Published in final edited form as:

J Am Chem Soc. 2010 May 12; 132(18): 6412–6418. doi:10.1021/ja100346w.

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

Hidenori Kinoshita, Oscar J. Ingham, Winnie W. Ong, Aaron B. Beeler, and John A. Porco Jr

Department of Chemistry and Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, Boston, Massachusetts 02215, porco@bu.edu

Abstract

Reaction screening of nucleophilic reaction partners for addition to *N*-diphenylphosphinylimines employing lanthanum (III) triflate as catalyst and trifluoroacetic anhydride (TFAA) as 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*-phosphinylimines¹ and carbon nucleophiles using a La(OTf)₃ · nH₂O/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·nH₂O under microwave irradiation led to production of Friedel Crafts product **3**. Alternatively, use of methylenecyclopentene **4** as nucleophile led to homoallylic amide **5** in good yield (82%). In order to study the scope and limitations of these reactions and expand their utility, we undertook reaction screening³ 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 reaction scope and mechanism.

Results and Discussion

Thirty three nucleophilic reaction partners were selected for the reaction screen with a number of entries based on reported iminoene reactions (Figure 1).⁴ Reactions were conducted using *N*-phosphinylimine **1** (0.015 mmol) as substrate, La(OTf)₃·nH₂O (20 mol%), 5.0 equivalents of TFAA (0.075 mmol), and 100 μL of CH₃CN under microwave irradiation at 80 °C.⁵ After the reaction (10 min), the mixtures were filtered and evaluated using ultra performance 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 ten-fold (0.15 mmol) and the products isolated. Results of initial reaction screening indicated that 17 of 33 reactions afforded major products; nine of 17 reactions afforded products corresponding to adducts between the *N*-phosphinylimine substrate and alkene reaction partner. Based on the screening

Correspondence to: John A. Porco, Jr.

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>

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} which was 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 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).

Secondly, 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% yield, 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*-Prins⁹- intramolecular Friedel-Crafts cyclization which may be operative if the 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 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, d.r. = 8 : 1) in which the ring junction proton is *syn* to the trifluoroacetamide and the uncyclized, trisubstituted alkene **47** (29% yield, d.r. = 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 (d.r. = 17 : 1 and >20 : 1, respectively). Reaction with indene (**48**) (entry 2) afforded the cyclized tetrahydroindanoindane derivative **49** exclusively in moderate diastereoselectivity (71% yield, d.r. = 4 : 1). Reaction with 1,2-dihydronaphthalene (**50**) afford a mixture of tetracycle **51** in 83% yield (d.r. = 5 : 1) along with the acyclic, conjugated product **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, d.r. = 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, d.r. = 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, d.r. = 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 (CH₃NO₂)¹⁵ it may be possible to obtain higher levels of cyclized products. Reaction of **45** with *N*-phosphinylimine **1** utilizing CH₃NO₂ 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 CH₃CN afforded the cyclized product **64** in 47% yield (d.r. = 8 : 1) along with acyclic product **65** in 46% yield (d.r. = 2.5 : 1) (entry 2). However, use of CH₃NO₂ 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 CH₃NO₂ in reaction with *N*-phosphinylimines **31** and **34**. We also observed a noticeable reduction of cyclized products as 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 CH₃CN as solvent. Efforts to promote cyclization with CH₃NO₂ were unsuccessful yielding only **70** (d.r. = 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, c). Utilization of *trans*-cinnamaldehyde-derived phosphinyl imine **75** afford exclusively acyclic adduct **76** (d.r. = 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 CH₃NO₂ 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 NaBH₄¹⁷ using microwave irradiation afforded benzylic amine **77** (92% yield). The fused piperidine ring was constructed utilizing a modified Pomeranz-Fritsch-Bobbitt reaction¹⁸ 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/NaBH₄), affording isoquinoline **80** in 54% yield.

