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Tandem Processes Identified from Reaction Screening: Nucleophilic Addition to Aryl *N*-Phosphinylimines Employing La(III)-TFAA Activation

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Abstract: Reaction screening of nucleophilic reaction partners for addition to *N*-diphenylphosphinylimines employing lanthanum(III) triflate as a catalyst and trifluoroacetic anhydride (TFAA) as an activator is reported. A number of tandem processes leading to novel chemotypes including *aza*-Prins/intramolecular Friedel−Crafts annulations have been identified, and both reaction scope and mechanism further investigated.

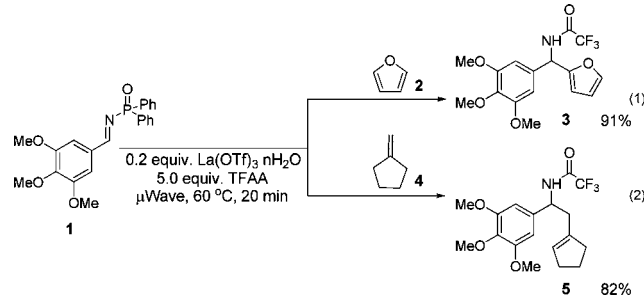
Introduction

We recently reported Friedel−Crafts and *aza*-ene reactions between *N*-phosphinylimines[1] and carbon nucleophiles using a $La(OTf)_3 \cdot nH_2O$/TFAA activation protocol (Scheme 1).[2] For example, treatment of *N*-diphenylphosphinylimine **1** and furan **2** with trifluoroacetic anhydride (TFAA) and catalytic $La(OTf)_3 \cdot nH_2O$ under microwave irradiation led to production of Friedel−Crafts product **3**. Alternatively, use of methylenecyclopentene **4** as a nucleophile led to homoallylic amide **5** in good yield (82%). To study the scope and limitations of these reactions and expand their utility, we undertook reaction screening[3] of a panel of nucleophilic reaction partners. Herein, we report the results of this study, identification of a number of tandem reaction processes producing novel chemotypes, and follow-up studies to investigate the reaction scope and mechanism.

Results and Discussion

For the reaction screen, 33 nucleophilic reaction partners were selected with a number of entries based on reported imino-ene reactions (Figure 1).[4] Reactions were conducted using *N*-phosphinylimine **1** (0.015 mmol) as a substrate, $La(OTf)_3 \cdot nH_2O$ (20 mol %), 5.0 equiv of TFAA (0.075 mmol), and 100 μL of CH_3CN under microwave irradiation at 80 °C.[5] After the reaction (10 min), the mixtures were filtered and evaluated using ultraperformance liquid chromatography (UPLC)-MS/ELS.[6] Based on analytical data,[5] decisions to conduct scale-up reactions to elucidate products were made. Reactions were scaled up 10-fold (0.15 mmol), and the products isolated. Results of initial reaction screening indicated that 17 of 33 reactions afforded major products; 9 of 17 reactions afforded products corresponding to adducts between the *N*-phosphinylimine substrate and alkene reaction partner. Based on the screening results, products were grouped into three major classes. The first reaction type identified in the screen involved *aza*-Friedel−Crafts reactions (Table 1).[7] Thiophene **6** afforded the *aza*-Friedel−Crafts product **7** (Table 1, entry 1) as expected[7d] in contrast to pyrrole which was unreactive under the reaction conditions (data not shown). Interestingly, 2-methylindene **8** also provided *aza*-Friedel−Crafts product **9** in 62% yield (Table 1, entry 2). Cyclopropylbenzene **12** provided product **13** in 33% yield along with the cyclic product **14** (6%). In this case, cyclopropane ring cleavage of **12** to afford *trans*-β-methylstyrene occurred *in situ* under

Scheme 1. Friedel−Crafts and *Aza*-ene Reactions with **1**



(1) Weinreb, S. M.; Orr, R. K. *Synthesis* **2005**, 1205.
(2) Ong, W. W.; Beeler, A. B.; Kesavan, S.; Panek, J. S.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2007**, *46*, 7470.
(3) Beeler, A. B.; Su, S.; Singleton, C. A.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413.
(4) For examples of imino-ene reactions, see: (a) Drury, W. J., III.; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. (b) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury, W. J., III.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. (c) Caplan, N. A.; Hancock, F. E.; Bulman, P. C.; Hutchings, G. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1685. (d) Aburel, P. S.; Zhuang, W.; Hazell, R. G.; Jorgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2344. (e) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254.
(5) See Supporting Information for complete experimental details.
(6) (a) Mazzeo, J. R.; Neue, U. D.; Kele, M.; Plumb, R. S. *Anal. Chem.* **2005**, *77*, 460 A. (b) Nováková, L.; Matysová, L.; Solich, P. *Talanta* **2006**, *68*, 908.
(7) For recent examples of *aza*-Friedel−Crafts alkylations, see: (a) Saaby, S.; Bayón, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352. (b) Luo, Y.; Li, C.-J. *Chem. Commun.* **2004**, 1930. (c) Esquivisas, J.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 629. (d) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621. (e) Liu, C.-R.; Li, M.-B.; Yang, C.-F.; Tian, S.-K. *Chem. Commun.* **2008**, 1249.

