehyde was added and the resulting mixture was stirred for 2 h. $NaBH(OAc)_3$ and glacial acetic acid were then added and the mixture was stirred for an additional 2 h.

The mixture was then concentrated and partitioned between CH_2Cl_2 and 50% saturated brine solution (100 mL each), and the organic layer was collected. The aqueous layer was washed with additional CH_2Cl_2 (100 mL), and the combined organic layers were concentrated and further purified by silica chromatography.



1-(Benzylamino)naphthalen-2-ol. This compound was prepared according to the General Procedure for Benzylation of Amines using CH_2Cl_2 (250 mL), 1-amino-2-naphthol hydrochloride (10.0 g, 51.1 mmol), triethylamine (5.43 g, 53.7 mmol), benzaldehyde (6.51 g, 61.3 mmol), $NaBH(OAc)_3$ (13.5 g, 63.9 mmol), and glacial acetic acid (3.84 g, 63.9 mmol).

After extraction and silica chromatography (5% → 10% ethyl acetate in hexanes), the product was isolated as a light-pink solid (6.39 g, 50%).

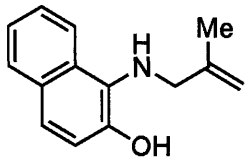
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1 H), 7.52 (ddd, J = 1.3, 6.9, 8.2 Hz, 1H), 7.47–7.33 (m, 6H), 7.25 (dd, J = 8.8, 1.7 Hz, 1 H), 7.19 (br s, 1H), 4.17 (s, 2H), 3.23 (br s, 1 H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.4, 139.3, 130.9, 129.2, 129.0, 128.7, 128.2, 127.6, 127.1, 126.6, 125.1, 122.9, 120.3, 116.5, 54.1;

IR (film): 3328, 3061, 3029, 2859, 1629, 1602, 1581, 1517, 1472, 1392, 1311, 1272, 1221, 1079, 955, 810 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{17}H_{16}NO$ [M + H^+]: 250.1; found: 250.1;

mp 111–112 °C.



1-(2-Methylallylamino)naphthalen-2-ol. This compound was prepared according to the General Procedure for Benzylation of Amines using CH_2Cl_2 (200 mL), 1-amino-2-naphthol hydrochloride (5.0 g, 25.6 mmol), triethylamine (2.72 g, 26.8 mmol), methacrolein (2.15 g, 30.7 mmol), $NaBH(OAc)_3$ (6.77 g, 32.0 mmol), and glacial acetic acid (1.92 g, 32.0 mmol).

After extraction and silica chromatography (5% → 10% ethyl acetate in hexanes), the product was isolated as a light-yellow solid (3.21 g, 59%).

^1H NMR ($CDCl_3$, 500 MHz): δ 7.81 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8.8 Hz, 1H), 7.51 (ddd, J = 1.2, 6.9, 8.3 Hz, 1H), 7.33 (ddd, J = 1.1, 6.8, 8.1 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.19 (br s, 1H), 5.18 (s, 1H), 5.00 (s, 1H), 3.54 (s, 2H), 3.10 (br s, 1H), 1.92 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.0, 143.8, 130.8, 129.1, 128.9, 126.7, 126.5, 125.6, 122.9, 120.2, 116.5, 111.2, 55.8, 21.0;

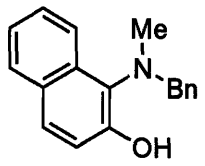
IR (film): 3331, 3064, 2970, 2361, 1628, 1602, 1519, 1469, 1392, 1273, 1221, 1145, 1095, 901, 807 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{14}H_{16}NO$ [M + H^+]: 214.1; found: 214.1;

mp 79–83 °C.

General Procedure for Methylation of Amines. The mono-alkylated aminol was stirred into ethanol, and then formaldehyde solution, $NaBH_3CN$, and glacial acetic acid were added sequentially to the mixture, which was then stirred for 1 h.

The mixture was then concentrated and partitioned between CH_2Cl_2 and 50% saturated brine solution (100 mL each), and the organic layer was collected. The aqueous layer was washed with additional CH_2Cl_2 (100 mL), and the combined organic layers were concentrated and further purified by silica chromatography.



1-(Benzyl(methyl)amino)naphthalen-2-ol. This compound was prepared according to the General Procedure for Methylation of Amines using ethanol (150 mL), 1-(benzylamino)naphthalen-2-ol (5.68 g, 22.6 mmol), aqueous formaldehyde solution (2.37 mL, 31.6 mmol), $NaBH_3CN$ (1.99 g, 31.6 mmol), and glacial acetic acid (1.90 g, 31.6 mmol).

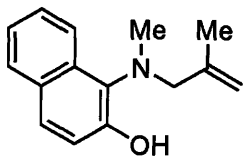
After extraction and silica chromatography (5% ethyl acetate in hexanes), the product was obtained as a clear, yellow oil (5.82 g, 98%).

^1H NMR ($CDCl_3$, 300 MHz): δ 7.90 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.44 (ddd, J = 1.3, 6.9, 8.4 Hz, 1H), 7.28-7.23 (m, 6H), 7.20 (br s, 1H), 7.16 (d, J = 8.8 Hz, 1H), 4.41 (d, J = 13.1 Hz, 1H), 4.23 (d, J = 13.0 Hz, 1H), 2.91 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.6, 139.0, 131.9, 129.58, 129.59, 129.5, 128.9, 128.6, 128.3, 127.5, 126.1, 122.5, 122.0, 116.1, 61.2, 41.1;

IR (film): 3283, 3061, 3029, 2850, 1623, 1599, 1520, 1520, 1466, 1392, 1348, 1273, 1208, 1148, 1116, 1049, 961, 817, 749 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{18}H_{18}NO$ [M + H^+]: 264.1; found: 264.1.



1-(Methyl(2-methylallyl)amino)naphthalen-2-ol. This compound was prepared according to the General Procedure for Methylation of Amines using ethanol (100 mL), 1-(2-methylallylamino)naphthalen-2-ol (1.44 g, 6.74 mmol), aqueous formaldehyde solution (2.37 mL, 9.44 mmol), $NaBH_3CN$ (593 mg, 9.44 mmol), and glacial acetic acid (567 mg, 9.44 mmol).

After extraction and silica chromatography (4% ethyl acetate in hexanes), the product was obtained as a clear, colorless oil (1.14 g, 75%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (br s, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.48 (ddd, J = 1.3, 6.9, 8.4 Hz, 1H), 7.32 (ddd, J = 1.1, 6.9, 8.0 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 5.07 (s, 1H), 4.97 (s, 1H), 4.05 (d, J = 13.8 Hz, 1H), 3.57 (d, J = 13.8 Hz, 1H), 2.95 (s, 3H), 1.89 (s, 3H);

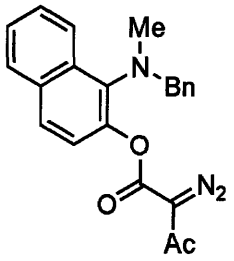
^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.7, 142.6, 131.8, 130.1, 129.6, 129.5, 128.2, 126.0, 122.5, 122.1, 116.1, 113.4, 63.6, 40.7, 20.6;

IR (film): 3290, 3076, 2972, 2940, 1623, 1599, 1519, 1468, 1451, 1393, 1342, 1270, 1206, 1149, 1119, 1051, 964, 901, 816, 747 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{15}H_{18}NO$ [M + H^+]: 228.1; found: 228.1.

General Procedure for Diazo-transfer.[80] The dialkylated aminol was dissolved into dry THF and cooled to -15 °C in an isopropanol-ice bath. LHMDS (ca. 1.06 M THF solution; Alfa Aesar) was added via syringe, whereupon the solution turned dark red in color, and then diketene was added by syringe. After stirring for the indicated time, p-acetamidobenzenesulfonyl azide (p-ABSA; Alfa Aesar) was added, and the cold solution was allowed to warm to room temperature overnight.

The mixture was then concentrated and partitioned between CH_2Cl_2 and 50% saturated brine solution (100 mL each), and the organic layer was collected. The aqueous layer was washed with additional CH_2Cl_2 (100 mL), and the combined organic layers were concentrated and further purified by silica chromatography.



1-(Benzyl(methyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. This compound was prepared according to the General Procedure for Diazo-transfer. Dry THF (10 mL), 1-(benzyl(methyl)amino)naphthalen-2-ol (3.00 g, 11.4 mmol), LHMDS solution (11.3 mL, 12.0 mmol), and diketene (1.05 g, 12.5 mmol) were stirred together for 30 min, followed by the addition of p-ABSA (3.28 g, 13.7 mmol).

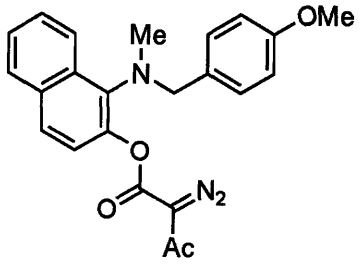
After extraction and silica chromatography (4% → 12% ethyl acetate in hexanes), the product was obtained as an amber-colored resin (2.16 g, 51%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.47 (dd, J = 0.6, 8.5 Hz, 1H), 7.90 (dd, J = 0.6, 8.0 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.61 (ddd, J = 1.3, 6.8, 8.4 Hz, 1H), 7.55 (ddd, J = 1.3, 6.9, 8.1 Hz, 1H), 7.41–7.29 (m, 5H), 7.24 (d, J = 8.9 Hz, 1H), 4.31 (s, 2H), 2.86 (s, 3H), 2.58 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.8, 160.2, 144.1, 139.4, 138.9, 132.9, 132.6, 128.6, 128.3, 128.2, 127.2, 126.5, 126.1, 126.0, 124.4, 122.2, 60.7, 40.8, 28.3; the resonance of the diazo-bearing carbon was not detected;

IR (film): 3061, 3029, 2846, 2800, 2268, 2140 (C=N), 1732, 1662, 1594, 1454, 1396, 1365, 1313, 1060, 1039, 965, 731 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{22}H_{20}N_3O_3$ [M + H$^+$]: 374.2; found: 374.1.



1-((4-Methoxybenzyl)(methyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. This compound was prepared beginning with the General Procedure for Benzylation of Amines using CH_2Cl_2 (150 mL), 1-amino-2-naphthol hydrochloride (2.50 g, 12.8 mmol), triethylamine (1.42 g, 14.1 mmol), p-anisaldehyde (1.92 g, 14.1 mmol), $NaBH(OAc)_3$ (2.98 g, 14.1 mmol), and glacial acetic acid (0.846 g, 14.1 mmol). After extraction and silica chromatography (10% → 12.5% ethyl acetate in hexanes), and the benzylated intermediate was isolated as a waxy, red solid (1.51 g).

The benzylated intermediate was then methylated according to General Procedure for Methylation of Amines using ethanol (100 mL), aqueous formaldehyde solution (0.610 mL, 8.12 mmol), $NaBH_3CN$ (510 mg, 8.12 mmol), and glacial acetic acid (0.488 mg, 8.12 mmol). After extraction and silica chromatography (7.5% → 10% ethyl acetate in hexanes), the methylated intermediate was obtained as a clear, yellow oil (1.52 g).

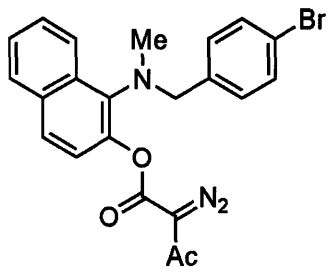
Finally, the methylated intermediate was diazatized according to the General Procedure for Diazo-transfer using dry THF (10 mL), LHMDS solution (1.04 mL, 4.82 mmol), and diketene (473 mg, 5.62 mmol) stirred together for 1 h, followed by the addition of *p*-ABSA (1.47 g, 6.12 mmol). After extraction and silica chromatography (7.5% → 15% ethyl acetate in hexanes), the product was obtained as a clear, yellow resin (0.895 g, 17%; three steps).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.42 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.60-7.51 (m, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.9 Hz, 1H), 6.87 (d, J = 8.3 Hz, 2H), 4.22 (s, 2H), 3.81 (s, 3H), 2.82 (s, 3H), 2.55 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.8, 160.1, 158.7, 144.1, 139.3, 132.9, 132.6, 130.9, 129.8, 128.1, 126.4, 126.0, 124.4, 122.2, 113.6, 60.0, 55.1, 40.6, 28.3; the resonance of the diazo-bearing carbon was not detected;

IR (film): 3057, 3000, 2935, 2836, 2256, 2139 (C=N), 1732, 1662, 1610, 1512, 1465, 1365, 1247, 1143, 1059, 803, 730 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{23}H_{22}N_3O_4$ [M + H^+]: 404.2; found: 404.1



1-((4-Bromobenzyl)(methyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. This compound was prepared beginning with the General Procedure for Benzylation of Amines using CH_2Cl_2 (100 mL), 1-amino-2-naphthol hydrochloride (2.50 g, 12.8 mmol), triethylamine (1.30 g, 12.8 mmol), 4-bromobenzaldehyde (2.94 g, 15.9 mmol), $NaBH(OAc)_3$ (2.98 g, 14.1 mmol), and glacial acetic acid (846 mg, 14.1 mmol). After extraction and silica chromatography (7.5% ethyl acetate in hexanes), and the product was isolated as a light-yellow solid (1.14 g, 27%).

That intermediate was then methylated according to General Procedure for Methylation of Amines using ethanol (10 mL), aqueous formaldehyde solution (311 mL, 4.15 mmol), $NaBH_3CN$ (261 mg, 4.15 mmol), and glacial acetic acid (250 mg, 4.16 mmol). After extraction and silica chromatography (7.5% ethyl acetate in hexanes), the product **A** was obtained as a clear, colorless oil (769 mg, 65%).

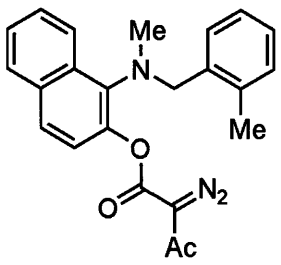
Finally, the second intermediate (**A**; 750 mg, 2.19 mmol) was diazatized according to the General Procedure for Diazo-transfer using dry THF (10 mL), LHMDS solution (2.17 mL, 2.30 mmol), and diketene (184 mg, 2.30 mmol) stirred together for 20 min, followed by the addition of *p*-ABSA (685 mg, 2.85 mmol). After extraction and silica chromatography (5% → 10% ethyl acetate in hexanes), the product was obtained as a clear, amber-colored resin (150 mg, 15%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.38 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.9 Hz, 1H), 7.59 (ddd, J = 1.3, 6.9, 8.4 Hz, 1H), 7.55–7.52 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 4.23 (s, 2H), 2.82 (s, 3H), 2.56 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.8, 160.2, 144.1, 139.0, 137.9, 133.0, 132.5, 131.4, 130.3, 128.3, 126.6, 126.4, 126.1, 124.2, 122.2, 121.1, 60.1, 41.0, 28.4; the resonance of the diazo-bearing carbon was not detected;

IR (film): 3056, 2849, 2364, 2139 (C=N), 1732, 1662, 1593, 1507, 1487, 1312, 1247, 1211, 1060, 1038, 964, 801 cm^{-1};

LR-MS (ES/APCI): calculated for the deacylated product **A**, $C_{18}H_{17}BrNO$ [M + H^+]: 342.1; found: 342.0.



