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Dual Activation in Asymmetric Allylsilane Addition to Chiral *N*-Acylhydrazones: Method Development, Mechanistic Studies, and Elaboration of Homoallylic Amine Adducts

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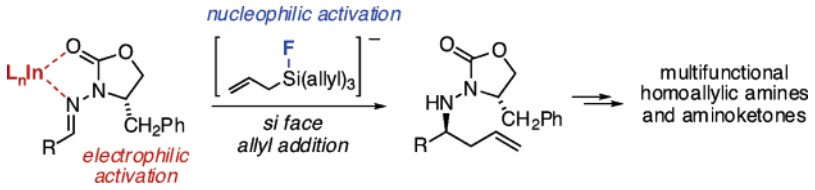

Chiral *N*-acylhydrazones derived from commercially available 4-benzyl-2-oxazolidinone provide a rigid, conformationally restricted template to impart facial selectivity in additions to C═N bonds. In the presence of indium(III) trifluoromethanesulfonate [In(OTf)$_3$], *N*-acylhydrazones undergo highly diastereoselective fluoride-initiated additions of allylsilanes (aza-Sakurai reaction). Mechanistic studies including control experiments and comparisons with allyltributylstannane, allylmagnesium bromide, and allylindium species implicate a dual activation mechanism involving addition of an allylfluorosilicate species to a chelate formed from In(OTf)$_3$ and the chiral *N*-acylhydrazone. The N−N bonds of the adducts are readily cleaved in a two-step protocol to provide synthetically useful homoallylic *N*-trifluoroacetamides. Further elaboration of the latter compounds through Wacker oxidation and olefin metathesis provides diversely functionalized building blocks and expands the potential applications of this C−C bond construction approach to asymmetric amine synthesis.

Introduction

Chiral homoallylic amines enjoy a privileged position among chiral amines because of their value as versatile building blocks for natural product synthesis.[1] For example, transformations from the terminal alkene have provided key intermediates en route to natural products such as indolizomycin,[2] (+)-desoxoprosopinine,[3] and various azacyclic targets including anabasine[4] and the spirocyclic core of halichlorine.[5] In addition, medicinally important immunostimulating lipopeptides[6] and dual metalloprotease inhibitors[7] have been synthesized with use of allylglycine derivatives. Homoallylic amines are not only valuable building blocks, but are found in their native form within a variety of compounds of biological relevance, including the natural products cryptophycin 337,[8] angustifoline,[9] and eponemycin.[10] Allylglycine residues in synthetic renin inhibitors[11] and aspartic proteinase inhibitors[12] further exemplify the widespread importance of homoallylic amines.

Asymmetric amine synthesis by addition of allylic nucleophiles to the C═N bond of carbonyl imino derivatives offers direct access to these substructures by introducing a stereogenic

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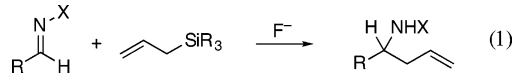
center and carbon−carbon bond in one step. As a result, extensive efforts have been directed toward stereoselective allyl addition to chiral imines, iminium ions, and related C═N electrophiles.[13] The arsenal of more general procedures for alkyl addition to the C═N bond[14] has also been applied to allyl additions; the latter often benefit from enhanced asymmetric induction through chelation and formation of chair transition states.[1] Despite the value of organometallic nucleophiles for various additions to imino acceptors, particularly those which are nonenolizable, the strongly basic or harsh Lewis acidic conditions often employed for these reactions may be problematic.[14] Complications of competitive metalloenamine formation and functional group incompatibilities often interfere with broader application, so development of milder conditions for stereocontrolled allylmetal addition to the C═N bond is of considerable importance. Nonbasic main group organometallics such as allylsilanes offer an attractive solution to these problems, but have been rarely applied in additions to neutral, isolable imines. This inattention may be attributed to an historical perception that allylsilanes are rather unreactive toward imines without resort to iminium ions or the use of strong Lewis acids.[15] Recent studies have explored activation of allylsilane reagents[16] with ring strain,[17] nucleophiles,[18] or transition metal-catalyzed processes,[19] resulting in several elegant stereocontrolled additions to imino acceptors.