10.1021/ja100346w

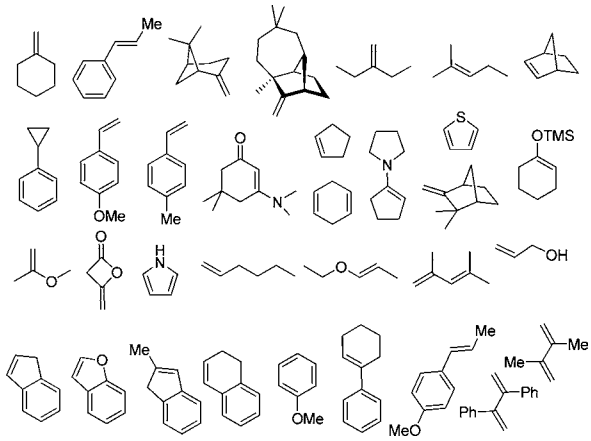
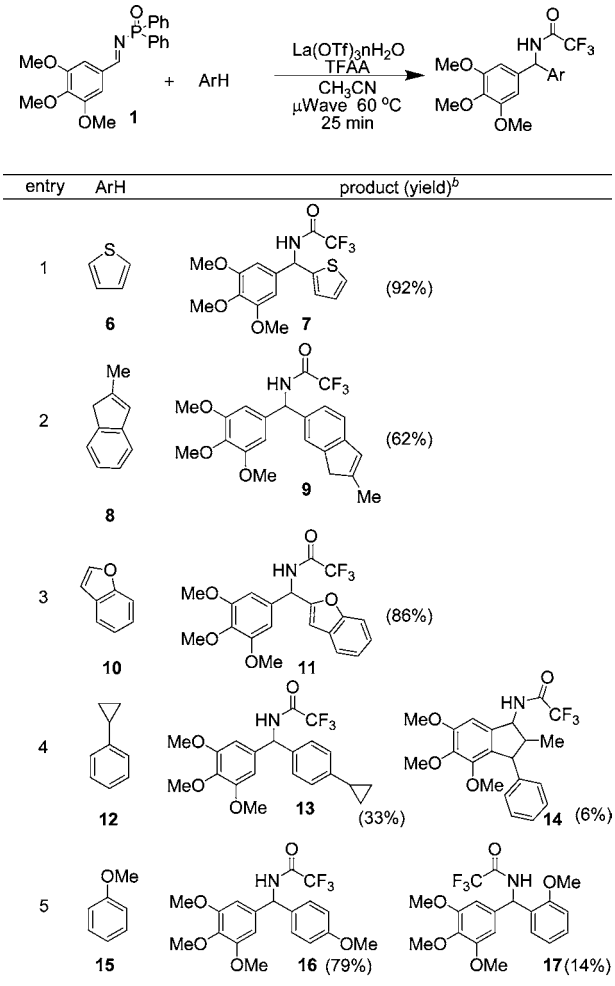


Figure 1. Reaction Partners.

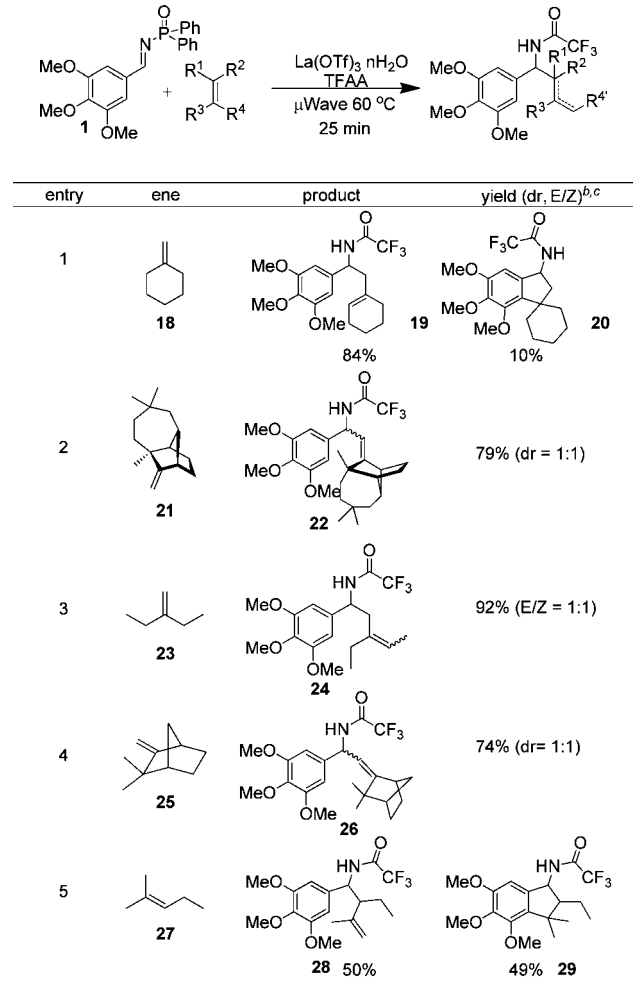
Table 1. *Aza*-Friedel−Crafts Reactions[a]



[a] *N*-Phosphinylimine **1** (0.152 mmol), ArH (0.76 mmol, 5 equiv), and TFAA (0.76 mmol, 5 equiv) were incubated with 0.038 mmol (25 mol %) of $La(OTf)_3 \cdot nH_2O$ in 0.7 mL of CH_3CN. [b] Isolated yield after silica gel chromatography.

the reaction conditions; subsequent reaction with *N*-phosphinylimine **1** afforded indane product **14**, the same product observed employing *trans*-β-methylstyrene (*vide infra*).[8] In addition, anisole **15** led to Friedel−Crafts addition to afford the *para*- and *ortho*- isomers **16** and **17** (Table 1, entry 5).