1-(Methyl(2-methylbenzyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. This compound was prepared starting with the General Procedure for Benzylation of Amines using CH_2Cl_2 (150 mL), 1-amino-2-naphthol hydrochloride (3.00 g, 15.3 mmol), triethylamine (1.55 g, 15.3 mmol), 2-methylbenzaldehyde (2.03 g, 16.9 mmol), $NaBH(OAc)_3$ (3.57 g, 16.8 mmol), and glacial acetic acid (1.01 g, 16.8 mmol). After extraction and silica chromatography (5% → 10% ethyl acetate in hexanes), the product was isolated as a pink solid and directly carried forward to the next step.

That intermediate was then methylated according to General Procedure for Methylation of Amines using ethanol (100 mL), aqueous formaldehyde solution (1.61 mL, 21.4 mmol), $NaBH_3CN$ (1.34 g, 21.4 mmol), and glacial acetic acid (1.29 g, 21.4 mmol). After extraction and silica chromatography (5% ethyl acetate in hexanes), the product was obtained as a clear, colorless oil (1.81 g, 43%; two steps).

Finally, the second intermediate was diazatized according to the General Procedure for Diazo-transfer using dry THF (20 mL), LHMDS solution (6.16 mL, 6.53 mmol), and diketene (604 mg, 7.18 mmol) stirred together for 20 min, followed by the addition of *p*-ABSA (2.04 g, 7.18 mmol). After extraction and silica chromatography (6% → 8% ethyl

acetate in hexanes), the diazoester product was obtained as a clear, amber-colored resin (0.66 g, 26%).

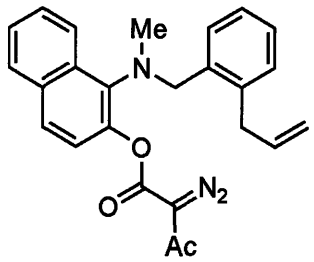
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.39 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.58–7.51 (m, 2H), 7.46–7.44 (m, 1H), 7.25–7.20 (m, 4H), 4.32 (s, 2H), 2.88 (s, 3H), 2.59 (s, 3H), 2.26 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.7, 160.3, 144.00, 143.98, 139.9, 136.8, 132.9, 132.5, 130.4, 129.2, 128.2, 127.2, 126.4, 126.1, 126.0, 125.6, 124.4, 122.3, 58.1, 41.3, 28.3, 19.1; the resonance of the diazo-bearing carbon was not detected;

IR (film): 3057, 2945, 2849, 2257, 2140 (C=N), 1733, 1663, 1594, 1463, 1463, 1365, 1313, 1143, 1039, 802, 744 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{23}H_{22}N_3O_3$ [M + H^+]: 388.2; found: 388.2;

mp 83–86 °C.



1-((2-Allylbenzyl)(methyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. This compound was prepared starting with the General Procedure for Benzylation of Amines using CH_2Cl_2 (150 mL), 1-amino-2-naphthol hydrochloride (4.66 g, 23.8 mmol), triethylamine (2.53 g, 25.0 mmol), 2-allylbenzaldehyde[94](4.00 g, 27.4 mmol), $NaBH(OAc)_3$ (6.31 g, 29.8 mmol), and glacial acetic acid (1.79 g, 29.8 mmol). After extraction and silica chromatography (5% → 15% ethyl acetate in hexanes), the product was isolated as a pink solid (2.62 g, 38%).

That intermediate was then methylated according to General Procedure for Methylation of Amines using ethanol (100 mL), aqueous formaldehyde solution (951 mL,

[94] Knight, J.; Parsons, P. J. *J. Chem. Soc., Perkin Trans. I* **1989**, 979–984.

12.7 mmol), $NaBH_3CN$ (797 mg, 12.7 mmol), and glacial acetic acid (761 mg, 12.7 mmol). After extraction and silica chromatography (3% ethyl acetate in hexanes), the product **B** was obtained as a clear, colorless oil (2.57 g, 93%).

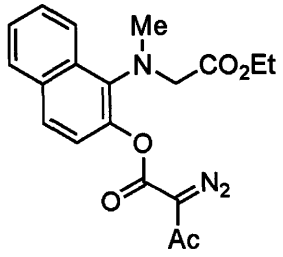
Finally, the second intermediate (**B**; 2.57g, 8.47 mmol) was diazatized according to the General Procedure for Diazo-transfer using dry THF (20 mL), LHMDS solution (8.00 mL, 8.47 mmol), and diketene (784 mg, 9.32 mmol) stirred together for15 min, followed by the addition of *p*-ABSA (2.85 g, 11.9 mmol). After extraction and silica chromatography (5% → 10% ethyl acetate in hexanes), the diazoester product was obtained as a clear, amber-colored resin (1.64 g, 47%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.39 (d, J = 8.3 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 8.9 Hz, 1H), 7.58–7.51 (m, 3H), 7.30–7.20 (m, 4H), 5.90 (ddt, J = 6.1, 10.1, 16.3 Hz, 1H), 5.00 (ddt, J = 1.6, 3.2, 10.1 Hz, 1H), 4.81 (ddt, J = 1.8, 1.8, 17.1 Hz, 1H), 4.32 (s, 2H), 3.39 (ddd, J = 1.5, 1.5, 6.1 Hz, 2H), 2.86 (s, 3H), 2.58 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.7, 160.3, 144.0, 139.9, 138.2, 136.8, 136.7, 133.0, 132.6, 129.9, 129.4, 128.2, 127.4, 126.4, 126.3, 126.2, 126.0, 124.4, 122.3, 115.8, 57.3, 41.3, 36.7, 28.4; the resonance of the diazo-bearing carbon was not detected;

IR (film): 3060, 2977, 2848, 2379, 2268, 2140 (C=N), 1733, 1663, 1594, 1394, 1365, 1313, 1142, 1039, 755, 635 cm^{-1};

LR-MS (ES/APCI): calculated for the deacylated product **B,** $C_{21}H_{22}NO$ [M + H$^+$]: 304.2; found: 304.2;



1-((2-Ethoxy-2-oxoethyl)(methyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. A 1 L round-bottomed flask was charged with 1-amino-2-naphthol hydrochloride (2.50 g, 14.4 mmol), triethylamine (1.46g, 14.4 mmol), and ethanol (600 mL). $NaBH_3CN$ (2.72, 43.3

mmol) and acetic acid (2.60 g, 43.3 mmol) were then stirred into solution, and ethyl glyoxalate solution (ca. 50% solution in toluene, 6.0 mL; 30.7 mmol; Fluka) was added to the mixture portionwise (6 × 1.0 mL each) by syringe, over the course of 1.5 hours. The mixture was then stirred an additional 2 hours at room temperature. The mixture was then concentrated and partitioned between CH_2Cl_2 and water (100 mL each), and the organic layer was collected. The aqueous layer was washed with additional CH_2Cl_2 (100 mL), and the combined organic layers were concentrated and purified by silica chromatography (15% ethyl acetate in hexanes), and the product was obtained as a clear, red oil (523 mg, 15%).

That intermediate (823 mg, 3.40 mmol; combined from multiple runs) was then methylated according to General Procedure for Methylation of Amines using ethanol (50 mL), aqueous formaldehyde solution (0.360 mL, 4.80 mmol), $NaBH_3CN$ (300 mg, 4.77 mmol), and glacial acetic acid (285 mg, 4.75 mmol). After extraction and silica chromatography (10% ethyl acetate in hexanes), the methylated intermediate was obtained as a clear, red oil (683 mg, 77%).

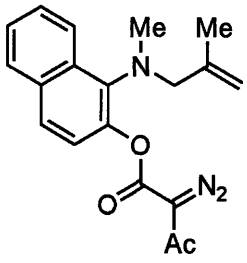
Finally, the dialkylated aminol was diazotized according to the General Procedure for Diazo-transfer using dry THF (10 mL), LHMDS solution (2.48 mL, 2.63 mmol), and diketene (310 mg, 3.68 mmol) stirred together for 20 min, followed by the addition of *p*-ABSA (885 mg, 3.68 mmol). After extraction and silica chromatography (15% ethyl acetate in hexanes), the product was obtained as a clear, amber-colored resin (403 mg, 41%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.35 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.71 (d, J = 8.8 Hz, 1H), 7.57 (ddd, J = 1.3, 6.8, 8.4 Hz, 1H), 7.51 (ddd, J = 1.3, 6.8, 8.1 Hz, 1H), 7.22 (d, J = 8.9 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.91 (s, 2H), 3.03 (s, 3H), 2.57 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.9, 171.0, 160.4, 144.1, 138.6, 133.0, 132.6, 128.2, 126.6, 126.5, 126.0, 124.4, 122.0, 60.6, 57.4, 41.9, 28.3, 14.2; the resonance of the diazo-bearing carbon was not detected;

IR (film): 3449, 3305, 3058, 2982, 2904, 2379, 2268, 2142 (C=N), 1733, 1662, 1594, 1508, 1473, 1401, 1366, 1316, 1248, 1215, 1141, 965 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{19}H_{20}N_3O_5$ [M + H^+]: 370.1; found: 370.1.



1-(Methyl(2-methylallyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. This compound was prepared according to diazo-transfer procedure using dry THF (20 mL), 1-(methyl(2-methylallyl)amino)naphthalen-2-ol (474 mg, 2.09 mmol), LHMDS solution (2.10 mL, 2.23 mmol), diketene (193 mg, 2.29 mmol), and *p*-ABSA (703 mg, 2.93 mmol). After silica chromatography (5% → 10% ethyl acetate in hexanes), the product was obtained as a white, crystalline solid (240 mg, 34%).

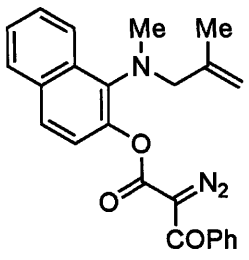
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.40 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.56 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.51 (ddd, J = 1.4, 6.8, 8.1 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 5.05 (s, 1H), 4.95 (s, 1H), 3.64 (s, 2H), 2.80 (s, 3H), 2.58 (s, 3H), 1.85 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.9, 160.3, 144.0, 143.1, 139.9, 132.95, 132.89, 128.1, 126.1, 126.0, 124.3, 122.2, 115.4, 113.0, 63.2, 40.8, 28.4, 20.6; the resonance of the diazo-bearing carbon was not detected;

IR (film): 3073, 2973, 2941, 2845, 2381, 2139 (C=N), 1733, 1664, 1593, 1508, 1365, 1312, 1247, 1207, 1142, 1039, 801, 731 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{19}H_{20}N_3O_3$ [M + H$^+$]: 338.2; found: 338.1;

mp 99–102 °C.



1-(Methyl(2-methylallyl)amino)naphthalen-2-yl 2-diazo-3-oxo-3-phenyl-propanoate. A 40-mL vial was charged with 1-(methyl(2-methylallyl)amino)naphthalen-2-ol (1.20 g, 5.28 mmol), 3-oxo-3-phenylpropanoic acid[95] (867 mg, 5.28 mmol), and dry CH_2Cl_2 (20 mL). Then *N,N*-dicyclohexylcarbodiimide (667 mg, 5.28) was added via syringe, and the reaction mixture was stirred for 1 h at room temperature, partitioned between DCM and 0.50 M aqueous HCl (100 mL each), and the organic layer was collected. The aqueous layer was washed with additional CH_2Cl_2 (100 mL), and the combined organic layers were concentrated and further purified by silica chromatography (4% ethyl acetate in hexanes). The β-ketoester intermediate was obtained as a clear, colorless oil (602.2 mg, 32 %), along with recovered starting material (660 mg, 55%).

The β-ketoester intermediate (259 mg, 0.723 mmol) was dissolved into dry acetonitrile (20 mL) and then tosyl azide (155 mg, 0.788 mmol) and triethylamine (87.8 mg, 0.868 mmol) were added to the mixture. After 30 minutes, second additions of tosyl azide (155 mg, 0.788 mmol) and triethylamine (87.8 mg, 0.868 mmol) were made, and the reaction was stirred at room temperature overnight. The crude reaction mixture was then concentrated, and purified by silica chromatography (4% → 8% ethyl acetate in hexanes) to afford the diazoester product as a clear yellow resin (150 mg, 52%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.55–7.41 (m, 5H), 7.19 (d, J = 8.9 Hz, 1H), 5.06 (s, 1H), 4.94 (s, 1H), 3.60 (s, 3H), 2.75 (s, 3H), 1.84 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 186.4, 159.9, 144.2, 143.2, 139.90, 139.86, 132.9, 132.6, 132.3, 128.5, 128.1, 128.0, 126.3, 126.0, 125.9, 124.3, 122.2, 112.9, 63.1, 40.7, 20.6; the resonance of the diazo-bearing carbon was not detected;

IR (film): 3445, 2917, 2849, 2142 (C=N), 1814, 1737, 1633, 1448, 1390, 1306, 1294, 1063, 801 cm^{-1};

LR-MS (ES/APCI): calculated for the deacylated fragment, 1-(methyl(2-methylallyl)amino)naphthalen-2-ol, $C_{15}H_{18}NO$ [M + H$^+$]: 228.1; found: 228.1.

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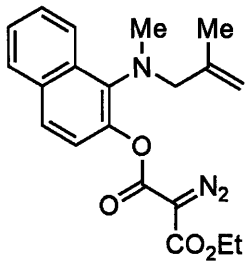
[95] Barnick, J. W. F. K.; Van Der Baan, J. L.; Bickelhaupt, F. *Synthesis* **1979**, 787–788.



1-Ethyl 3-(1-(methyl(2-methylallyl)amino)naphthalen-2-yl) 2-diazomalonate. A 40-mL vial was charged with 1-(methyl(2-methylallyl)amino)naphthalen-2-ol (577 mg, 2.54 mmol), ethyl 3-chloro-2-diazo-3-oxopropanoate[96] (718 mg, 4.06 mmol), and dry CH_2Cl_2 (20 mL). The reaction mixture was stirred overnight at room temperature, and then partitioned between DCM and 50% brine solution (100 mL each), and the organic layer was collected. The aqueous layer was washed with additional CH_2Cl_2 (100 mL), and the combined organic layers were concentrated and further purified by silica chromatography (4% → 6% ethyl acetate in hexanes) which afforded the diazoester product as a yellow resin (491 mg, 53 %).

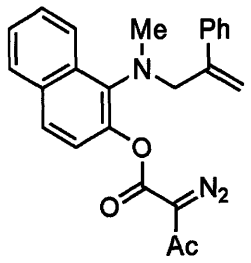
^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.42 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 9.0 Hz, 1H), 7.54 (ddd, J = 1.4, 6.8, 8.4 Hz, 1H), 7.49 (ddd, J = 1.3, 6.8, 8.0 Hz, 1H), 7.22 (d, J = 8.9 Hz, 1H), 5.07 (s, 1H), 4.94 (s, 1H), 4.41 (q, J = 7.1 Hz, 2H), 3.65 (s, 2H), 2.80 (s, 3H), 1.86 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.6, 159.9, 144.4, 143.4, 139.8, 132.9, 132.8, 128.0, 126.2, 125.9, 125.8, 124.3, 122.5, 112.8, 63.0, 62.1, 40.7, 20.6, 14.4; the resonance of the diazo-bearing carbon was not detected;

IR (film): 2980, 2846, 2144 (C=N), 1770, 1737, 1704, 1594, 1446, 1394, 1371, 1319, 1210, 1088, 1052, 898, 756 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{20}H_{22}N_3O_4$ [M + H$^+$]: 368.2; found: 368.2.