We envisioned a dual activation scenario wherein both allylsilane donor and acceptor would be activated in complementary fashion to promote C−C bond construction under relatively mild conditions.[20−22] Nucleophilic activation may be readily accomplished with allyltrichlorosilanes, but these reagents are highly moisture-sensitive and corrosive. To maintain ease of handling and nonacidic conditions, we chose allylsilanes bearing alkyl substituents, while recognizing that a less electrophilic Si atom could make nucleophilic activation of these silanes more challenging. Although fluoride ion is perhaps the most obvious choice of activator for this purpose, there are surprisingly few examples of simple fluoride-promoted addition of allylsilanes to C═N bonds (aza-Sakurai reaction, eq 1).[23−25]



(1)

It was our hope that the dual activation concept, employing a mild Lewis acid together with fluoride in an aza-Sakurai reaction, would overcome this lack of reactivity. Thus this concept would require two separate, mutually compatible activators; the difficulty in identifying an effective Lewis acid that is compatible with fluoride was anticipated to be a significant obstacle in the initial stages of method development.

Turning to the issue of stereoselectivity, we chose to exploit chiral *N*-acylhydrazones (Figure 1) wherein Lewis acid activation and restriction of rotamer populations were key design elements.[26,27] These had previously proved to be excellent acceptors for stereoselective radical addition,[28,29] hydride reduction,[30] and other reactions.[31] The stereocontrol is quite simple and predictable, and is easily understood by considering the spatial relationship between the oxazolidinone substituent and the C═N π system (Figure 2). In *N*-acylhydrazone **A**, chelation of a Lewis acid exposes the *si* face to addition, while

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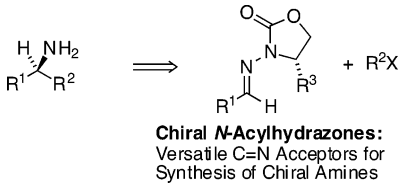


FIGURE 1. Application of chiral *N*-acylhydrazones for asymmetric amine synthesis via addition and N−N bond cleavage.

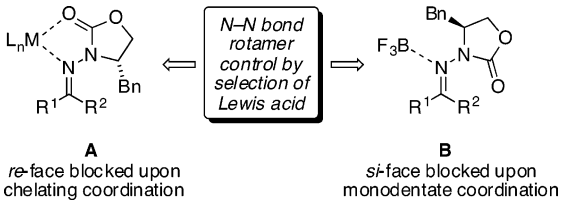
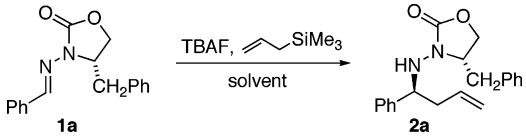


FIGURE 2. Stereocontrol models involving chiral *N*-acylhydrazones−Lewis acid combinations.

SCHEME 1



TBAF, equiv	Solvent	Yield	dr
1.0	THF	56%	5:1
0.1	THF	45%	5:1
1.0	CH_2Cl_2	40%	5:1

monodentate interaction of *N*-acylhydrazone **B** with BF_3 induces addition to the *re* face. The complementary selectivities presumably originate from preferential population of different N−N bond rotamers.

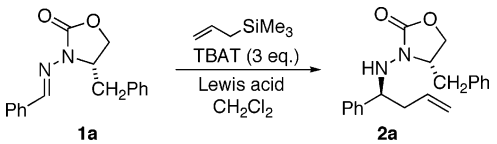
Finally, we anticipated merging the allylsilane addition with application of a recently disclosed TFA-activated N−N bond cleavage method,[32] ultimately generating homoallylic *N*-trifluoroacetamides as synthetically useful building blocks. To establish broader utility, brief exploration of alkene oxidation and metathesis transformations of these building blocks was envisioned.

The hypotheses outlined above offered fertile territory for new reaction development. Here we disclose complete details of development of convenient, highly stereoselective allylsilane additions using dual activation by fluoride and indium(III) trifluoromethanesulfonate.[33] In this study, mechanistic insights have been gained through comparison with other allylmetal additions, and expanded scope was demonstrated, including the merger of allylsilane addition with oxidation and metathesis reactions.