Table 2. *Aza*-ene Reactions[a]



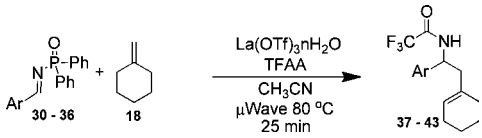
[a] *N*-Phosphinylimine **1** (0.152 mmol), alkene (0.76 mmol, 5 equiv), and TFAA (0.76 mmol, 5 equiv) were used with 0.038 mmol (25 mol %) of $La(OTf)_3 \cdot nH_2O$ in 0.7 mL of CH_3CN. [b] Isolated yield after silica gel chromatography. [c] Dr values and *E*/*Z* ratios determined by ^1H NMR analysis.

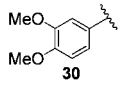
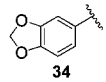
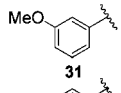
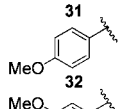
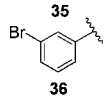
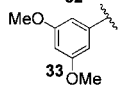
Second, a number of alkenes afforded *aza*-ene products in good to excellent yields (Table 2). Reactions utilizing methylene cyclohexane (**18**) and 2-methyl-2-propene (**27**) afforded cyclic products **20** and **29** which were obtained in 10% and 49% yields, respectively, along with *aza*-ene products **19** and **28** (Table 2, entries 1 and 5). These observations suggested that reactions may proceed through a stepwise *aza*-Prins[9]-intramolecular Friedel−Crafts cyclization which may be operative if the

(8) For formation of *trans*-β-methylstyrene from cyclopropyl-benzene, see: Mochalov, S. S.; Gazzaeva, R. A.; Fedotov, A. N.; Shabarov, Y. S.; Zefirov, N. S. *Chem. Heterocycl. Compd.* **2003**, *39*, 794.

(9) For aza-Prins reactions, see: (a) Dobbs, A. P.; Guesné, S. J. J.; Coles, S. J.; Hursthouse, M. B. *Synlett* **2003**, 1740. (b) Hanessian, S.; Tremblay, M.; Petersen, J. F. W. *J. Am. Chem. Soc.* **2004**, *126*, 6064. (c) Liu, J.; Hsung, R. P.; Peters, S. D. *Org. Lett.* **2004**, *6*, 3989. (d) Hanessian, S.; Tremblay, M.; Marzi, M.; Del Valle, J. R. *J. Org. Chem.* **2005**, *70*, 5070. (e) Armstrong, A.; Shanahan, S. E. *Org. Lett.* **2005**, *7*, 1335. (f) Sarkar, T. K.; Hazra, A.; Gangopadhyay, P.; Panda, N.; Slanina, Z.; Lin, C.-C.; Chen, H.-T. *Tetrahedron* **2005**, *61*, 1155. (g) Shimizu, M.; Baba, T.; Toudou, S.; Hachiya, I. *Chem. Lett.* **2007**, *36*, 12. (h) Murty, M. S. R.; Ram, K. R.; Yadav, J. S. *Tetrahedron Lett.* **2008**, *49*, 1141. (i) Yadav, J. S.; Reddy, B. V. S.; Chaya, D. N.; Kumar, G. G. K. S. N.; Aravind, S.; Kunwar, A. C.; Madavi, C. *Tetrahedron Lett.* **2008**, *49*, 3330. (j) Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864.

Table 3. Evaluation of *N*-Phosphinylimine Substitution[a]



entry	phosphinylimine	yield	entry	phosphinylimine	yield
1	 **30**	92% **37**	5	 **34**	96% **41**
2	 **31**	95% **38**	6	 **35**	96% **42**
3	 **32**	92% **39**	7	 **36**	74% **43**
4	 **33**	18% **40**			

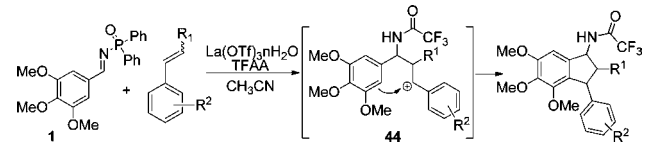
[a] 2 equiv of **18**, 1.5 equiv of TFAA, and 25 mol % $La(OTf)_3 \cdot nH_2O$ in 0.7 mL of CH_3CN.

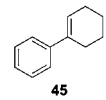
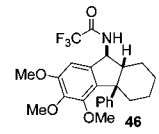
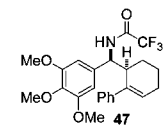
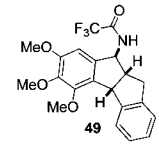
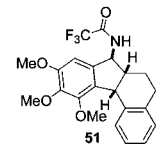
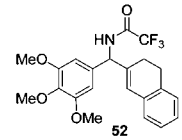
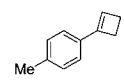
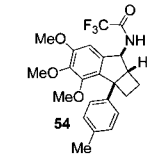
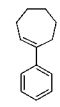
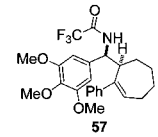
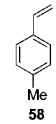
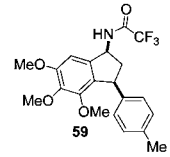
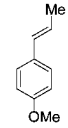
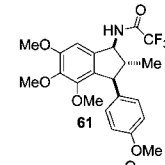
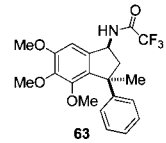
carbocation intermediate generated after the initial imino-ene reaction was appropriately stabilized.[10] Although tandem Prins/Friedel−Crafts reactions have precedent,[11] successive use of *aza*-Prins and intramolecular Friedel−Crafts reactions are less well developed.[9]

As part of the study, we also evaluated a series of *N*-phosphinylimines **30**−**36** using methylenecyclohexane (**18**) as an alkene partner (Table 3). Using standard conditions, *aza*-Prins reactions proceeded in high yield to afford adducts **37**−**43** with the exception of 3,5-dimethoxy-*N*-phosphinylimine (**33**) (Table 3, entry 4). The major product in this case was the hydrolysis product 3,5-dimethoxybenzaldehyde. In all cases, spirocyclic ring formation (*cf.* Table 2, entry 1) was not observed.