[96] Marino, J. P.; Osterhout, M. H.; Price, A. T.; Sheehan, S. M.; Padwa, A. *Tetrahedron Lett.* **1994**, *35*, 849–852.



1-(Methyl(2-phenylallyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. This compound was prepared starting with the General Procedure for Benzylation of Amines using CH_2Cl_2 (250 mL), 1-amino-2-naphthol hydrochloride (4.69 g, 27.1 mmol), triethylamine (2.74 g, 27.1 mmol), 2-phenylacrylaldehyde[97] (3.58 g, 27.1 mmol), $NaBH(OAc)_3$ (6.32 g, 29.8 mmol), and glacial acetic acid (1.79 g, 29.9 mmol). After extraction the reaction mixture was passed across a pad of silica (10% ethyl acetate in hexanes), and the crude product mixture was directly carried forward to the next step.

The crude intermediate underwent methylation according to General Procedure for Methylation of Amines using ethanol (100 mL), aqueous formaldehyde solution (1.22 mL, 16.3 mmol), $NaBH_3CN$ (1.02 g, 16.2 mmol), and glacial acetic acid (979 mg, 16.3 mmol). After extraction and silica chromatography (2.5% ethyl acetate in hexanes) the intermediate, 1-(methyl(2-phenylallyl)amino)naphthalen-2-ol, was obtained as a clear, colorless oil (525 mg, 11%; two steps).

Finally, the 1-(methyl(2-phenylallyl)amino)naphthalen-2-ol was diazotized according to the General Procedure for Diazo-transfer using dry THF (20 mL), LHMDS solution (1.71 mL, 1.81 mmol), and diketene (168 mg, 2.00 mmol) stirred together for 30 min, followed by the addition of *p*-ABSA (545 mg, 2.27 mmol). After extraction and silica chromatography (4% → 8% ethyl acetate in hexanes), the diazoester product was obtained as an amber-colored resin (479 mg, 66%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.47–7.27 (m, 7H), 7.22 (d, J = 8.8 Hz, 1H), 5.50 (s, 1H), 5.39 (s, 1H), 4.17 (s, 2H), 2.82 (s, 3H), 2.57 (s, 3H);

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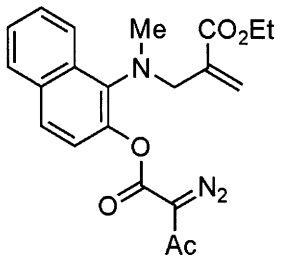
[97] Nsanzumuhire, C.; Clement, J.-L.; Ouari, O.; Karoui, H.; Finet., J.-H.; Tordo, P. *Tetrahedron Lett.* **2004**, *45*, 6385–6389.

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.8, 160.3, 145.5, 144.2, 139.7, 139.6, 132.9, 132.8, 128.2, 127.9, 127.5, 126.5, 126.2, 126.1, 126.0, 124.7, 122.1, 114.8, 60.7, 41.0, 28.4; the resonance of the diazo-bearing carbon was not detected;

IR (film): 2980, 2847, 2425, 2143 (C=N), 1770, 1737, 1508, 1394, 1372, 1320, 1211, 1089, 1052, 756 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{24}H_{22}N_3O_3$ [M + H^+]: 400.2; found: 400.1.



1-((2-(Ethoxycarbonyl)allyl)(methyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. A dry 100-mL round-bottomed flask was charged with NaH (287 mg, 12.0 mmol) and dry DMF (10 mL), and cooled to 0 °C. Then a solution of 1-amino-2-naphthol hydrochloride (4.69 g, 27.1 mmol) in dry DMF (20 mL) was added carefully over the course of 5 minutes, followed by the addition of ethyl 2-(bromomethyl)acrylate (1.1 g, 5.7 mmol; TCI) by syringe. The reaction mixture was allowed to warm to room temperature overnight, and then it was partitioned between diethyl ether and saturated aqueous ammonium chloride (150 mL each), and the organic layer was collected. The aqueous layer was then washed with additional diethyl ether (150 mL), and the combined organic layers were concentrated and further purified by silica chromatography (15% ethyl acetate in hexanes, loaded with the aid of toluene). The allylamine intermediate was obtained as a clear, red oil (520 mg, 34 %).

That allylamine intermediate was then methylated according to General Procedure for Methylation of Amines using ethanol (100 mL), aqueous formaldehyde solution (201 mL, 2.68 mmol), $NaBH_3CN$ (170 mg, 2.68 mmol), and glacial acetic acid (162 mg, 2.68 mmol). After extraction and silica chromatography (10% ethyl acetate in hexanes), the product **C** was obtained as a clear, colorless oil (394 mg, 72%).

Finally, the second intermediate (**C**) was diazotized according to the General Procedure for Diazo-transfer using dry THF (20 mL), LHMDS solution (1.30 mL, 1.38

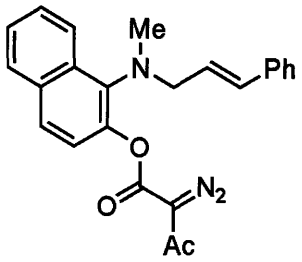
mmol), and diketene (128 mg, 1.52 mmol) stirred together for 10 min, followed by the addition of *p*-ABSA (464 mg, 1.93 mmol). After extraction and silica chromatography (7% → 15% ethyl acetate in hexanes), the diazoester product was obtained as an amber-colored resin (403 mg, 74%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.27 (d, J = 8.2 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.55–7.48 (m, 2H), 7.21 (d, 8.9 Hz, 1H), 6.28 (s, 1H), 5.81 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 4.00 (s, 2H), 2.86 (s, 3H), 2.58 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 189.8, 166.8, 160.3, 144.2, 139.2, 137.7, 132.9, 132.8, 128.1, 126.41, 126.36, 126.05, 126.03, 124.3, 122.1, 60.7, 57.0, 41.4, 28.4, 13.9; the resonance of the diazo-bearing carbon was not detected;

IR (film): 2982, 2850, 2380, 2268, 2141 (C=N), 1732, 1663, 1594, 1472, 1395, 1366, 1314, 1248, 1207, 1144, 1039, 964, 803, 732 cm^{-1};

LR-MS (ES/APCI): calculated for the deacylated fragment **C**, $C_{17}H_{20}NO_3$ [M + H$^+$]: 286.1; found: 286.1.



(E)-1-(Cinnamyl(methyl)amino)naphthalen-2-yl 2-diazo-3-oxobutanoate. This compound was prepared beginning with the General Procedure for Benzylation of Amines using CH_2Cl_2 (150 mL), 1-amino-2-naphthol hydrochloride (5.00 g, 25.6 mmol), triethylamine (2.59 g, 25.6 mmol), *trans*-cinnamaldehyde (3.73 g, 28.2 mmol), $NaBH(OAc)_3$ (5.97 g, 28.2 mmol), and glacial acetic acid (1.69 g, 28.2 mmol). After extraction and silica chromatography (10% → 15% ethyl acetate in hexanes), the product was isolated as a brown solid (800 mg, 11%).

That intermediate was then methylated according to General Procedure for Methylation of Amines using ethanol (150 mL), aqueous formaldehyde solution (0.33 mL, 4.4 mmol), $NaBH_3CN$ (275 mg, 4.37 mmol), and glacial acetic acid (262 mg, 4.37 mmol). After extraction and silica chromatography (15% ethyl acetate in hexanes), the product was obtained as a clear yellow oil (545 mg, 65%).

Finally, the dialkylated aminol was diazotized according to the General Procedure for Diazo-transfer using dry THF (10 mL), LHMDS solution (1.77 mL, 1.88 mmol), and diketene (174 mg, 2.07 mmol) stirred together for 30 min, followed by the addition of *p*-ABSA (587 mg, 2.44 mmol). After extraction and silica chromatography (10% ethyl acetate in hexanes), the product was obtained as a clear, amber-colored resin (327 mg, 44%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H), 7.58 (ddd, J = 1.4, 6.9, 8.4 Hz, 1H), 7.52 (ddd, J = 1.3, 6.8, 8.0 Hz, 1H), 7.39–7.25 (m, 5H), 7.21 (d, J = 9.0 Hz, 1H), 6.59 (d, J = 15.8 Hz, 1H), 6.30 (dt, J = 6.6, 15.8 Hz, 1H), 3.89 (d, J = 6.5 Hz, 2H), 2.94 (s, 3H), 2.52 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.8, 160.3, 144.0, 139.1, 136.8, 133.0, 132.8, 132.4, 128.6, 128.2, 127.5, 127.0, 126.4, 126.3, 126.1, 126.0, 124.4, 122.2, 58.8, 40.8, 28.3; the resonance of the diazo-bearing carbon was not detected;

IR (film): 3058, 3026, 2931, 2378, 2269, 2139 (C=N), 1949, 1732, 1663, 1594, 1579, 1472, 1449, 1397, 1365, 1313, 1209, 965, 802, 747, 694 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{24}H_{22}N_3O_3$ [M + H^+]: 400.2; found: 400.1;

III. C–N Insertion Reactions

General Procedure for Table Entries. In a nitrogen-filled glovebox, a 40-mL vial was charged with the diazoester (0.50 mmol), CuOTf • ½ benzene (13 mg, 0.050 mmol), ligand (+)-**1** (22 mg, 0.065 mmol), and DMA (7.0 mL) resulting in a white, colloidal reaction mixture. The vial was then sealed with a Teflon cap, removed from the glovebox, and placed into a heated oil bath where it was stirred for the indicated time. After that time had elapsed, the reaction mixture was directly purified by flash chromatography.

The second runs were performed with ligand (–)-**1**. The absolute stereochemistries of products in table entries 3 and 9 were determined by X-ray crystallography (see Section IV). All other assignments were made by analogy.

Reaction notes: Use of higher temperatures results in higher rates of conversion, at the cost of lower enantioselectivity. Very low conversion was observed in reactions contaminated with air. Use of CuTC[98] as catalyst reduces the reaction sensitivity to air, but gives lower product yields (55% yield, 90% ee; under analogous conditions to those of Table 3.2, entry 1).

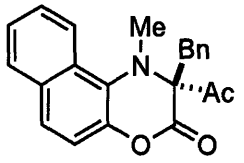


Table 3.2, entry 1. This product was prepared according to the General Procedure for Table Entries using 187 mg (0.500 mmol) of diazoester substrate, stirred for 2.0 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Further purification by silica chromatography (5% ethyl acetate, 0.3% triethylamine in hexanes → 8% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) afforded the product as a white, waxy solid.

1st run: 143 mg (83%; 91% ee);

[98] CuTC (copper (I) thiophene-2-carboxylate) is available from Aldrich. For a method of preparation, see: Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748–2749.

The ee's were determined via HPLC on an AS-H column (eluent: 3% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 30.0 min (major) and 21.3 min (minor).

$[\alpha]^{23}_{D} = -230$ ($c = 0.0016$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.22 (d, $J = 8.4$ Hz, 1H), 7.86 (d, $J = 8.2$ Hz, 1H), 7.69 (d, $J = 9.1$ Hz, 1H), 7.68–7.64 (m, 1H), 7.53–7.30 (m, 6H), 7.19 (d, $J = 9.0$ Hz, 1H), 3.82 (d, $J = 14.6$ Hz, 1H), 3.47 (d, $J = 14.6$ Hz, 1H), 3.03 (s, 3H), 1.36 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.3, 165.6, 144.4, 134.0, 131.3, 129.4, 129.1, 128.7, 128.4, 128.0, 127.7, 127.5, 126.9, 125.8, 121.9, 117.2, 78.1, 38.1, 37.0, 26.1;

IR (film): 3584, 3063, 2969, 1774, 1718, 1629, 1598, 1466, 1391, 1353, 1249, 1226, 1181, 1115, 1029, 992, 812, 733, 701 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{22}H_{20}NO_3$ [M + H^+]: 346.1; found: 346.1;

mp 122–125 °C;

2nd run: 136 mg (79%; 91% ee).

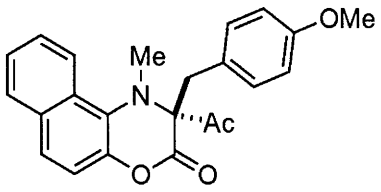


Table 3.2, entry 2. This product was prepared according to the General Procedure for Table Entries using 202 mg (0.500 mmol) of diazoester substrate, stirred for 3.0 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Further purification by silica chromatography (8% ethyl acetate, 0.3% triethylamine in hexanes → 13% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) afforded the product as a yellow oil.

1st run: 146 mg (78%; 91% ee).

The ee's were determined via HPLC on an IA-H column (eluent: 5% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 18.5 min (major) and 20.5 min (minor).

$[\alpha]^{23}_{D} = -120$ ($c = 0.0045$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (d, J = 8.4Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.69 (d, J = 9.1 Hz, 1H), 7.65 (ddd, J = 1.1, 7.9, 8.2 Hz, 1H), 7.53–7.49 (m, 1H), 7.39 (d, J = 8.7 Hz, 2H), 7.19 (d, J = 9.0 Hz, 1H), 6.89 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.77 (d, J = 14.6 Hz, 1H), 3.40 (d, J = 14.6 Hz, 1H), 3.01 (s, 3H), 1.40 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.1, 165.1, 159.7, 144.4, 131.48, 131.46, 131.3, 128.7, 127.9, 127.7, 125.8, 121.9, 117.2, 116.6, 114.2, 114.0, 78.0, 55.2, 38.0, 36.3, 25.9;

IR (film): 3418, 2922, 2851, 1770, 1631, 1513, 1463, 1248, 1225, 1179, 1115, 1029, 992, 810 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{23}H_{22}NO_4$ [M + H$^+$]: 376.2; found: 376.2;

2nd run: 133 mg (71%; 95% ee).

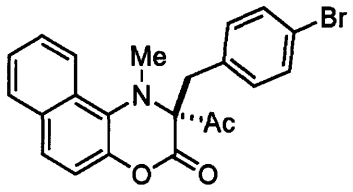


Table 3.2, entry 3. This product was prepared according to the General Procedure for Table Entries using 226 mg (0.500 mmol) of diazoester substrate, stirred for 4.0 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Further purification by silica chromatography (6% ethyl acetate, 0.3% triethylamine in hexanes → 12% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) afforded the product as a white, crystalline solid.

1st run: 127 mg (60%; 90% ee).

The ee's were determined via HPLC on an AD-H column (eluent: 1% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 20.7 min (major) and 24.6 min (minor). Crystals suitable for X-Ray crystallographic analysis were grown by slow CH_2Cl_2 → hexanes diffusion, see Section V.