Results and Discussion

Method Development. Our initial studies examined the aza-Sakurai reaction of allyltrimethylsilane with chiral hydrazone **1a**[34] (Scheme 1), using tetrabutylammonium fluoride (TBAF) as a fluoride source for nucleophilic activation. With 1 equiv of TBAF in THF, allyltrimethylsilane underwent smooth reaction with enantiopure hydrazone **1a** at ambient temperature to afford the allyl adduct **2a** in 56% yield (dr 5:1) in 1 h. A catalytic amount of TBAF (10 mol %) afforded slightly lower yield (45%) and the same diastereomeric ratio in 2 h. Under these catalytic TBAF conditions, a slight improvement in yield and diastereoselectivity was observed at 0 °C (60% yield, dr 6:1), although at −78 °C there was virtually no reaction (<2% yield). Switching the solvent to noncoordinating methylene chloride slowed the reaction. Control experiments showed no reaction occurred without TBAF, even under refluxing conditions, and other fluoride sources such as CeF_3 or CsF did not promote the allyl addition.

SCHEME 2



Lewis acid	Yield (%)	d.r.
$SnCl_4$	68	86:14
$InCl_3$	17	33:67
$In(OTf)_3$	58	94:6

Encouraged by the promising preliminary results showing nucleophilic activation with fluoride, we tested the dual activation hypothesis by incorporating various Lewis acids, including $ZnCl_2$, $TiCl_4$, $SnCl_4$, $Sc(OTf)_3$, $Yb(OTf)_3$, or indium(III) trifluoromethanesulfonate [$In(OTf)_3$]. Our concerns about their mutual compatibilities were not unwarranted; upon addition of a Lewis acid to the mixture of hydrazone, allylsilane, and TBAF in THF there was no reaction. Attributing this to incompatibility of Lewis acid with fluoride ion, we selected a new experimental protocol. Thus, two CH_2Cl_2 solutions were prepared separately, one consisting of hydrazone **1a** with Lewis acid and the other of allyltrimethylsilane with TBAF. After 4 h, these two solutions were combined at ambient temperature. With this protocol, the allyl addition did occur, but inefficiently. For example, the yield of **2a** was 28% with $SnCl_4$, 20% with $TiCl_4$, and 14% with $In(OTf)_3$.

Eventually, we found that the soluble, air-stable, nonhygroscopic fluoride source tetrabutylammonium triphenyldifluorosilicate (TBAT)[35] could effectively promote allyltrimethylsilane addition to the complex formed by mixing **1a** with a Lewis acid, providing **2a** with good stereoselectivity. From a broad range of Lewis acids screened, including $SnCl_4$ and $InCl_3$ (Scheme 2), $In(OTf)_3$ was chosen; no reaction was observed in the presence of numerous other Lewis acids.[36] The striking difference between $InCl_3$ and $In(OTf)_3$ suggests the importance of a nonnucleophilic counterion under these conditions. Use of 0.2 equiv of $In(OTf)_3$ led to no reaction. Despite their previously documented utility in radical additions to hydrazones,[26,37] $ZnCl_2$ and $Cu(OTf)_2$ led to no change of hydrazone **1a**.

Variations to the substituents on silicon were examined next (Table 1). Although allyltrialkoxysilanes and various allyl-

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(36) There was no reaction in the presence of the following Lewis acids: InF_3, $ZnCl_2$, $TiCl_4$, $Sc(OTf)_3$, $Yb(OTf)_3$, $Hf(OTf)_4$, $Zr(OTf)_4$, $Cu(OAc)_2$, $Cu(OTf)_2$, TMSOTf, NiF_2, NiI_2, and $In(OAc)_3$.
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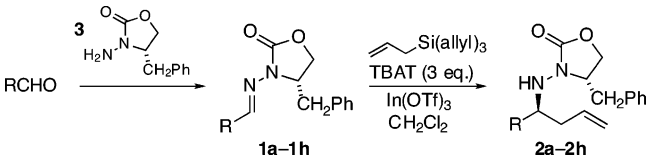
TABLE 1. Variation of Silicon Substituents in TBAT/In(OTf)$_3$-Promoted Addition of Allylsilanes to Hydrazone 1a (Scheme 2)[a]

[Si] of allylsilane	yield of **3a**,[b] %	dr[c]
$SiMe_3$	58	94:6
$SiPh_3$	0 (nr)	
$Si(OMe)_3$	0 (nr)	
$SiCl_3$	0 (nr)	
$SiMeCl_2$	0 (nr)	
$SiMe_2Cl$	0 (nr)	
$SiMe_2N(iPr)_2$	81	95:5
$Si(allyl)_3$	78	>99:1

[a] Reaction conditions: A solution of allylsilane (3 equiv) and TBAT (3 equiv), and a solution of In(OTf)$_3$ (1.3 equiv) and hydrazone **2a**, each in CH_2Cl_2 (0.1 M), were prepared separately. After 4 h at ca. 25 °C, the allylsilane/TBAT mixture was transferred by syringe to the hydrazone−In(OTf)$_3$ mixture. After 2 d at ca. 25 °C, the reaction mixture was washed with water, dried (anhydrous $MgSO_4$), concentrated, and purified by flash chromatography. [b] Isolated yields of purified diastereomer mixtures (nr: no reaction). [c] Diastereomer ratio by HPLC (Microsorb-MV C8, 2-PrOH/hexane).