Our reaction screening results also revealed that styrenic reaction partners underwent tandem *aza*-Prins/Friedel−Crafts reactions affording polycyclic scaffolds, likely due to aromatic-stabilized carbocationic intermediates (**44**, Table 4) which facilitate the Friedel−Crafts cyclization. Accordingly, we further evaluated various styrenic partners. Follow-up reactions were initially carried out employing conditions utilized for the reaction screen (*cf.* Table 2).[12] Reaction with 1-phenyl-1-cyclohexene (**45**) afforded both the cyclized product **46** (70% yield, dr = 8:1) in which the ring junction proton is *syn* to the trifluoroacetamide and the uncyclized, trisubstituted alkene **47** (29% yield, dr = 10:1) favoring the "*anti*" relative stereochemistry (Table 4, entry 1).[5,13] Lowering the reaction temperature to 0 °C had a strong effect on the diastereoselectivity of cyclized and uncyclized products (dr = 17:1 and >20:1, respectively).

Table 4. Tandem *Aza*-Prins/Friedel−Crafts Reactions



entry	alkene	products[a,b,c]	
1	 **45**	 **46** 70% (dr = 8 : 1)[c] 62% (dr = 17 : 1)[d]	 **47** 29% (dr = 10 : 1) 26% single diastereomer
2	 **48**	 **49** 68% (dr = 4 : 1)[d] 78% (dr = 4 : 1)[e]	
3	 **50**	 **51** 83% (dr = 5 : 1)[d] 79% (dr = 5.6 : 1)[e]	 **52** 15% 20%
4	 **53**	 **54** 82% (dr = 1 : 1.7)[d] 90% (dr = 1 : 1)[e]	
5	 **55**	 **56** 90% (dr = 1.7 : 1)[e]	 **57** 5% single dr
6	 **58**	 **59** 83% (dr = 1 : 1)[f]	
7	 **60**	 **61** 80% (dr = 1.2 : 1)[f]	
8	 **62**	 **63** 66% (dr = 1.5 : 1)[f]	

[a] Isolated yields. [b] Major diastereomer shown. [c] Diastereomeric ratios determined by ^{1}H NMR analysis. [d] Styrene (1.2 equiv), μWave, 80 °C, 25 min. [e] Styrene (1.2 equiv), 0 °C, 12 h. [f] Styrene (1.2 equiv), μWave, 60 °C, 25 min.

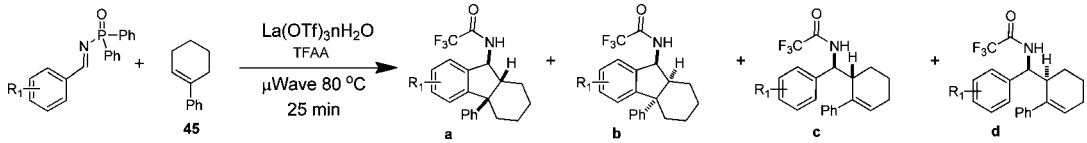
Reaction with indene (**48**) (entry 2) afforded the cyclized tetrahydroindanoindane derivative **49** exclusively in moderate diastereoselectivity (71% yield, dr = 4:1). Reaction with 1,2-dihydronaphthalene (**50**) affords a mixture of tetracycle **51** in 83% yield (dr = 5:1) along with the acyclic, conjugated product

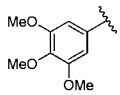
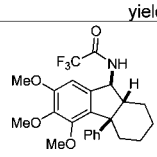
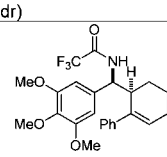
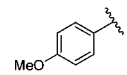
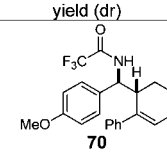
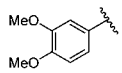
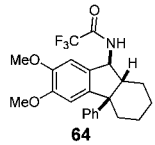
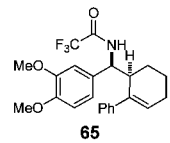
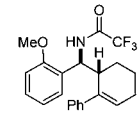
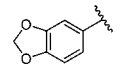
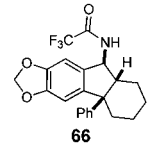
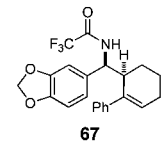
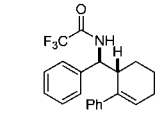
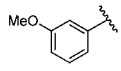
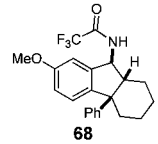
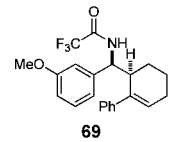
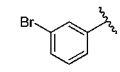
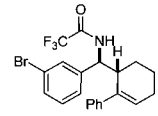
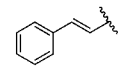
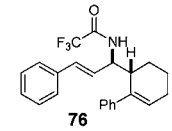
(10) For the formal [3 + 2] addition of alkenes to benzhydrol cations, see: (a) Lantaño, B.; Aguirre, J. M.; Finkielsztein, L.; Alesso, E. N.; Brunet, E.; Moltrasio, G. Y. *Synth. Commun.* **2004**, *34*, 625. (b) Lantaño, B.; Aguirre, J. M.; Ugliarolo, E. A.; Benegas, M. L.; Moltrasio, G. Y. *Tetrahedron* **2008**, *64*, 4090.