$[\alpha]^{23}_D$ = –240 (c = 0.0080, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 8.9 Hz, 1H), 7.66 (ddd, J = 1.2, 7.0, 8.3 Hz, 1H), 7.52 (ddd, J = 1.2, 7.0, 8.3 Hz,

1H), 7.48 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 7.20 (d, J = 9.0 Hz, 1H), 3.79 (d, J = 14.5 Hz, 1H), 3.37 (d, J = 14.5 Hz, 1H), 2.99 (s, 3H), 1.46 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.7, 165.5, 144.4, 133.1, 132.1, 131.8, 131.4, 128.9, 128.8, 128.3, 128.1, 127.8, 125.9, 121.8, 121.7, 117.1, 77.8, 38.0, 36.7, 26.0;

IR (film): 2969, 1775, 1717, 1598, 1490, 1466, 1490, 1466, 1391, 1354, 1275, 1248, 1226, 1194, 1116, 1074, 1012, 992, 813, 751 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{22}H_{19}NBrO_3$ [M+H$^+$]: 424.1; found: 424.0;

mp 197–199 °C;

2nd run: 111 mg (56%; 89% ee).

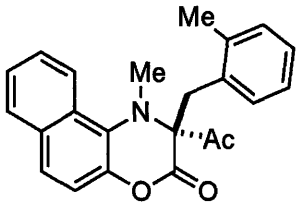


Table 3.2, entry 4. This product was prepared according to the General Procedure for Table Entries using 194 mg (0.500 mmol) of diazoester substrate, stirred for 5.0 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Further purification by silica chromatography (5% ethyl acetate, 0.3% triethylamine in hexanes → 8% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) afforded the product as a white, crystalline solid.

1st run: 114 mg (64%; 92% ee).

The ee's were determined via HPLC on an AS-H column (eluent: 3% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 20.8 min (major) and 17.7 min (minor).

$[\alpha]^{23}_D$ = –227 (c = 0.0122, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.72–7.66 (m, 3H), 7.52 (ddd, J = 1.0, 7.1, 8.1 Hz, 1H), 7.33–7.17 (m, 3H), 7.20 (d, J = 9.0 Hz, 1H), 4.00 (d, J = 15.6 Hz, 1H), 3.41 (d, J = 15.6 Hz, 1H), 3.06 (s, 3H), 2.36 (s, 3H), 1.17 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.6, 165.6, 144.4, 137.2, 132.6, 131.4, 130.9, 130.3, 129.4, 128.7, 128.6, 128.0, 127.8, 127.5, 126.3, 125.8, 121.9, 117.2, 78.0, 38.3, 31.1, 25.7, 20.2;

IR (film): 3457, 1776, 1706, 1465, 1390, 1352, 1249, 1227, 1187, 1118, 992, 812, 740 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{23}H_{22}NO_3$ [M + H^+]: 360.2; found: 360.2;

mp 142–144 °C;

2nd run: 108 mg (62%; 93% ee).

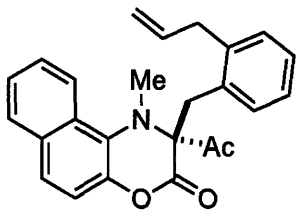


Table 3.2, entry 5. This product was prepared according to the General Procedure for Table Entries using 207 mg (0.500 mmol) of diazoester substrate, stirred for 5 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Further purification by silica chromatography (5% ethyl acetate, 0.3% triethylamine in hexanes → 10% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) followed with a second purification by silica chromatography (pure CH_2Cl_2) afforded the product as a clear, colorless oil.

1st run: 102 mg (53%; 92% ee).

The ee's were determined via HPLC on an AD-H column (eluent: 3% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 11.9 min (major) and 11.4 min (minor).

$[\alpha]^{23}_D = -140$ ($c = 0.0043$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.71–7.65 (m, 2H), 7.54–7.50 (m, 1H), 7.36–7.32 (m, 1H), 7.25–7.19 (m, 3H), 5.98 (dddd, J = 6.1, 6.1, 10.1, 16.5 Hz, 1H), 5.13 (dd, J = 1.5, 10.2 Hz, 1H), 5.02 (dd, J = 1.7, 17.1 Hz, 1H), 3.99 (d, J = 15.8 Hz, 1H), 3.51–3.35 (m, 2H), 3.40 (d, J = 15.7 Hz, 1H), 3.03 (s, 3H), 1.20 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 205.5, 165.6, 144.4, 138.8, 136.6, 132.6, 131.4, 130.6, 130.5, 129.3, 128.7, 128.5, 128.0, 127.8, 127.7, 126.8, 125.9, 121.9, 117.2, 116.2, 78.1, 38.3, 37.6, 30.6, 25.8;

IR (film): 3064, 1775, 1708, 1598, 1466, 1392, 1249, 1226, 1185, 1114, 993, 812, 746 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{25}H_{24}NO_3$ [M + H^+]: 386.2; found: 386.2;

2nd run: 116 mg (57%; 93% ee).

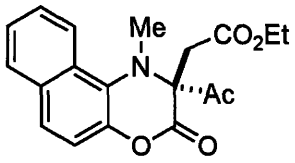


Table 3.2, entry 6. This product was prepared according to the General Procedure for Table Entries using 185 mg (0.500 mmol) of diazoester substrate, stirred for 4.0 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Purification by silica chromatography (15% ethyl acetate, 0.3% triethylamine in hexanes → 20% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) followed with a second purification by silica chromatography (pure CH_2Cl_2) afforded the product as a clear, colorless oil, which crystallized over a period of time.

1st run: 124 mg (73%; 93% ee).

The ee's were determined via HPLC on an IA-H column (eluent: 1% isopropanol in hexanes; flow rate: 0.800 mL/min). Retention times: 49.9 min (major) and 55.1 min (minor).

$[\alpha]^{23}_D = -170$ ($c = 0.0031$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.70 (d, J = 9.0 Hz, 1H), 7.67–7.62 (m, 1H), 7.53–7.49 (m, 1H), 7.21 (d, J = 9.0 Hz, 1H), 4.32–4.21 (m, 2H), 3.38 (d, J = 15.4 Hz, 1H), 3.19 (d, J = 15.4 Hz, 1H), 2.90 (s, 3H), 1.97 (s, 3H), 1.34 (t, J = 7.0 Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.5, 168.5, 165.3, 144.3, 131.5, 128.7, 128.3, 128.0, 127.71, 127.68, 125.8, 121.8, 117.0, 74.4, 61.6, 38.5, 37.6, 25.0, 14.0;

IR (film): 3428, 2095, 1773, 1738, 1630, 1512, 1467, 1390, 1374, 1349, 1279, 1228, 1161, 1119, 1040, 992, 950 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{19}H_{20}NO_5$ [M + H^+]: 342.1; found: 342.1;

mp 138–141 °C;

2nd run: 122 mg (72%; 93% ee).

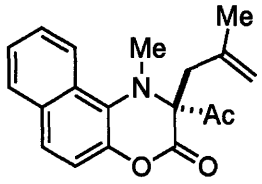


Table 3.3, entry 1. This product was prepared according to the General Procedure for Table Entries using 169 mg (0.500 mmol) of diazoester substrate, stirred for 1.5 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Purification by silica chromatography (4% ethyl acetate, 0.3% triethylamine in hexanes → 6% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) followed with a second purification by silica chromatography (pure CH_2Cl_2) afforded the product as a clear, colorless oil.

1st run: 128 mg (82%; 97% ee).

The ee's were determined via HPLC on an AS-H column (eluent: 3% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 11.4 min (major) and 9.8 min (minor).

$[\alpha]^{23}_D$ = –240 (c = 0.0094, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.9 Hz, 1H), 7.66 (ddd, J = 8.9 Hz, 1H), 7.52 (ddd, J = 2.2, 5.7, 9.6 Hz, 1H), 7.19 (d, J = 9.0 Hz, 1H), 4.99 (s, 1H), 4.98 (s, 1H), 3.21 (d, J = 14.1 Hz, 1H), 2.88 (d, J = 15.0 Hz, 1H), 2.85 (s, 3H), 2.03 (s, 3H), 1.81 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.9, 165.3, 144.4, 140.0, 131.4, 129.0, 128.7, 128.4, 127.9, 127.7, 125.8, 121.9, 117.5, 117.2, 77.6, 39.3, 37.7, 26.0, 23.4;

IR (film): 3411, 3072, 2972, 1777, 1716, 1599, 1467, 1391, 1353, 1249, 1226, 1115, 993, 906, 813, 752 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{19}H_{20}NO_3$ [M + H^+]: 310.1; found: 310.1;

2nd run: 131 mg (85%; 97% ee).

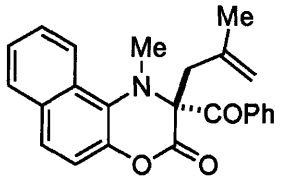


Table 3.3, entry 2. This product was prepared according to the General Procedure for Table Entries using 200 mg (0.500 mmol) of diazoester substrate, stirred for 4.0 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Purification by silica chromatography (5% ethyl acetate in hexanes → 10% ethyl acetate in hexanes; loaded with the aid of toluene) followed with a second purification by silica chromatography (pure CH_2Cl_2) afforded the product as a white, crystalline solid.

1st run: 110 mg (63%; 87% ee).

The ee's were determined via HPLC on an AD-H column (eluent: 3% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 12.7 min (major) and 14.0 min (minor).

$[\alpha]^{23}_D = -220$ ($c = 0.0024$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, J = 7.4 Hz, 2H), 7.95 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 8.9 Hz, 1H), 7.40 (ddd, J = 1.0, 7.0, 8.2 Hz, 1H), 7.34–7.30 (m, 1H), 7.26–7.13 (m, 4H), 4.78 (s, 1H), 4.70 (s, 1H), 3.46 (d, J = 13.6 Hz, 1H), 3.20 (d, J = 13.6 Hz, 1H), 2.90 (s, 3H), 1.87 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 195.2, 164.6, 145.0, 139.6, 134.4, 132.8, 130.9, 129.2, 129.0, 128.2, 128.1, 127.7, 127.6, 126.6, 125.2, 122.2, 118.1, 116.7, 77.4, 41.0, 37.6, 23.6;

IR (film): 3441, 2972, 1774, 1672, 1597, 1580, 1468, 1448, 1379, 1333, 1277, 1249, 1225, 1185, 992, 929, 810 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{24}H_{22}NO_3$ [M + H$^+$]: 372.2; found: 372.1;

mp 162–164 °C

2nd run: 123 mg (66%; 92%ee).

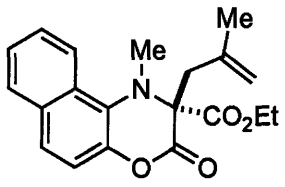


Table 3.3, entry 3. This product was prepared according to the General Procedure for Table Entries using 184 mg (0.500 mmol) of diazoester substrate, stirred for 3 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Further purification by silica chromatography (5% ethyl acetate, 0.3% triethylamine in hexanes → 8% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) afforded the product as a clear, colorless oil.

1st run: 122 mg (72%; 71% ee).

The ee's were determined via SFC on an OD-H column (eluent: 5% methanol in supercritical carbon dioxide; flow rate: 1.0 mL/min). Retention times: 6.0 min (major) and 6.3 min (minor).

$[\alpha]^{23}_{D} = -229$ ($c = 0.0198$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.23 (d, $J = 8.4$ Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 1H), 7.66 (d, $J = 8.9$ Hz, 1H), 7.62 (ddd, $J = 1.1, 6.9, 8.3$ Hz, 1H), 7.49 (ddd, $J = 1.2, 6.9, 8.1$ Hz, 1H), 7.20 (d, $J = 8.9$ Hz, 1H), 5.11 (s, 1H), 4.96 (s, 1H), 3.89–3.77 (m, 2H), 3.25 (d, $J = 15.2$ Hz, 1H), 2.95 (d, $J = 15.1$ Hz, 1H), 2.83 (s, 3H), 2.05 (s, 3H), 0.77 (t, $J = 15.1$ Hz, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.1, 164.1, 143.9, 139.9, 131.3, 130.4, 129.0, 128.2, 127.2, 127.0, 125.7, 122.9, 116.5, 115.9, 72.2, 61.7, 38.6, 37.3, 23.4, 13.5;

IR (film): 2976, 1777, 1754, 1599, 1466, 1390, 1230, 1179, 1118, 1069, 991, 900, 811, 749 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{20}H_{22}NO_4$ [M + H$^+$]: 340.2; found: 340.2;

2nd run: 130 mg (77%; 72% ee).

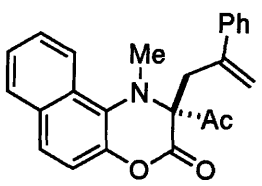


Table 3.3, entry 4. This product was prepared according to the General Procedure for Table Entries using 200 mg (0.500 mmol) of diazoester substrate, stirred for 3.5 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Further purification by silica chromatography (5% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) afforded the product as a feathery, white solid.

1st run: 133 mg (72%; 97% ee).

The ee's were determined via HPLC on an AD-H column (eluent: 2% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 17.3 min (major) and 18.5 min (minor). Crystals suitable for X-Ray crystallographic analysis were grown by slow CH_2Cl_2 → hexanes diffusion, see Section IV.

$[\alpha]^{23}_D = -210$ ($c = 0.0032$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 8.2$ Hz, 1H), 7.66 (d, $J = 9.0$ Hz, 1H), 7.61 (ddd, $J = 1.1$, 7.0, 8.2 Hz, 1H), 7.49 (ddd, $J = 1.1$, 7.0, 8.1 Hz, 1H), 7.44–7.30 (m, 5H), 7.16 (d, $J = 9.0$ Hz, 1H), 5.63 (s, 1H), 5.48 (s, 1H), 3.70 (d, $J = 15.2$ Hz, 1H), 3.34 (d, $J = 15.2$ Hz, 1H), 2.77 (s, 3H), 1.50 (s, 3H);

^{13}C NMR ($CDCl_3$, 125 MHz): δ 205.4, 165.2, 144.1, 142.4, 142.1, 131.1, 129.3, 128.6, 128.5, 128.4, 127.80, 127.76, 127.6, 127.0, 125.7, 121.9, 120.1, 117.1, 77.6, 37.8, 36.9, 26.3;

IR (film): 3405, 1777, 1710, 1627, 1599, 1513, 1494, 1464, 1390, 1353, 1250, 1226, 1180, 992, 917, 820 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{24}H_{22}NO_3$ [M + H$^+$]: 372.2; found: 372.2;

mp 181–182 °C;

2nd run: 138 mg (74%; 97% ee).

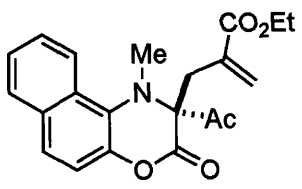


Table 3.3, entry 5. This product was prepared according to the General Procedure for Table Entries using 198 mg (0.500 mmol) of diazoester substrate, stirred for 3.0 days. The reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Further purification by silica chromatography (15% ethyl acetate, 0.3% triethylamine in hexanes → 20% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) followed with a second purification by silica chromatography (pure CH_2Cl_2) afforded the product as a clear, colorless oil.

1st run: 103 mg (56%; 95% ee).

The ee's were determined via HPLC on an AD-H column (eluent: 3% isopropanol in hexanes; flow rate: 1.0 mL/min). Retention times: 13.8 min (major) and 13.1 min (minor).