TABLE 2. Preparation of Various Aldehyde Hydrazones 1 and TBAT/In(OTf)$_3$-Promoted Addition of Tetraallylsilane[a]



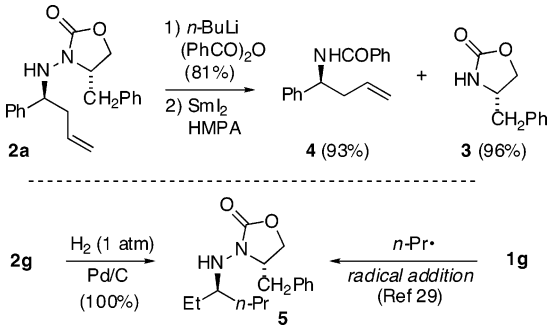
R	hydrazone[b]	allyl adduct[c]	dr[d]
phenyl	**1a**, 80%	**2a**, 78%	>99:1
p-tolyl	**1b**, 94%	**2b**, 94%	98:2
m-nitrophenyl	**1c**, 91%	**2c**, 71%	>99:1
2-naphthyl	**1d**, 92%	**2d**, 82%	98:2
2-furyl	**1e**, 92%	**2e**, 58%	96:4
−CH=CHPh (*E*)	**1f**, 97%	**2f**, 60%	95:5
$-CH_2CH_3$	**1g**, 92%	**2g**, 51%	82:18
3,4-dimethoxyphenyl	**1h**, 98%	**2h**, 54%[e]	96:4

[a] Reaction conditions for hydrazone formation: aldehyde (0.4 mmol), **3** (0.25 mmol), anhydrous $MgSO_4$ (200 mg), *p*-toluenesulfonic acid (ca. 5 mol %) in toluene (10 mL), reflux 10 min. For allyl addition conditions see Table 1. [b] Isolated yield. [c] Isolated yields of purified diastereomer mixtures. [d] Diastereomer ratio by HPLC (see Table 1). [e] Reaction scale: 4.5 mmol of hydrazone.

chlorosilanes were ineffective under these conditions, allyl(diisopropylamino)dimethylsilane led to significant improvement, providing **2a** in high yield and stereoselectivity. A superior allyl donor proved to be commercially available tetraallylsilane, which gave **2a** in 78% yield with excellent stereocontrol (dr >99:1). The improved yield and selectivity of tetraallylsilane versus allyltrimethylsilane may be attributable to a slightly more electrophilic silicon atom, leading to greater fluoride ion affinity, increased hypervalent silicate population, and a later transition state.[38]

Reaction Scope. With effective reaction conditions at hand, a brief survey of the scope of the reaction was undertaken with a series of aldehyde hydrazones (Table 2). Aromatic aldehyde hydrazones **1b**−**h** generally gave homoallylic amines in good yield with excellent stereoselectivity. Stereocontrol varied only slightly with the electronic properties of the aromatic system, although electron-rich 2-furyl and veratryl groups diminished

SCHEME 3



the yield. The α,β-unsaturated hydrazone (*E*)-**2f** underwent chemoselective addition to the C=N bond; here the adduct offers further potential for functionalization of the olefinic moiety from cinnamaldehyde. Although propionaldehyde hydrazone **2g**[26] also participated in the reaction, stereoselectivity was modest. Improved selectivity has been reported for saturated substrates by using indium(0)-promoted allyl addition.[31b]

To compare the reactivity of the TBAT/allylsilane system with a strongly basic allylmetal reagent, allylmagnesium bromide addition to hydrazone **1a** was performed in CH_2Cl_2. Allyl adduct **2a** was obtained in 47% yield after 18 h, with the predominant configuration (*S*) at the new stereogenic center (dr 86:14). A complex mixture of byproducts was also obtained, which appeared by NMR analysis to result from allyl addition to the oxazolidinone moiety. On the other hand, allyltributyltin (70% yield) or tetraallyltin (43% yield) gave better stereoselectivity (dr 93:7 and 97:3, respectively), although no reaction occurred in the absence of In(OTf)$_3$.