(11) (a) Basavaiah, D.; Sharada, D. S.; Veerendhar, A. *Tetrahedron Lett.* **2004**, *45*, 3081. (b) Yang, X.-F.; Wang, M.; Zhang, Y.; Li, C.-J. *Synlett* **2005**, *12*, 1912. (c) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176. (d) Basavaiah, D.; Reddy, K. R. *Org. Lett.* **2007**, *9*, 57.

(12) Attempts to reduce catalyst loading resulted in significantly lower yields. For example, use of 10 mol% $La(OTf)_3$ afforded a 23% isolated yield of **46**.

Table 5. Use of Alternative *N*-Phosphinylimines[a,b]



entry	phosphinylimine	solvent	yield (dr)		entry	phosphinylimine	solvent	yield (dr)	
1	 **1**		 **46**	 **47**	5	 **32**	no cyclic products	 **70**	
		CH_3CN	70% (dr a/b = 8 : 1)	29% (dr c/d = 1 : 10.1)			CH_3CN	93% (dr c/d = 1 : 1)	
		CH_3NO_2	76% (dr a/b = 5 : 1)	17% single dr			CH_3NO_2	60% (dr c/d = 2.3 : 1)	
		CH_3NO_2 0 °C	76% (dr a/b = 5 : 1)	17% single dr					
2	 **30**		 **64**	 **65**	6	 **71**	no cyclic products	 **72**	
		CH_3CN	47% (dr a/b = 17.3 : 1)	46% (dr c/d = 1 : 2.5)			CH_3CN	—	
		CH_3NO_2	80% (dr a/b = 6.3 : 1)	trace			CH_3NO_2	79% (dr c/d = 1.6 : 1)	
		CH_3NO_2 0 °C	64% (dr a/b = 12.6 : 1)	22% single dr					
3	 **34**		 **66**	 **67**	7	 **35**	no cyclic products	 **73**	
		CH_3CN	23% single dr	68% (dr c/d = 1 : 1.9)			CH_3CN	86% (dr c/d = 1.6 : 1)	
		CH_3NO_2	71% single dr	15% (dr c/d = 1 : 3.2)			CH_3NO_2	79% (dr c/d =1.6 : 1)	
		CH_3NO_2 r.t.	55% single dr	38% (dr c/d = 1 : 3.9)					
4	 **31**		 **68**	 **69**	8	 **36**	no cyclic products	 **74**	
		CH_3CN	44% (dr a/b = 2.4 : 1)	48% (dr c/d = 1 : 1)			CH_3CN	80% (dr c/d = 1.9 : 1)	
		CH_3NO_2	61% (dr a/b = 2.1 : 1)	24% (dr c/d = 1 : 1.5)			CH_3NO_2	92% (dr c/d = 3 : 1)	
		CH_3NO_2 0 °C	68% (dr a/b = 2.8 : 1)	22% (dr c/d = 1 : 2.5)					
					9	 **75**		 **76**	
							CH_3CN	95% (dr c/d = 1 : 1)	
							CH_3NO_2	92% (dr c/d = 1 : 1)	

[a] *N*-Phosphinylimine (0.152 mmol), $La(OTf)_3 \cdot nH_2O$ (25 mol %), TFAA (1.5 equiv), and 2.0 equiv of 1-phenyl-1-cyclohexene in 0.7 mL of solvent. Reaction time at rt or 0 °C was 12 h. [b] Relative stereochemistry of the major diastereomer shown.

52 (15% yield) (entry 3). Use of 1-(4-methylphenyl)-1-cyclobutene (**53**)[14] afforded the benzobicyclo [3.2.0] derivative **54** in good yield but in low diastereoselectivity (82% yield, dr = 1.7:1, entry 4) slightly favoring the "*syn*" product. Reaction with 1-phenyl-1-cycloheptene **55** afforded the cyclized product **56** in excellent yield (90% yield, dr = 1.7:1) along with a trace amount of acyclic product **57**. Reactions with styrenes **58** and **60** afforded high yields and low diastereoselectivity with exclusive formation of cyclized products **59** and **61**. Interestingly, reaction with α-methyl styrene **62** afforded the cyclized product **63** which contains an all-carbon quaternary center (66% yield, dr = 1.5:1).

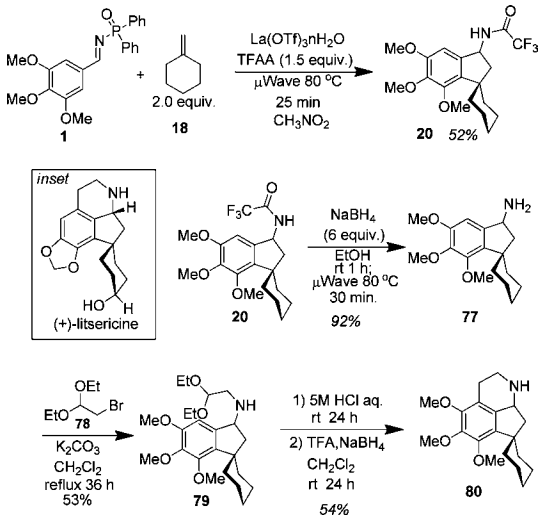
We next evaluated a number of substituted *N*-phosphinylimines as reaction partners (Table 5). We anticipated that by utilizing the cation-stabilizing solvent nitromethane (CH_3NO_2)[15] it may be possible to obtain higher levels of cyclized products. Reaction of **45** with *N*-phosphinylimine **1** utilizing CH_3NO_2 as solvent at room temperature did not have a dramatic effect on the yield of cyclized product but did negatively affect the diastereomeric ratio (5:1) (entry 1). Reaction with dimethoxy-*N*-phosphinylimine **30** in CH_3CN afforded the cyclized product **64** in 47% yield (dr = 8:1) along with acyclic product **65** in 46% yield (d.r. = 2.5: 1) (entry 2). However, use of CH_3NO_2 as solvent significantly increased the isolated yield of **64** albeit in lower diastereoselectivity which could be increased by lowering the temperature to 0 °C. We observed a similar increase in cyclization products utilizing CH_3NO_2 in reaction with *N*-phosphinylimines **31** and **34**. We also observed a noticeable reduction of cyclized products as

(13) Relative stereochemistry was determined by NMR and X-ray crystallographic analyses.