$[\alpha]^{23}_D = -290$ ($c = 0.0018$, $CHCl_3$);

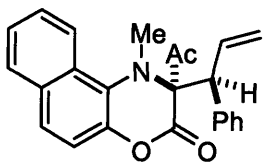
^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (d, $J = 8.3$ Hz, 1H), 7.86 (d, $J = 8.2$ Hz, 1H), 7.69 (d, $J = 9.0$ Hz, 1H), 7.65 (ddd, $J = 1.6, 5.1, 8.3$ Hz, 1H), 7.51 (ddd, $J = 1.2, 7.0, 8.1$ Hz, 1H), 7.18 (d, $J = 9.0$ Hz, 1H), 6.49 (s, 1H), 6.17 (s, 1H), 4.31–4.20 (m, 2H), 3.40 (d, $J = 14.6$ Hz, 1H), 3.33 (d, $J = 14.6$ Hz, 1H), 2.90 (s, 3H), 1.81 (s, 3H), 1.34 (t, $J = 7.1$ Hz, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 204.7, 167.2, 165.2, 144.2, 133.8, 131.5, 131.4, 128.9, 128.7, 128.3, 127.8, 127.7, 125.8, 121.9, 117.1, 77.1, 61.3, 37.7, 31.9, 25.8, 14.2;

IR (film): 2981, 1778, 1716, 1628, 1599, 1513, 1467, 1355, 1267, 1227, 1186, 1144, 1091, 992, 813 cm^{-1};

LR-MS (ES/APCI): calculated for $C_{21}H_{22}NO_5$ [M + H$^+$]: 368.2; found: 368.2;

2nd run: 107 mg (58%; 95% ee).



(*R,S*)-**3.8**

Table 3.3, entry 6. This product was prepared according to the General Procedure for Table Entries using 68 mg (0.17 mmol) of diazoester substrate, stirred for 4.0 days. The

reaction mixture was then passed through a short pad of silica gel (1:1 diethyl ether in hexanes) to remove the copper, ligand, and most of the DMA. Further purification by silica chromatography (3% ethyl acetate, 0.3% triethylamine in hexanes → 5% ethyl acetate, 0.3% triethylamine in hexanes; loaded with the aid of toluene) afforded both diastereomers of product.

(*R,S*)-**3.8** as a clear, colorless oil; 1st run: 33 mg (52%; 72% ee).

The ee's were determined via HPLC on an AD-H column (eluent: 3% isopropanol in hexanes; flow rate: 0.750 mL/min). Retention times: 13.1 min (major) and 13.6 min (minor).

$[\alpha]^{23}_{D} = +73$ ($c = 0.0050$, $CHCl_3$);

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, $J = 8.2$ Hz, 1H), 7.85 (d, $J = 8.2$ Hz, 1H), 7.67 (d, $J = 9.0$ Hz, 1H), 7.63 (ddd, $J = 1.1$, 7.0, 8.2 Hz, 1H), 7.53–7.47 (m, 3H), 7.34–7.24 (m, 3H), 7.18 (d, $J = 8.9$ Hz, 1H), 6.79 (ddd, $J = 8.0$, 10.2, 17.2 Hz, 1H), 5.24 (d, $J = 10.2$ Hz, 1H), 5.17 (d, $J = 17.1$ Hz, 1H), 4.37 (d, $J = 8.0$ Hz, 1H), 2.98 (s, 3H), 1.68 (s, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.1, 165.2, 144.4, 139.0, 138.5, 131.4, 129.9, 129.1, 128.72, 128.67, 128.0, 127.9, 127.6, 127.5, 125.7, 121.9, 117.9, 116.9, 79.9, 53.9, 39.9, 26.3;

IR (film): 3412, 3064, 1773, 1716, 1629, 1600, 1467, 1352, 1250, 1228, 1185, 1116, 994, 911, 813, 731, 703 cm^{-1};

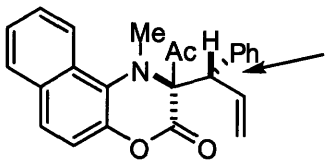
LR-MS (ES/APCI): calculated for $C_{24}H_{22}NO_3$ [M + H$^+$]: 372.2; found: 372.2;

2nd run: 32 mg (50%; 70% ee).

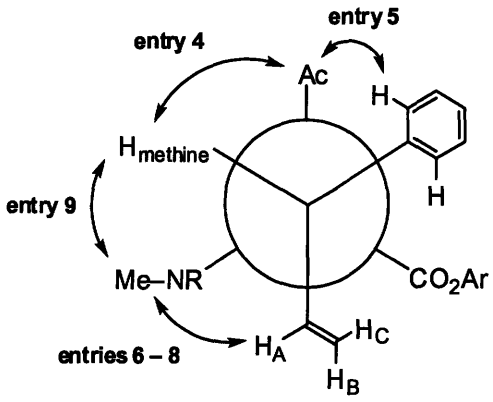
The relative stereochemistry of (+)-(*R,S*)-**3.8** was tentatively set by a 2D ^{1}H–^{1}H NOESY experiment, with a mixing time of 200 ms ($CDCl_3$, 500 MHz). The relative cross-peak volumes are listed in Table 3.4.

Table 3.4. Relative NOESY cross-peak volumes and corresponding Newman projection for (*R,S*)-**3.8**.

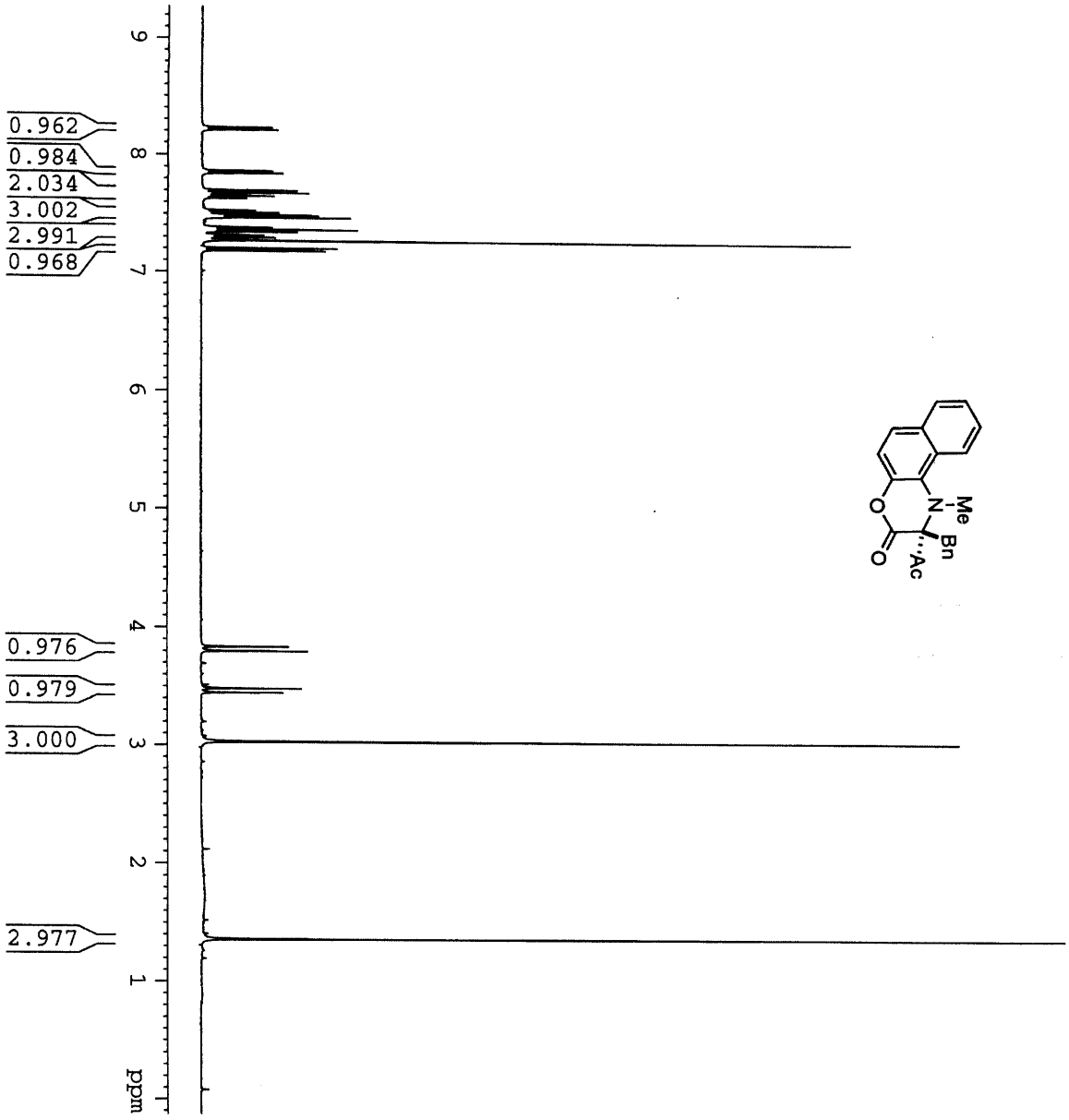
entry	left peak (ppm); tentative assignment	right peak (ppm); tentative assignment	relative cross-peak volume
1	1.68; acyl methyl	6.81; vinyl A	0.050
2		5.23; vinyl B	0.004
3		5.17; vinyl C	0.051
4		4.37; methine	0.381
5		7.53; *ortho*-Ph	0.373
6	2.98; N–Me	6.81; vinyl A	0.373
7		5.23; vinyl B	0.099
8		5.17; vinyl C	0.321
9		4.37; methine	1.000
10		7.53; *ortho*-Ph	0.163



(*R,S*)-**3.8**



IV. ^{1}H NMR Spectra of C–N Insertion Products

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PROCNO                        1

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TD                     65536
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FIDRES              0.126314 Hz
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RG                       256
DW                    60.400 usec
DE                     6.00 usec
TE                    293.2 K
D1                    1.00000000 sec
TD0                        1

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PL1                    0.00 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
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WDW                       EM
SSB                        0
LB                      0.30 Hz
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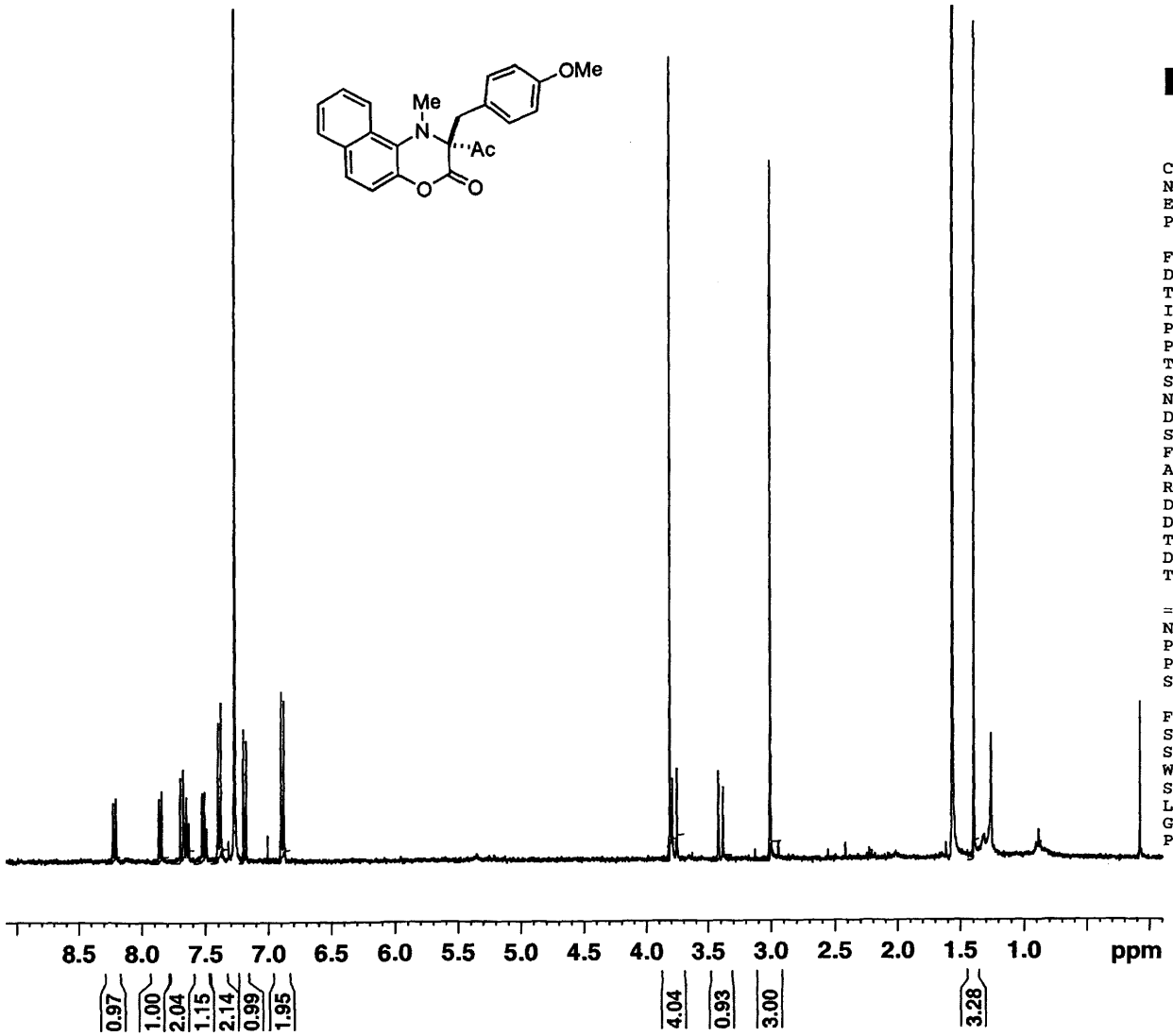

BRUKER

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PROCNO 1

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PULPROG zg30
TD 65536
SOLVENT CDCl3
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DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 406.4
DW 60.400 usec
DE 6.00 usec
TE 293.2 K
D1 1.00000000 sec
TD0 1