Configurational Assignment and N−N Bond Cleavage. Assignment of configuration of **2a**, derived from allyl addition to the benzaldehyde hydrazone, was accomplished by chemical correlation. Lithiation (*n*-BuLi) and acylation with benzoic anhydride, followed by reductive removal of the auxiliary with samarium(II) iodide (SmI_2), afforded known benzamide (*S*)-**4**[39] (Scheme 3), with the configuration identified by optical rotation in comparison with material of known configuration.[40] The stereochemical outcome of addition was found to be the same in the major product from allyl addition to the propionaldehyde hydrazone: Hydrogenation of **2g** gives **5**, a derivative of (*R*)-3-aminohexane,[41] which was identical with the known compound obtained from *n*-propyl radical addition to **1g** (Scheme 3).[29]

Although the reductive N−N bond cleavage with SmI_2 could succeed in preserving the synthetically useful alkene functionality in the allyl adducts (in contrast to hydrogenolysis), related studies indicated that a *N*-benzoyl group was required to facilitate the process.[42] To access the primary amines after N−N

(38) Similar explanations have been advanced regarding enhanced reactivity of bis(allyl)silanes. Shibato, A.; Itagaki, Y.; Tayama, E.; Hokke, Y.; Asao, N.; Maruoka, K. *Tetrahedron* **2000**, *56*, 5373−5382.

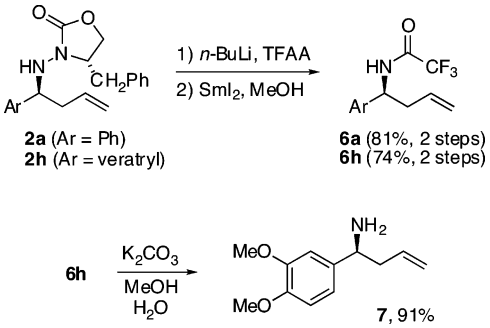
(39) (a) Wang, X.; Li, J.; Zhang, Y. *Synth. Commun.* **2003**, *33*, 3575−3581. (b) Katritzky, A. R.; Koeditz, J.; Lang, H. *Inorg. Chim. Acta* **1994**, *220*, 67−72. (c) Also see ref 31b.

(40) (a) Specific optical rotation of **4**, $[\alpha]^{20}_D$ −20 (*c* 0.34, $CHCl_3$), was within experimental error of an authentic sample, $[\alpha]^{20}_D$ −22 (*c* 0.34, $CHCl_3$), prepared from the known homoallylic amine. Basile, T.; Bocoum, A.; Savoia, D.; Umani-Ronchi, A. *J. Org. Chem.* **1994**, *59*, 7766−7773. (b) The specific rotations of several compounds (including **4**) were recorded erroneously in the preliminary report (ref 33); corrected data are provided in the Supporting Information.

(41) The difference in *R*/*S* nomenclature between **4** and **5** reflects the different priorities of substituents, not a difference in mechanism.

(42) Substituting the benzoyl with other acyl groups such as methoxycarbonyl resulted in no reaction. See ref 26b.

SCHEME 4



bond cleavage would then still require a difficult benzamide hydrolysis. Fortunately, an alternative N−N bond cleavage method based on the activating effect of a trifluoroacetamide (*N*-TFA) group leaves a more functional TFA protecting group.[43,44] After *N*-trifluoroacetylation, the SmI_2-mediated N−N bond cleavage of hydrazines **2a** and **2h** occurs smoothly (Scheme 4) to afford the trifluoroacetamides **6a** and **6h**.[45] As in other N−N bond cleavages of this type with SmI_2, the oxazolidinone component may also be recovered in high yield. Furthermore, as expected from ample precedent,[46] removal of the TFA protecting group from **6h** was achieved under mild basic conditions, affording free amine **7** in 91% yield.[32]

Mechanistic Studies. With the basic reaction method established, questions regarding the mechanism warranted further attention. A series of control experiments with **1a** gave some mechanistic insight to better understand the roles of the reactants. First, the importance of $In(OTf)_3$ and TBAT was assessed by carrying out reactions in their absence. Without $In(OTf)_3$ a lower yield (15%) was found due to incomplete conversion, which was accompanied by lower stereoselectivity (dr 67:33). Without TBAT, the yield was also lowered (30%), but the diastereoselectivity remained high (dr 94:6). Thus, both $In(OTf)_3$ and TBAT are required for good reactivity, while $In(OTf)_3$ also is important for stereocontrol. If both $In(OTf)_3$ and TBAT are omitted, no reaction occurs.