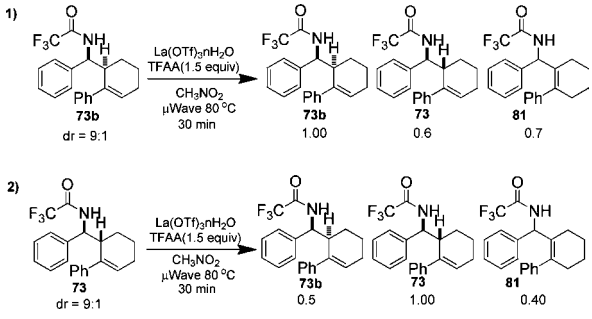
(14) Juteau, H.; Gareau, Y. *Synth. Commun.* **1998**, *28*, 3795.

(15) (a) Brătulescu, G.; Bigot, Y. L.; Delmas, M. *Synth. Commun.* **2001**, *31*, 3309. (b) Grundl, M. A.; Kaster, A.; Beaulieu, E. D.; Trauner, D. *Org. Lett.* **2006**, *8*, 5429. (c) Li, S.; Chiu, P. *Tetrahedron Lett.* **2008**, *49*, 1741.

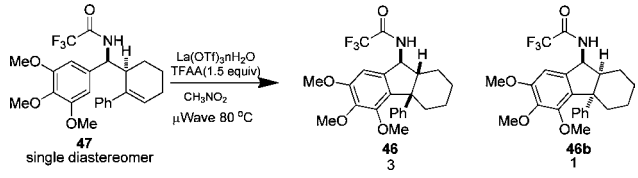
Scheme 2. Synthesis of an Alkaloidal Core Structure



Scheme 3. Equilibration of Acyclic Products **73b**, **73**, and **81**



Scheme 4. Equilibration of Acyclic Products **46** and **46b**



the aryl ring of the *N*-phosphinylimine became less electron rich. For example, 4-methoxyphosphinylimine substrate (**32**) afforded exclusively the acyclic product **70** in good yield and low diastereoselectivity using CH_3CN as the solvent. Efforts to promote cyclization with CH_3NO_2 were unsuccessful yielding only **70** (dr = 2.3:1). Less nucleophilic aryl *N*-phosphinylimines (entries 6−8) afforded similar results as observed for substrate **32** with a slight preference observed for the "*syn*" diastereomer (*cf.* Table 5, entry 5). Utilization of *trans*-cinnamaldehyde-derived phosphinyl imine **75** affords exclusively acyclic adduct **76** (dr = 1:1) in excellent yield (95%).

We also evaluated solvent effects for the tandem reaction employing methylenecyclohexane (**18**) and *N*-phosphinylimine **1** (Scheme 2). As anticipated, use of CH_3NO_2 as solvent led to increased formation of spirocycle **20** (52%). In an effort to exploit the rapid synthesis of this spirocyclic scaffold, we envisioned the synthesis of the tetracyclic framework of the isoquinoline alkaloid litsericine (*inset*).[16] Deprotection of trifluoroacetamide **20** with $NaBH_4$[17] under microwave irradiation afforded benzylic amine **77** (92% yield). The fused piperidine ring was constructed utilizing a modified Pomeranz−Fritsch−Bobbitt reaction[18] which was initiated by alkylation of amine **77** with 2-bromoacetaldehyde diethyl acetal (**78**) to afford amino acetal **79** (53% yield). Cyclization under acidic conditions, followed by subsequent dehydroxylation (TFA/$NaBH_4$), affords isoquinoline **80** in 54% yield.

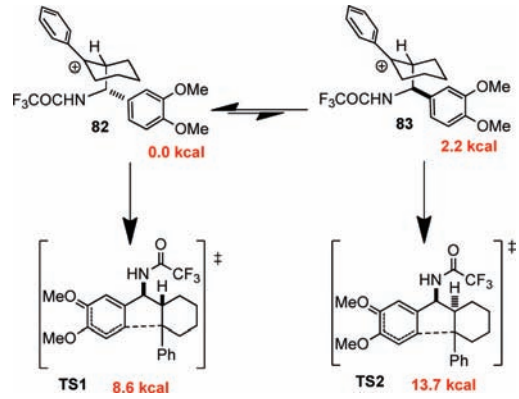


Figure 3. DFT transition state calculations.

To probe the mechanistic pathway for the tandem *aza*-Prins/Friedel−Crafts alkylation process, we conducted a number of control experiments. The first experiment involved reaction of acyclic products **73** and **73b** which are unable to further cyclize (Scheme 3). When an enriched mixture of stereoisomer **73b** (dr = 9:1) was incubated in the presence of $La(OTf)_3$ and TFAA and irradiated in the microwave, we observed an equilibration of the products to afford both diastereomers and the alternative elimination product (**73b**/**73**/**81** = 1:0.6:0.7). In a similar fashion treatment of an enriched sample of stereoisomer **73** led to equilibration affording the same three products (0.5:1:0.4). Additional experiments involved incubation of the acyclic stereoisomer **47** in CH_3NO_2 under microwave irradiation (Scheme 4). We observed the formation of cyclized products **46** and **46b** (3:1) indicating a similar equilibration prior to cyclization. We also carried out experiments to determine if cyclized products such as **46** and **46b** are capable of equilibration *via* retro-Friedel−Crafts reactions.[19] Under standard reaction conditions in the microwave at 80 °C, there was no change in the product distribution as well as no change when the product was incubated in the presence of TFA. Based on these observations, we believe that acyclic products such as **47** and **73** are capable of isomerization allowing for thermodynamic equilibration.[20]