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P1 15.07 usec
PL1 0.00 dB
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F2 - Processing parameters
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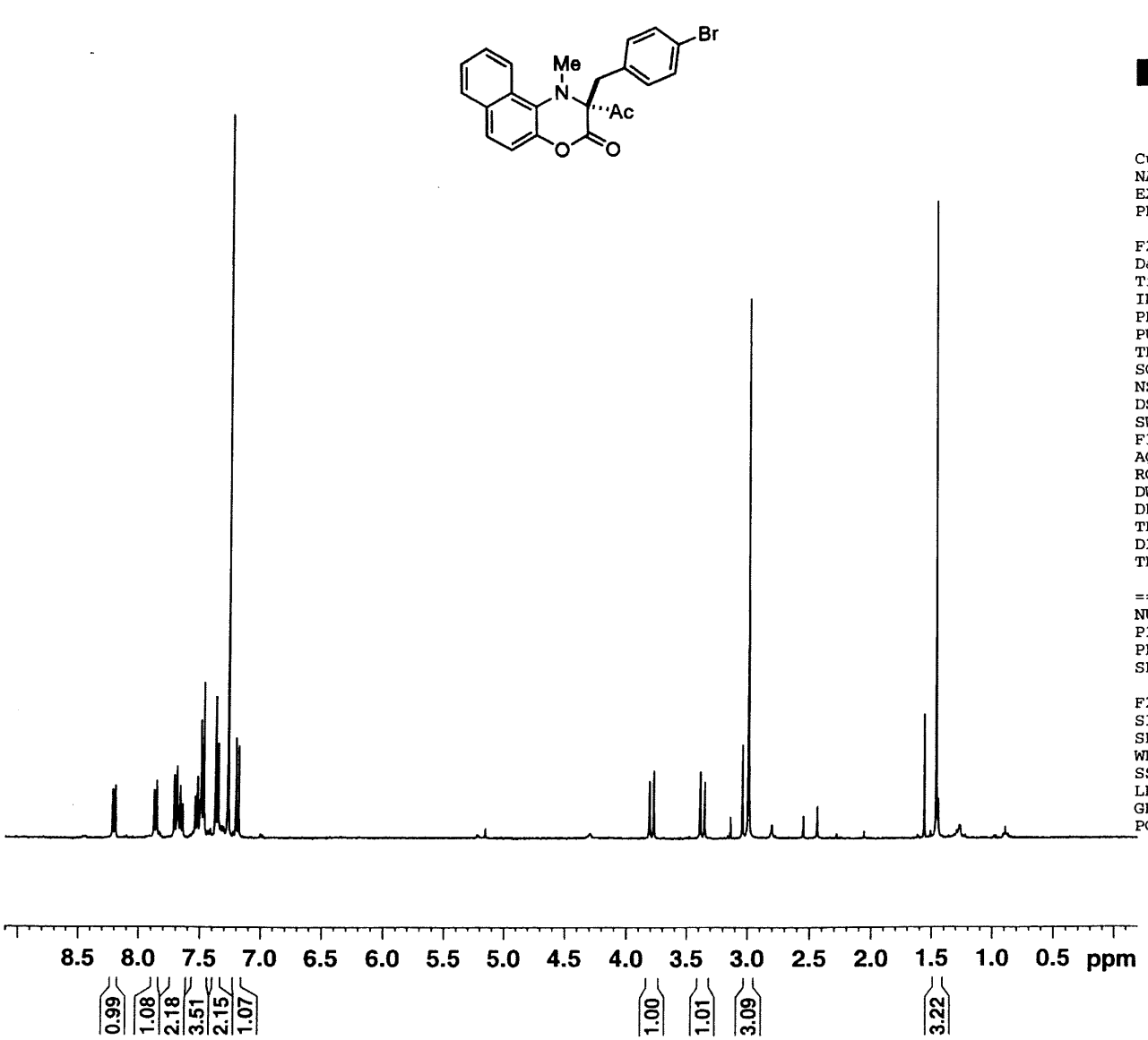
PC 1.00



BRUKER

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PROCNO 1

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SOLVENT CDCl3
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DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.00 usec
TE 293.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 15.07 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
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SF 400.1300054 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

STANDARD PROTON PARAMETERS
Solvent: CDCl3
Ambient temperature
INOVA-500 "rocky"
PULSE SEQUENCE
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Width 10000.0 Hz
8 repetitions
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DATA PROCESSING
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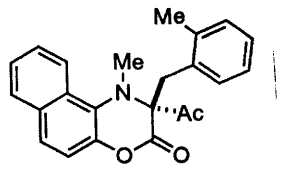
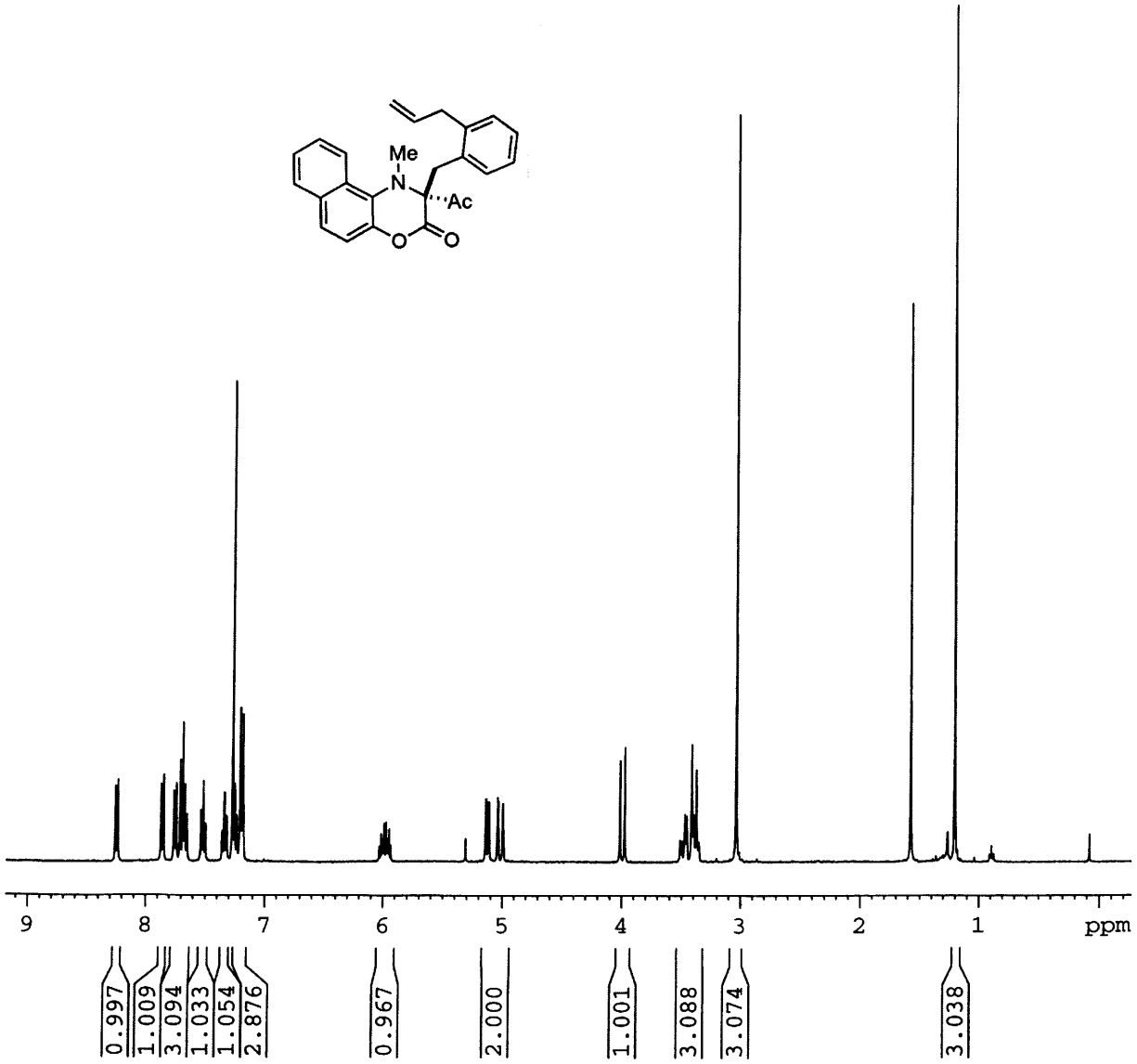
Total time 1 minute





BRUKER

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EXPNO 1
PROCNO 1

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FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
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DE 6.00 usec
TE 293.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
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PL1 0.00 dB
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F2 - Processing parameters
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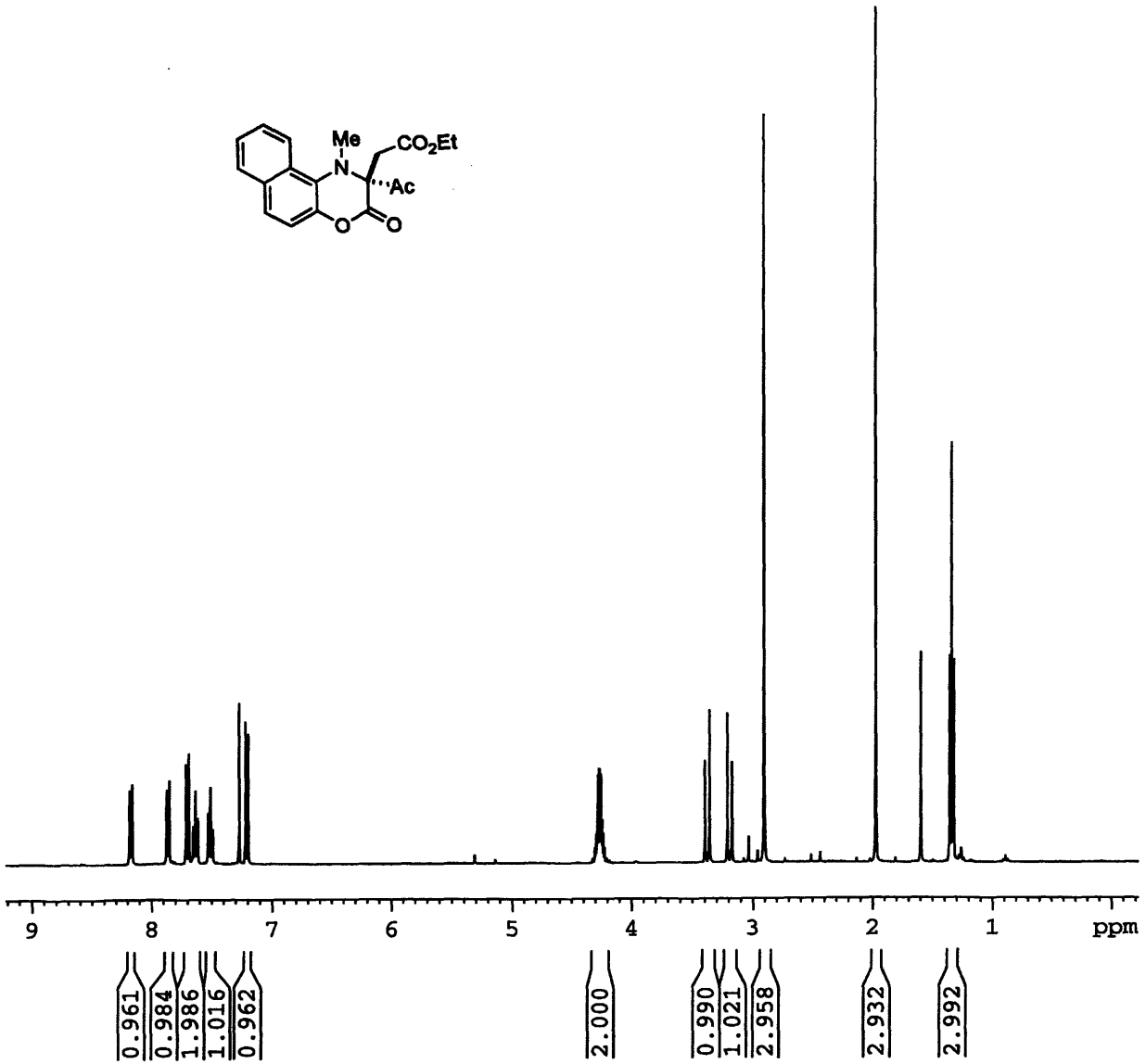

BRUKER

Current Data Parameters

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EXPNO	1
PROCNO	1

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PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	11
DS	2
SWH	8278.146 Hz
FIDRES	0.126314 Hz
AQ	3.9584243 sec
RG	362
DW	60.400 usec
DE	6.00 usec
TE	293.2 K
D1	1.00000000 sec
TD0	1

======== CHANNEL f1 ========

NUC1	1H
P1	14.00 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

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WDW	EM
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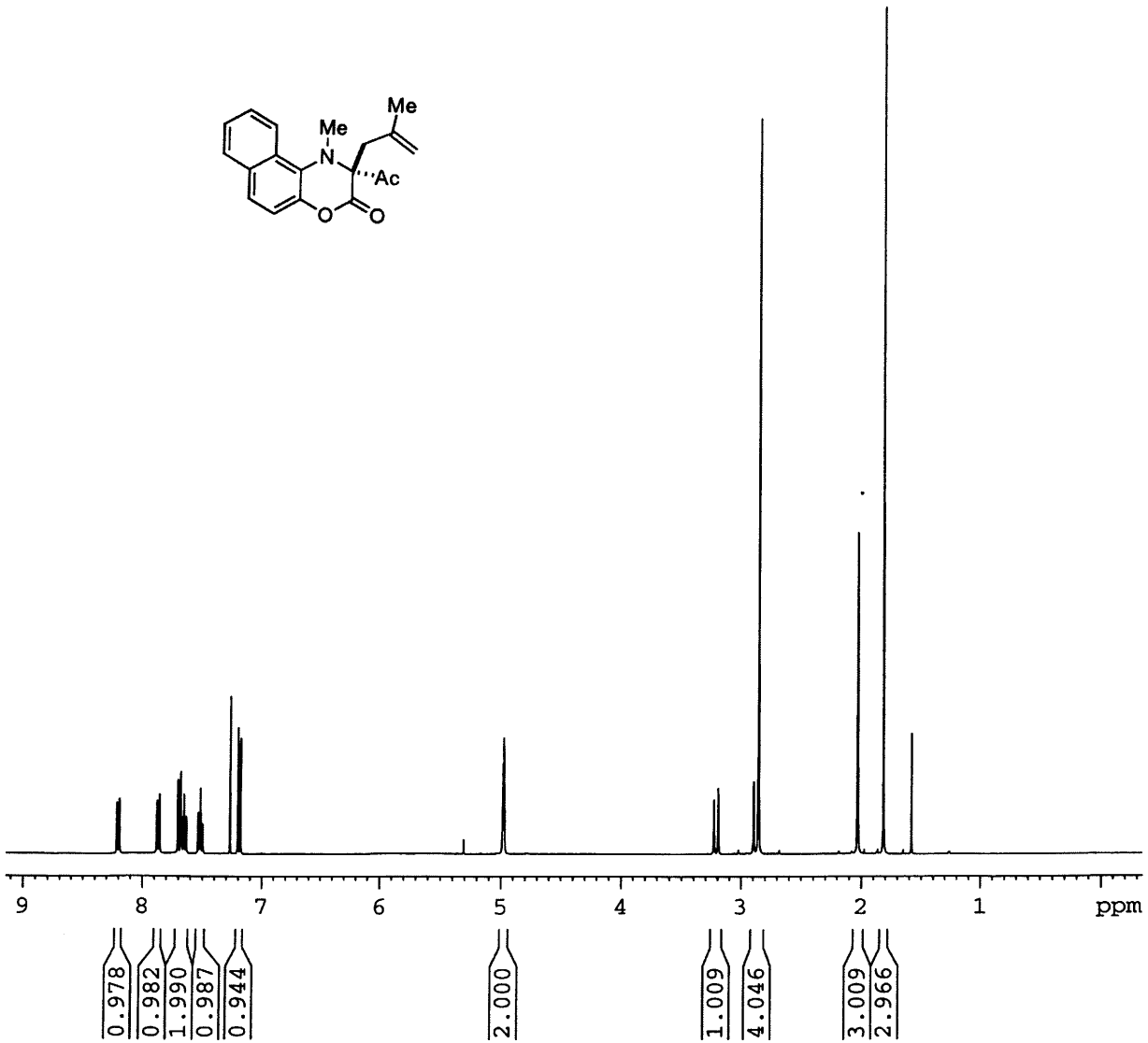

BRUKER

Current Data Parameters
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EXPNO 1
PROCNO 1

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TD 65536
SOLVENT CDCl3
NS 9
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 228.1
DW 60.400 usec
DE 6.00 usec
TE 293.2 K
D1 1.00000000 sec
TD0 1