In order 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** (d.r. = 9 : 1) was incubated in the presence of La(OTf)₃ and TFAA and irradiated in the microwave, we observed equilibration of 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 affordinh the same three products (0.5 : 1 : 0.4). Additional experiments involved incubation of the acyclic stereoisomer **47** in CH₃NO₂ 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 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 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 1,2-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 addition²² may be trapped by intramolecular Friedel-Crafts cyclization with either aryl group. We also observed a similar transformation with 1,2-dimethyl diene **88** to afford the benzylcycloheptene product **89** in 61% yield.

In follow up studies, we also 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. In order 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 sp³ 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** appears to be restricted to cyclization to 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·nH₂O/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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was generously supported by the NIGMS CMLD Initiative (P50 GM067041). We thank Dr. Emil Lobkovsky (Cornell University) for X-ray crystal structure analysis, Dr. Paul Ralifo (Boston University) for assistance with NMR, and Professors Richard Johnson (University of New Hampshire), John Snyder, Scott Schaus, and Corey Stephenson (Boston University) for helpful discussions. NMR (CHE-0619339) and MS (CHE-0443618) facilities at Boston University are supported by the NSF and computational resources were provided by the Boston University Scientific Computing and Visualization Center. We also thank Waters Corporation and CEM Corporation for assistance with instrumentation.

References

1. Weinreb SM, Orr RK. *Synthesis* 2005;1205.
2. Ong WW, Beeler AB, Kesavan S, Panek JS, Porco JA Jr. *Angew Chem. Int. Ed* 2007;46:7470.
3. Beeler AB, Su S, Singleton CA, Porco JA Jr. *J. Am. Chem. Soc* 2007;129:1413. [PubMed: 17263426]
4. For examples of imino-ene reactions, see: (a) Drury WJ 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 WJ III, Ryzhkov L, Taggi AE, Lectka T. *J. Am. Chem. Soc* 2002;124:67. [PubMed: 11772063] (c) Caplan NA, Hancock FE, Bulman PC, Hutchings GJ. *Angew. Chem., Int. Ed* 2004;43:1685. (d) Aburel PS, Zhuang W, Hazell RG, Jorgensen KA. *Org. Biomol. Chem* 2005;3:2344. [PubMed: 16010370] (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 JR, Neue UD, Kele M, Plumb RS. *Anal. Chem* 2005;77:460 A. (b) Nováková L, Matyssová L, Solich P. *Talanta* 2006;68:908. [PubMed: 18970409]
7. For recent examples of *aza*-Friedel Crafts alkylations, see: (a) Saaby S, Bayón P, Aburel PS, Jørgensen KA. *J. Org. Chem* 2002;67:4352. [PubMed: 12054974] (b) Luo Y, Li C-J. *Chem. Commun* 2004:1930. (c) Esquivias J, Arrayás RG, Carretero JC. *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. [PubMed: 16597125] (e) Liu C-R, Li M-B, Yang C-F, Tian S-K. *Chem. Commun* 2008:1249.
8. For formation of *trans*- β -methylstyrene from cyclopropylbenzene, see: Mochalov SS, Gazzaeva RA, Fedotov AN, Shabarov YS, Zefirov NS. *Chem. Het. Comp* 2003;39:794.
9. For *aza*-Prins reactions, see: (a) Dobbs AP, Guesné SJJ, Coles SJ, Hursthouse MB. *Synlett* 2003:1740. (b) Hanessian S, Tremblay M, Petersen JFW. *J. Am. Chem. Soc* 2004;126:6064. [PubMed: 15137772] (c) Liu J, Hsung RP, Peters SD. *Org. Lett* 2004;6:3989. [PubMed: 15496081] (d) Hanessian S, Tremblay M, Marzi M, Del Valle JR. *J. Org. Chem* 2005;70:5070. [PubMed: 15960507] (e) Armstrong A, Shanahan SE. *Org. Lett* 2005;7:1335. [PubMed: 15787500] (f) Sarkar TK, 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 MSR, Ram KR, Yadav JS. *Tetrahedron Lett* 2008;49:1141. (i) Yadav JS, Reddy BVS, Chaya DN, Kumar GGKSN, Aravind S, Kunwar AC, Madavi C. *Tetrahedron Lett* 2008;49:3330. (j) Lee HM, Nieto-Oberhuber C, Shair MD. *J. Am. Chem. Soc* 2008;130:16864. [PubMed: 19053422]
10. For the formal [3+2] addition of alkenes to benzhydrol cations, see: (a) Lantaño B, Aguirre JM, Finkielstein L, Alesso EN, Brunet E, Moltrasio GY. *Synth. Commun* 2004;34:625. (b) Lantaño B, Aguirre JM, Uglierolo EA, Benegas ML, Moltrasio GY. *Tetrahedron* 2008;64:4090.