Utilizing computational analysis (B3LYP/6-31G(d)) of stereoisomeric carbocation intermediates **82** and **83** (Figure 3), we have determined that the "*syn*" carbocation is thermodynamically favored by 2.2 kcal/mol.[5] Structural optimizations of transition states for Friedel−Crafts alkylation leading to both cyclization

(16) (a) Nakasato, T.; Asada, S. *Yakugaku Zasshi* **1966**, *86*, 134. (b) Nakasato, T.; Asada, S. *Yakugaku Zasshi* **1966**, *86*, 1205. (c) Lu, S.-T.; Su, T.-L.; Wang, E.-C. *J. Chin. Chem. Soc.* **1975**, *22*, 349.

(17) Kudzin, Z. H.; Łyẇa, P.; Łuczak, J.; Andrijewski, G. *Synthesis* **1997**, 44.

(18) Grajewska, A.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 557.

(19) Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753.

(20) Initial studies to probe the mechanism of equilibration were carried out. An attempted crossover experiment utilizing compound **73** and a differentially substituted derivative under the *aza*-Prins/Friedel−Crafts conditions ($La(OTf)_3$/TFAA) did not lead to observable crossover indicating that the retro-*aza*-Prins process is likely not operative.

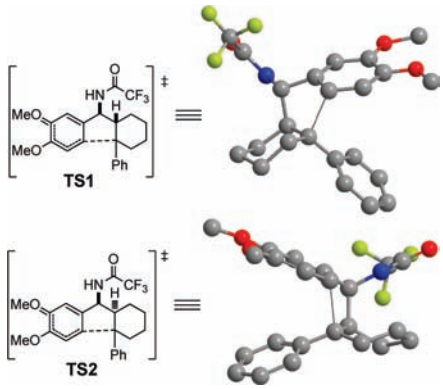
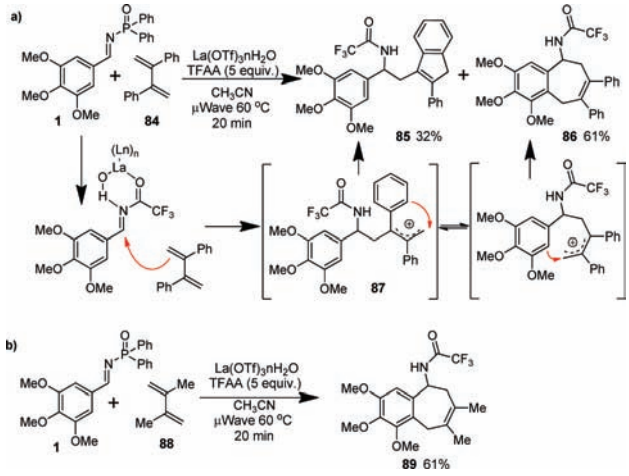


Figure 4. Transition states for Friedel−Crafts cyclization.

Scheme 5. Tandem Reactions with 1,3-Dienes



products were also performed (Figure 3).[5] **TS1** derived from the "*syn*" carbocation requires 8.6 kcal/mol while **TS2** derived from the "*anti*" carbocation requires 11.5 kcal/mol. Closer examination of both **TS1** and **TS2** reveals that the conformation of the cyclohexane bearing the carbocation may be responsible for the energy differences (Figure 4). **TS1** is in a preferred chair conformation while **TS2** adopts an energetically disfavored boat conformation. Overall, our computational results suggest that the reaction with dimethoxy-substrate **30** which affords high diastereoselectivity may likely be under thermodynamic equilibration of the stereoisomeric cationic intermediates. Furthermore, there is also strong evidence for a kinetic preference for cyclization of one stereoisomer which likely improves the resulting diastereoselectivity. In a similar manner, lower diastereoselectivities, as is the case for the reaction with cycloheptene **55** (Table 4), are likely due to each stereoisomer having a similar energy barrier for cyclization as supported by transition state calculations.[5]

A related tandem process was also discovered in the reaction screen involving 2,3-diphenyl diene **84** which afforded indene **85** and the formal [4 + 3] cyclization product benzocycloheptene **86** in good overall yields (Scheme 5).[21] It appears that the allylic carbocation intermediate **87** generated after initial *aza*-Prins addition[22] may be trapped by intramolecular Friedel−Crafts cyclization with either aryl group. We also observed a similar

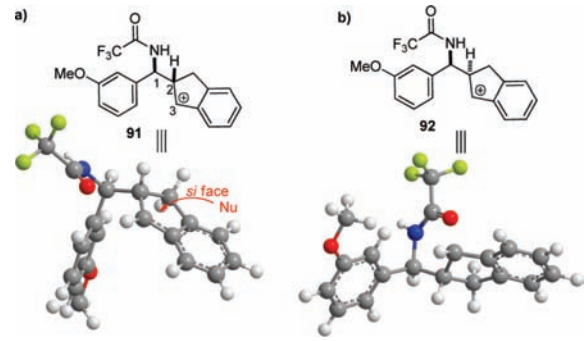
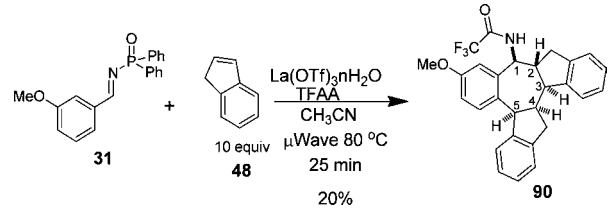


Figure 5. DFT structures for carbocationic intermediates en route to **90**. (a) DFT optimized structure for "*syn*" carbocation **91**. (b) DFT optimized structure for the "*anti*" carbocation **92**.