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PL1 0.00 dB
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F2 - Processing parameters
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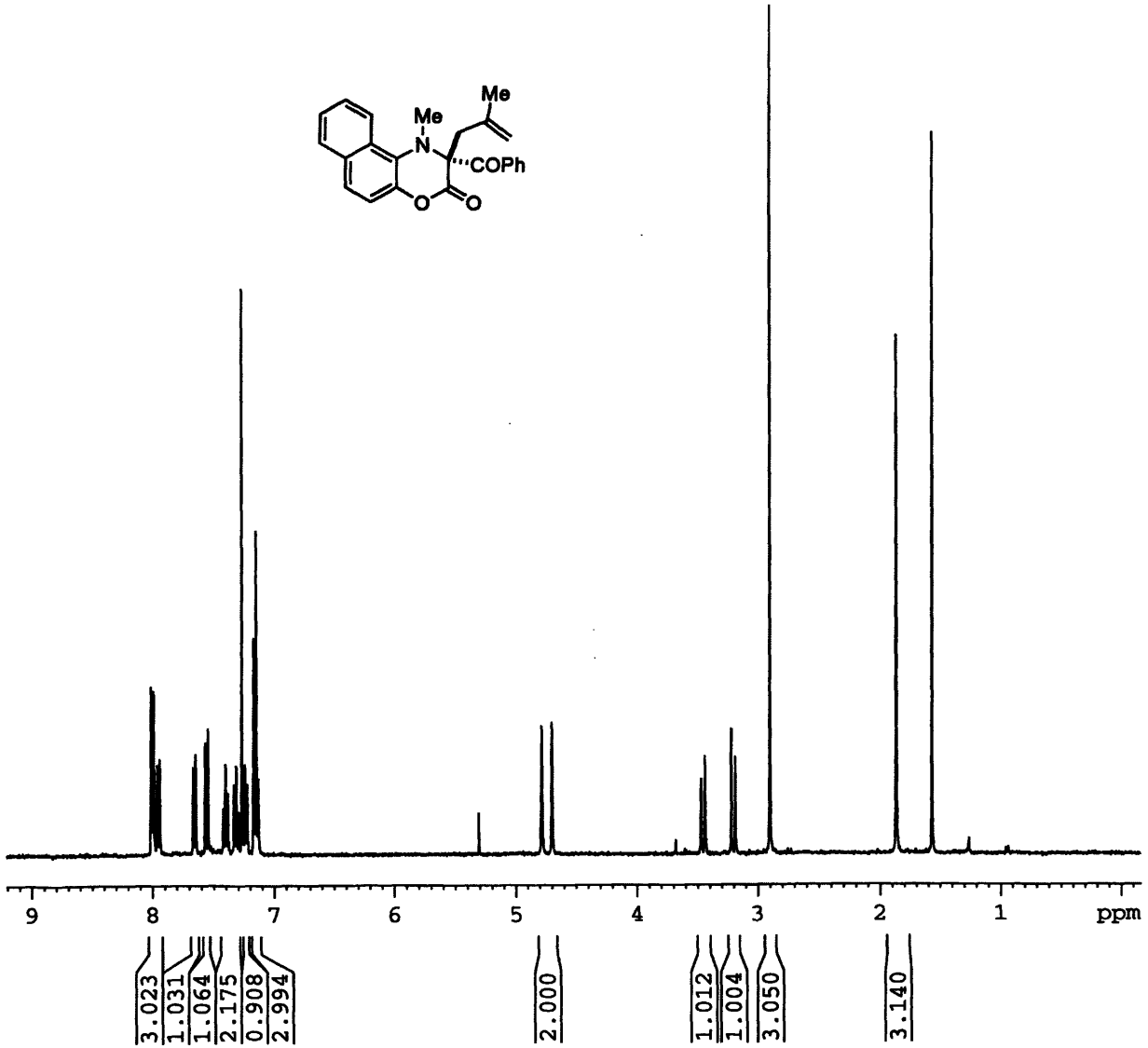

BRUKER

Current Data Parameters
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PROCNO 1

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INSTRUM spect
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SOLVENT CDCl3
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DS 2
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FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
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DE 6.00 usec
TE 293.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
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P1 14.00 usec
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SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300053 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

STANDARD PROTON PARAMETERS
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Ambient temperature
INOVA-500 "rocky"

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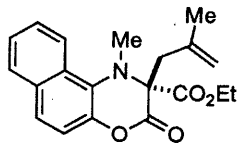
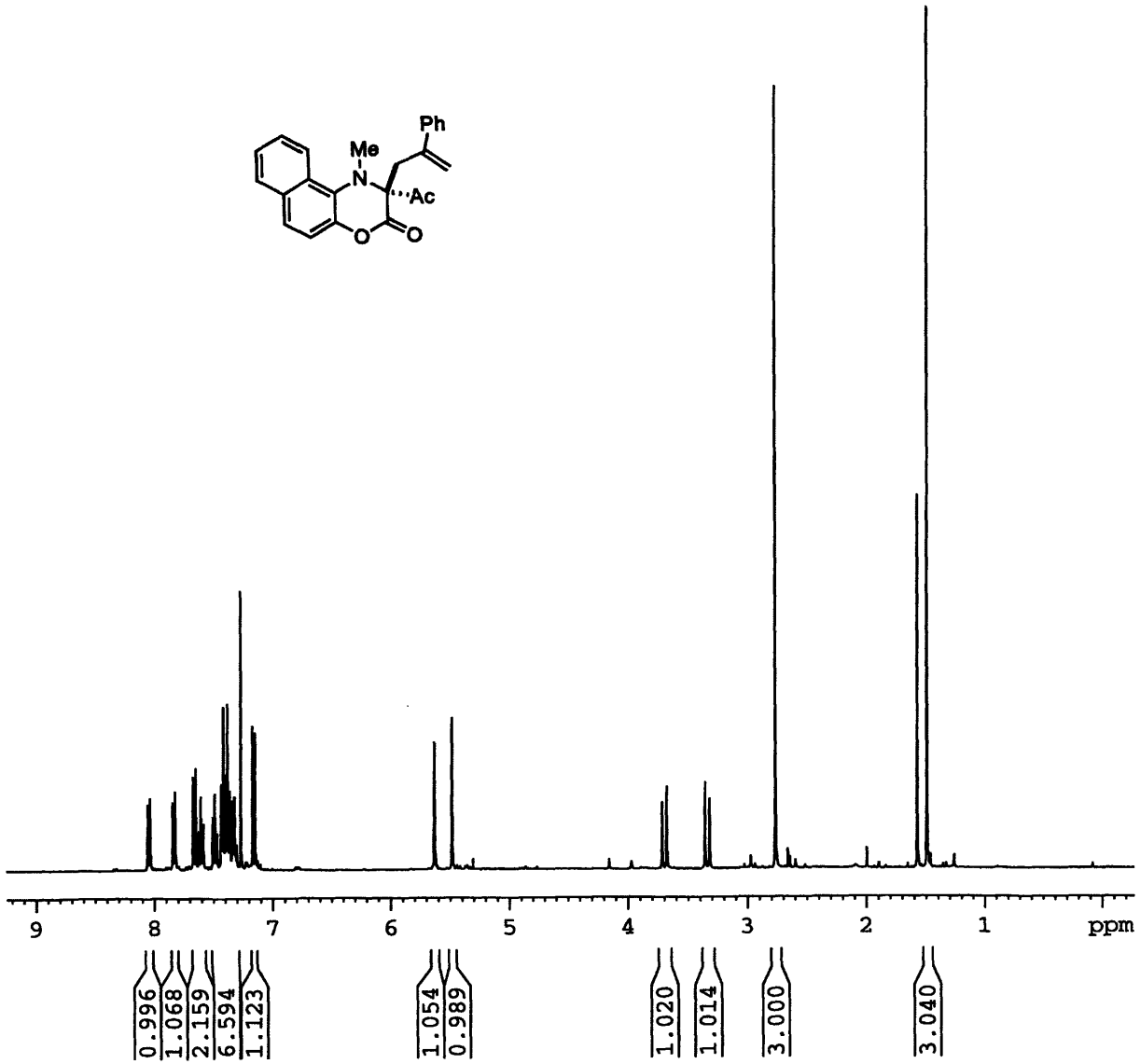
Total time 1 minute