11. (a) Basavaiah D, Sharada DS, 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 JJ, Rychnovsky SD. *J. Org. Chem* 2006;71:3176. [PubMed: 16599616] (d) Basavaiah D, Reddy KR. *Org. Lett* 2007;9:57. [PubMed: 17192084]
12. Attempts to reduce catalyst loading resulted in significantly lower yields. For example, use of 10 mol % $\text{La}(\text{OTf})_3$ afforded a 23% isolated yield of **46**.
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 YL, Delmas M. *Synth. Commun* 2001;31:3309. (b) Grundl MA, Kaster A, Beaulieu ED, Trauner D. *Org. Lett* 2006;8:5429. [PubMed: 17107039] (c) Li S, Chiu P. *Tetrahedron Lett* 2008;49:1741.
16. (a) Nakasato T, Asada S. *Yakugaku Zasshi* 1966;86:134. [PubMed: 5948467] (b) Nakasato T, Asada S. *Yakugaku Zasshi* 1966;86:1205. (c) Lu S-T, Su T-L, Wang E-C. *J. Chinese Chem. Soc* 1975;22:349.
17. Kudzin ZH, Łyżwa P, Łuczak J, Andrijewski G. *Synthesis* 1997:44.
18. Grajewska A, Rozwadowska MD. *Tetrahedron: Asymmetry* 2007;18:557.
19. Snyder SA, Breazzano SP, Ross AG, Lin Y, Zografos AL. *J. Am. Chem. Soc* 2009;131:1753. [PubMed: 19143488]
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 ($\text{La}(\text{OTf})_3/\text{TFAA}$) did not lead to observable crossover indicating that the retro-aza-Prins process is likely not operative
21. For reviews of [4+3] cyclizations, see: (a) Harmata M. *Acc. Chem. Res* 2001;34:595. [PubMed: 11456477] (b) Harmata M, Rashatasakhon P. *Tetrahedron* 2003;59:2371.
22. For stepwise addition of dienes to *N*-aryl imines, see: Hermitage S, Howard JAK, Jay D, Pritchard RG, Probert MR, Whiting A. *Org. Biomol. Chem* 2004;2:2451. [PubMed: 15326525]
23. Woodward RB, Brucher FV Jr. *J. Am. Chem. Soc* 1958;80:209. b) Norrild JC, Pedersen CA, Sotofte I. *Carb. Res* 1997;297:261.
24. For a review of privileged structures, see: Mason JS, Morize I, Menard PR, Cheney DL, Hulme C, Labaudiniere RF. *J. Med. Chem* 1999;42:3251. [PubMed: 10464012]

Figure 1.
Reaction Partners.

Figure 3.
DFT Transition State Calculations.

Figure 4.
Transition States for Friedel-Crafts Cyclization.

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**.

Figure 6.
DFT Structures for *Bis*-indane Carbocation Intermediates

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

Scheme 2.
Synthesis of an Alkaloidal Core Structure.

Scheme 3.
Equilibration of Acyclic Products.

Scheme 4.
Equilibration of Acyclic Products.