Scheme 6. A *Bis*-Indane from Reaction with Indene



transformation with 2,3-dimethyl diene **88** to afford the benzylcycloheptene product **89** in 61% yield.

In follow-up studies, we noted the formation of a new product in the reaction of *N*-phosphinylimine **31** and indene **48** (Scheme 6). X-ray crystal analysis revealed the structure to be the *bis*-indane **90**[5] which was produced in 20% yield as a single diastereomer. We propose that this product is obtained in a related tandem *aza*-Prins/alkene addition/Friedel−Crafts process to afford a complex, hexacyclic framework bearing five contiguous stereocenters. An intriguing aspect of this reaction is the formation of a single stereoisomer. To understand the stereochemical outcome, we conducted computational analysis of proposed intermediates in the reaction pathway (Figure 5). The C1 and C2 relative stereochemistry are likely derived from preferential addition of the second indene to the "*syn*" carbocationic intermediate **91**. DFT structural optimization of the intermediates reveals that the "*anti*" intermediate **92** is situated such that the carbonyl oxygen of the amide and the carbocation have a significant n−p interaction delocalizing the positive charge through an acetoxonium-like species (Figure 5).[23] Through this interaction, the carbocation begins to take on sp^3 character rendering **92** less reactive toward addition of the second indene. These models also indicate that only the *si* face of carbocation **91** is available for addition of the second indene, thus establishing the C3 stereocenter.

We propose that the *syn* relationship of C3 and C4 may be derived from the inability of the *anti* counterpart **93** to undergo cyclization (C5−C6 distance = 4.5 Å) thus leading to polymerization or elimination (Figure 6). The *syn* intermediate **94**

(21) For reviews of [4 + 3] cyclizations, see: (a) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595. (b) Harmata, M.; Rashatasakhon, P. *Tetrahedron* **2003**, *59*, 2371.

(22) For stepwise addition of dienes to *N*-aryl imines, see: Hermitage, S.; Howard, J. A. K.; Jay, D.; Pritchard, R. G.; Probert, M. R.; Whiting, A. *Org. Biomol. Chem.* **2004**, *2*, 2451.

(23) Woodward, R. B.; Brutcher, F. V., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 209. (b) Norrild, J. C.; Pedersen, C. A.; Sotofte, I. *Carbohydr. Res.* **1997**, *297*, 261.

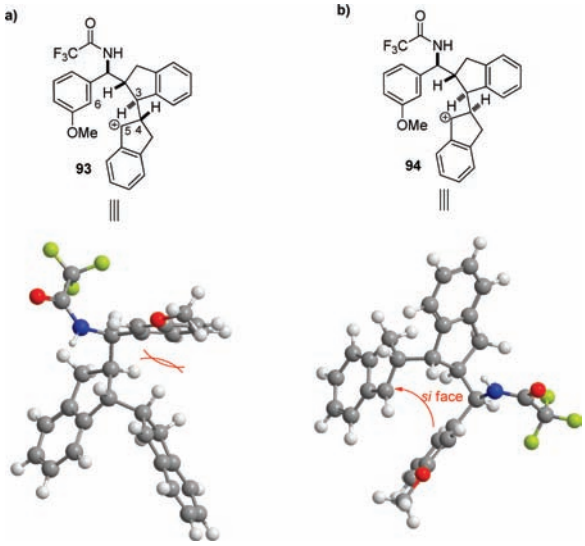


Figure 6. DFT structures for *bis*-indane carbocation intermediates. (a) DFT model of the C3/C4 *syn* carbocation intermediate **93**. (b) DFT model of the C3/C4 *anti* carbocation intermediate **94**.

appears to be restricted to cyclization at the *si* face (opposite to the C4 hydrogen) leading to the observed relative stereochemistry at C5.

Conclusion

We have utilized reaction screening to study additions of nucleophilic reaction partners to *N*-diphenylphosphinylimines using $La(OTf)_3 \cdot nH_2O$/TFAA activation. Based on screening results, we identified tandem *aza*-Prins/intramolecular Friedel−Crafts reactions between *N*-phosphinylimines and a number of styrenic and diene reaction partners which produce complex polycyclic frameworks, many bearing the privileged diarylmethane pharmacophore.[24] The scope and limitations of the process were studied and have led to the finding that substituents on the aromatic ring of *N*-phosphinylimines were crucial to obtain the cyclic products through intramolecular Friedel−Crafts cyclization. We also achieved spirocycle formation through tandem *aza*-Prins Friedel−Crafts reactions employing exocyclic alkenes as reaction partners and nitromethane as the solvent which has been found to stabilize carbocation intermediates. Mechanistic experiments support thermodynamic equilibration of stereoisomeric cationic intermediates as well as different barriers for Friedel−Crafts cyclization to establish acyclic−cyclic product distributions and stereochemistries. Further studies involving reaction screening to identify novel reactions and chemotypes as well as use of the polycyclic scaffolds obtained in library synthesis applications are ongoing in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, including X-ray structure analyses of compounds **46**, **49**, **74**, **86**, **90** (PDF). X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) For a review of privileged structures, see: Mason, J. S.; Morize, I.; Menard, P. R.; Cheney, D. L.; Hulme, C.; Labaudiniere, R. F. *J. Med. Chem.* **1999**, *42*, 3251.