BRUKER

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PROCNO                 1

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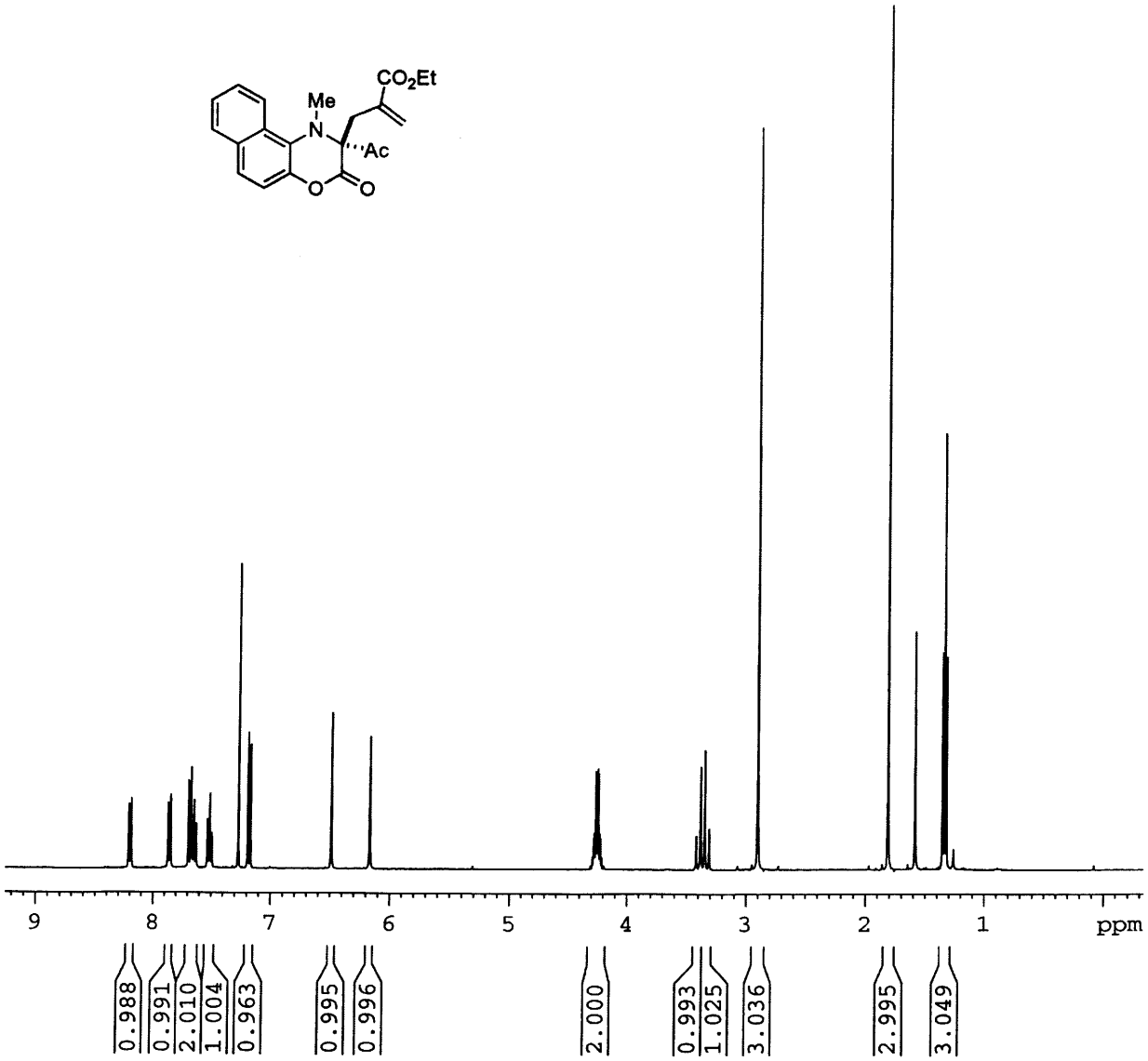
INSTRUM            spect
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                 65536
SOLVENT            CDCl3
NS                     9
DS                     2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                   362
DW                60.400 usec
DE                 6.00 usec
TE                293.2 K
D1           1.00000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  1H
P1                14.00 usec
PL1                0.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                 65536
SF           400.1300053 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                  1.00
```



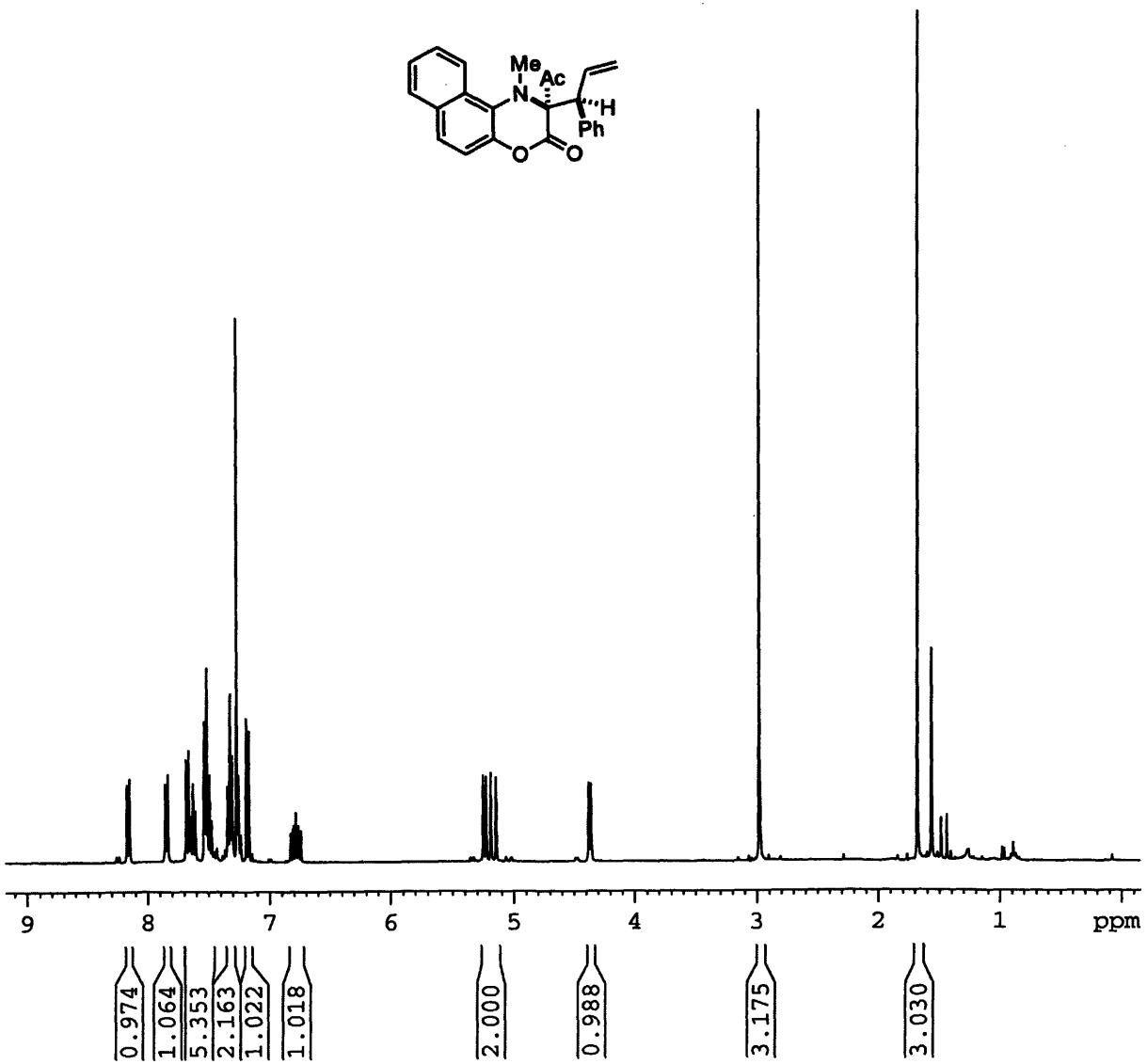
BRUKER

Current Data Parameters
NAME UnsatEthylester-Ac-PDT
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20080605
Time 17.22
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 9
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 287.4
DW 60.400 usec
DE 6.00 usec
TE 293.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 15.07 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300046 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.40



BRUKER

Current Data Parameters
NAME 6142d3d5
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20080407
Time 18.09
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 362
DW 60.400 usec
DE 6.00 usec
TE 293.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 15.07 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300052 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

V. X-Ray Crystallography

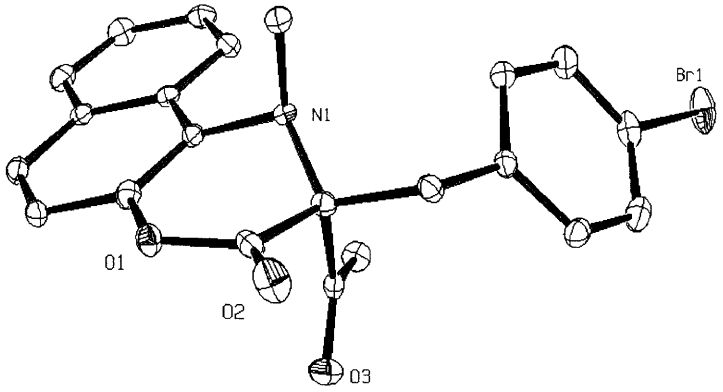


Figure 3.4. A portion of the unit cell, focusing on the insertion product (Table 3.2, entry 3).

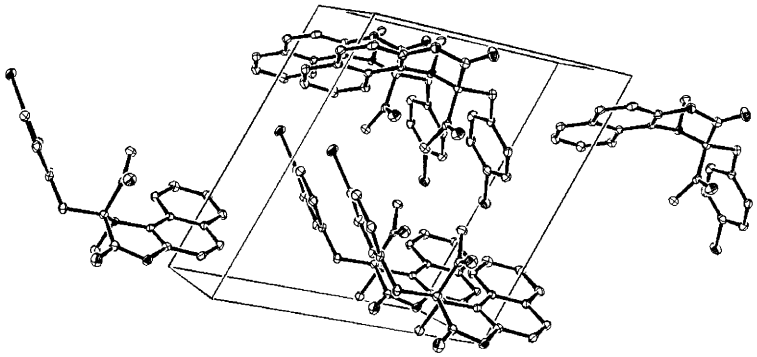


Figure 3.5. The entire unit cell (identification code 07054).

Table 1. Crystal data and structure refinement for 07054.

Identification code	07054	
Empirical formula	C22 H18 Br N O3	
Formula weight	424.28	
Temperature	90(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 11.299(2) Å	α= 90°.
	b = 7.0747(15) Å	β= 109.089(3)°.
	c = 12.317(3) Å	γ = 90°.
Volume	930.4(3) $Å^3$	
Z	2	
Density (calculated)	1.514 Mg/m^3	
Absorption coefficient	2.231 mm^{-1}	
F(000)	432	
Crystal size	0.50 x 0.15 x 0.10 mm^3	
Theta range for data collection	1.91 to 29.57°.	
Index ranges	-15<=h<=15, -9<=k<=9, -17<=l<=17	
Reflections collected	19192	
Independent reflections	5157 [R(int) = 0.0469]	
Completeness to theta = 29.57°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8077 and 0.4016	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5157 / 1 / 246	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0320, wR2 = 0.0798	
R indices (all data)	R1 = 0.0348, wR2 = 0.0808	
Absolute structure parameter	0.022(6)	
Largest diff. peak and hole	0.839 and -0.517 $e.Å^{-3}$	

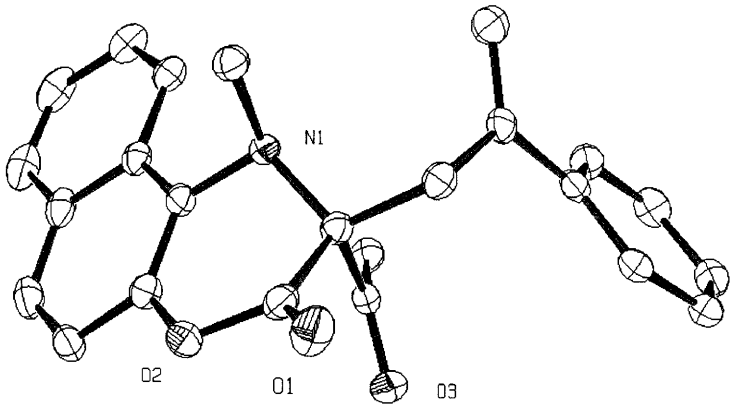


Figure 3.6. A portion of the unit cell, focusing on the insertion product (Table 3.3, entry 4).

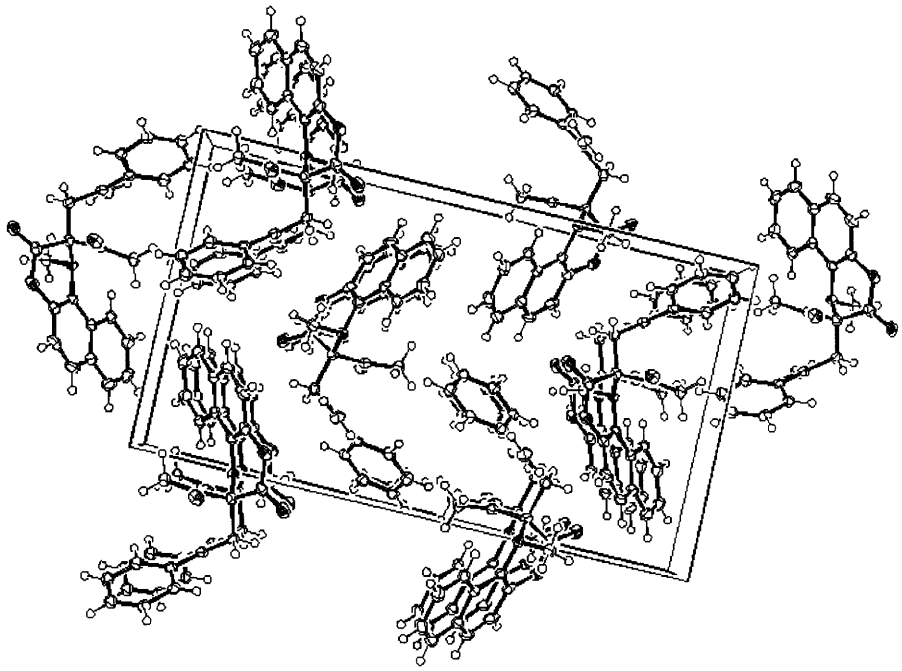
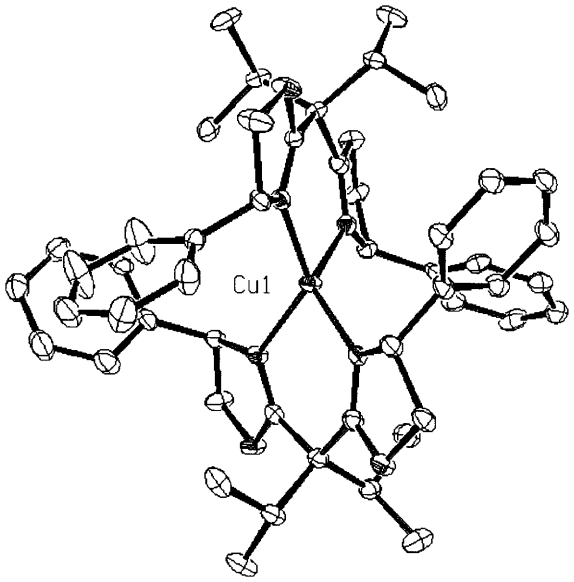
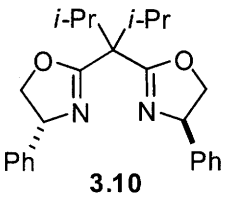


Figure 3.7. The entire unit cell (identification code d08020).

Table 1. Crystal data and structure refinement for d08020.

Identification code	d08020	
Empirical formula	C24 H21 N O3	
Formula weight	371.42	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 6.8367(2) Å	α= 90°.
	b = 12.3571(4) Å	β= 90°.
	c = 22.1285(7) Å	γ = 90°.
Volume	1869.46(10) $Å^3$	
Z	4	
Density (calculated)	1.320 Mg/m^3	
Absorption coefficient	0.697 mm^{-1}	
F(000)	784	
Crystal size	0.49 x 0.11 x 0.09 mm^3	
Theta range for data collection	4.00 to 67.68°.	
Index ranges	-8<=h<=8, -14<=k<=14, -26<=l<=26	
Reflections collected	34755	
Independent reflections	3383 [R(int) = 0.0301]	
Completeness to theta = 67.68°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9399 and 0.7265	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3383 / 0 / 255	
Goodness-of-fit on F^2	1.036	
Final R indices [I>2sigma(I)]	R1 = 0.0268, wR2 = 0.0694	
R indices (all data)	R1 = 0.0273, wR2 = 0.0697	
Absolute structure parameter	0.01(16)	
Largest diff. peak and hole	0.197 and -0.139 $e.Å^{-3}$	





3.10

Figure 3.8. A Portion of the unit cell, focusing on $Cu^{I}(\mathbf{3.10})_2$. The corresponding triflate counterions are shown in Figure 3.9.

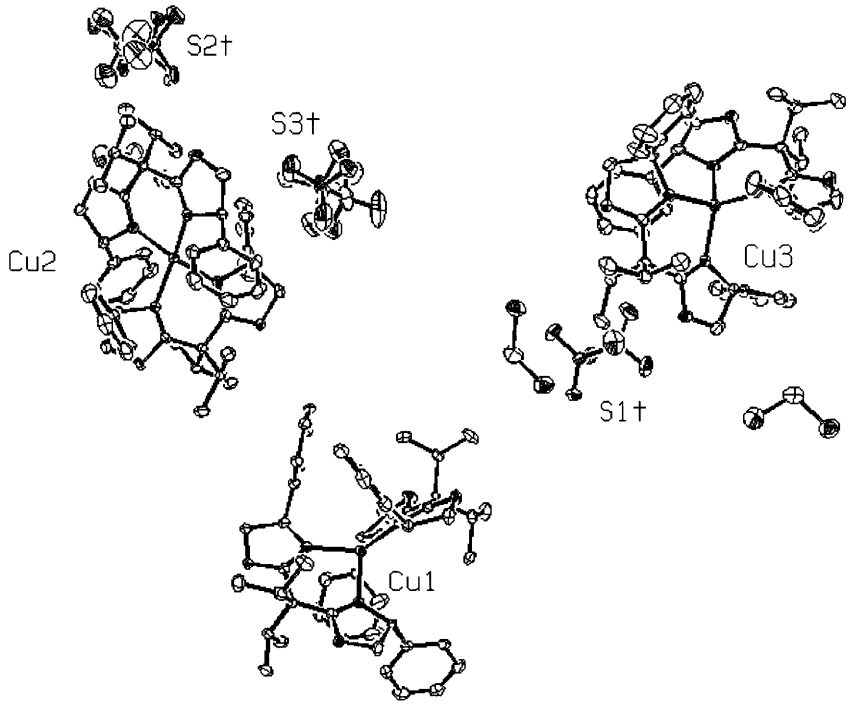


Figure 3.9. The entire unit cell: 3 × $Cu^{I}(\mathbf{3.10})_2$, 3 × OTf, and 2 × CH_2Cl_2 (identification code 08081).

Table 1. Crystal data and structure refinement for 08081.

Identification code	08081	
Empirical formula	C52 H62 Cl2 Cu F3 N4 O7 S	
Formula weight	1078.56	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 12.1014(12) Å	α= 78.616(2)°.
	b = 12.1428(12) Å	β= 85.976(2)°.
	c = 30.373(3) Å	γ = 61.855(2)°.
Volume	3856.7(7) $Å^3$	
Z	3	
Density (calculated)	1.393 Mg/m^3	
Absorption coefficient	0.635 mm^{-1}	
F(000)	1692	
Crystal size	0.47 x 0.36 x 0.07 mm^3	
Theta range for data collection	1.37 to 29.57°.	
Index ranges	-16<=h<=16, -16<=k<=16, -42<=l<=42	
Reflections collected	85656	
Independent reflections	41010 [R(int) = 0.0463]	
Completeness to theta = 29.57°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9569 and 0.7545	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	41010 / 943 / 1973	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I)]	R1 = 0.0753, wR2 = 0.1900	
R indices (all data)	R1 = 0.0909, wR2 = 0.1994	
Absolute structure parameter	0.045(9)	
Largest diff. peak and hole	1.723 and -1.240 $e.Å^{-3}$	

Curriculum Vitae

Education

Ph.D., Organic Chemistry, Massachusetts Institute of Technology, 2003 – 2008
B.S., Chemistry, University of Texas at Austin, 1999 – 2003
B.S., Mathematics, University of Texas at Austin, 1999 – 2003

Awards

Merck Summer Fellowship, 2007
Norman Hackerman Endowed Presidential Scholarship, 2003
University Co-op Research Fellowship, 2003 and 2002
Chemistry Faculty-Regents Scholarship, 2002 and 2001
University Honors List, 2002 and 2000
Marie P. Smith Scholarship, 2001
Advanced Placement Scholar with Honors, 1999

Publications

(4) **Kinetic Resolution of Indolines by a Nonenzymatic Acylation Catalyst**
J. Am. Chem. Soc. **2006**, *128*, 14264–14265
Arp, F. O.; Fu., G. C.

(3) **Catalytic Enantioselective Negishi Reactions of Racemic Secondary Benzylic Halides**
J. Am. Chem. Soc. **2005**, *127*, 10482–10483
Arp, F. O.; Fu., G. C.

Highlighted in the following article:

• **Bond with a Chemist over the Search for Asymmetry in Reactions**
Nature **2006**, *440*, 259
MacMillan, D. W. C.

(2) **Facile Syntheses of Quarter-, Penta-, and Sexipyrroles**
Org. Lett. **2005**, *7*, 1887–1890
Sessler, J. L.; Aguilar, A.; Sanchez-Garcia, Seidel, D.; Kohler, T.; Arp, F.; Lynch, V. M.

(1) **Formation and Properties of Cyclo[6] and Cyclo[7]pyrrole**
J. Am. Chem. Soc. **2003**, *125*, 6872–6873
Kohler, T.; Seidel, D.; Lynch, V.; Arp, F. O.; Ou, Z.; Kadish, K. M.; Sessler, J. L.