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

Table 1

Aza-Friedel-Crafts Reactions.^a

entry	ArH	Product (yield) ^b
1	6	7
2	8	9 (62%)

entry	ArH	Product (yield) ^b
3	 10	 11
4	 12	 13 (33%) 14 (6%)

entry

ArH

Product (yield)^b

5

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·nH₂O in 0.7 mL of CH₃CN.

b) Isolated yield after silica gel chromatography.

Table 2*Aza*-ene Reactions.^a

entry	ene
1	18

entry**ene**

2

21

entry**ene**

3

23

entry	ene
-------	-----

4

25

entry

ene

5

27

^a) *N*-Phosphinylimine **1** (0.152 mmol), alkene (0.76 mmol, 5 equiv.), TFAA (0.76 mmol, 5 equiv.) were used with 0.038 mmol (25 mol%) of La(OTf)₃·nH₂O in 0.7 mL of CH₃CN.

^b) Isolated yield after silica gel chromatography.

^c) D.r. and *E/Z* ratios determined by ¹H NMR analysis.

ylimine	yield	entry	phosphinylimine	yield
 $\text{Ar}-\text{C}(\text{Ph})=\text{N}^+\text{P}(\text{Ph})_2\text{O}^- \text{OTf}$ 30 - 36	92%	5	 34	96%
 $\text{Ar}-\text{C}(\text{Ph})=\text{N}^+\text{P}(\text{Ph})_2\text{O}^- \text{OTf}$ 37 - 43	92%	5	 41	96%

ylimine	ylid	entry	phosphinylimine	ylid
18	30 - 36	$\xrightarrow[\text{CH}_3\text{CN}, 80^\circ\text{C}, 25\text{ min}]{\text{La(OTf)}_3 \cdot n\text{H}_2\text{O}, \text{TFAA}}$ 37 - 43	42	96% 42

pylimine	ylimine	entry	phosphinylimine	yield
7		74% 43

ylimine	ylimine	phosphinylimine	yield	entry	ylimine
18	30 - 36	$\xrightarrow[\text{CH}_3\text{CN}, 80^\circ\text{C}, 25\text{ min}]{\text{La}(\text{OTf})_3 \cdot n\text{H}_2\text{O}, \text{TFAA}}$ 37 - 43	18%	40	

Table 4

Tandem *Aza*-Prins/Friedel-Crafts Reactions.

entry

alkene

1

45

entry	alkene
2	48

entry	alkene
3	50

entry

alkene

4

53

entry	alkene
-------	--------

5

55

entry

alkene

6

7

entry	alkene
8	62

a) Isolated yields.

b) Major diastereomer shown

c) Diastereomeric ratios determined by ^1H NMR analysis.

d) Styrene (1.2 equiv.), μ Wave, 80 °C, 25 min.

e) Styrene (1.2 equiv.), 0 °C, 12 h.

f) Styrene (1.2 equiv.), μ Wave, 60 °C, 25 min.

phosphinylimine

solvent

yield (dr)

CH₃CN 93% (dr c/d = 1 : 1)

CH₃NO₂ 60% (dr c/d = 2.3 : 1)

phosphinylamine

solvent

yield (dr)

72

no cyclic
productsCH₃CNCH₃NO₂ 79% (dr c/d = 1.6 : 1)

phosphinylimine

solvent

yield (dr)

73no cyclic
products

CH ₃ CN	86% (dr c/d = 1.6 : 1)
CH ₃ NO ₂	79% (dr c/d = 1.6 : 1)

35

phosphinylimine

solvent

yield (dr)

74no cyclic
productsCH₃CN

80% (dr c/d = 1.9 : 1)

CH₃NO₂

92% (dr c/d = 3 : 1)

36

phosphinylimine	solvent	yield (dr)
76	CH ₃ CN	95% (dr c/d = 1 : 1)
	CH ₃ NO ₂	92% (dr c/d = 1 : 1)

a) *N*-Phosphonylimine (0.152 mmol), $\text{La}(\text{OTf})_3 \cdot n\text{H}_2\text{O}$ (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.