The results of these control experiments were consistent with our working hypothesis based on dual activation of both the nucleophilic and electrophilic components. For the electrophilic interaction, a chelation model is envisioned, where two-point binding of a Lewis acid activates the *N*-acylhydrazone toward nucleophilic attack. Nucleophilic activation would involve addition of fluoride ion to the allylsilane, generating a hypervalent silicate. Several experimental tests were carried out to further examine this working hypothesis.

Coordination of the Lewis acid to the imine nitrogen is supported by ^1H NMR spectroscopy experiments (Figure 3); significant downfield shift of the hydrazone proton was observed upon mixing $In(OTf)_3$ (1.2 equiv) and **1a**. A new set of peaks appears in the spectrum, highlighted by a new hydrazone peak above 10.5 ppm (arrows in Figure 3). Two species persist even after 18 h.

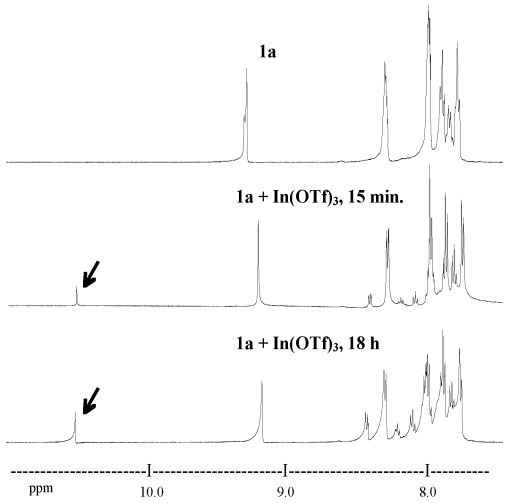
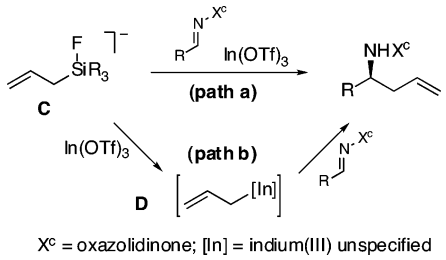


FIGURE 3. ^1H NMR spectra (500 MHz, CD_2Cl_2, 27 °C) of a mixture of **1a** and $In(OTf)_3$ (1.2 equiv): top, hydrazone **1a**; middle, **1a** + $In(OTf)_3$, 15 min; bottom, **1a** + $In(OTf)_3$, 18 h. Arrows denote the peaks assigned to the CH═N proton of the hydrazone−Lewis acid complex.

SCHEME 5



Xc = oxazolidinone; [In] = indium(III) unspecified

The configuration of the adduct shows that addition occurred on the *si* face, consistent with all other available evidence involving chelation-controlled additions to related *N*-acylhydrazones in the presence of Lewis acids capable of chelation (e.g., $ZnCl_2$, $InCl_3$, and $In(OTf)_3$). Since previous studies of closely related *N*-acylhydrazones showed that monodentate interaction ($BF_3{\cdot}OEt_2$) leads to addition on the *re* face (Figure 2B),[30] the stereochemical outcome here is significant evidence in support of a model involving Lewis acid chelation by the *N*-acylhydrazone.

For the nucleophilic component, two alternative types of allylic nucleophiles may be considered, depending on whether the allylsilicate undergoes transmetalation with In(III). An allylsilicate intermediate **C** (formed by addition of F^- to the allylsilane) could react directly with the *N*-acylhydrazone (Scheme 5, path a), or alternatively, its reaction with $In(OTf)_3$ could result in transmetalation to afford an allylindium species **D** as the active nucleophilic agent (path b).[47]

Further experiments garnered evidence to distinguish the alternative hypotheses of Scheme 5. Including additional $In(OTf)_3$ in the TBAT/allylsilane mixture led to 66% yield and dr >99:1, results which are very similar to those with the optimized conditions of Table 1. This suggests that any interaction of F^- with $In(OTf)_3$ under these conditions is slow, if it occurs at all. However, increasing the reaction time for

(43) Details including the scope of this reaction are reported elsewhere (ref 32).

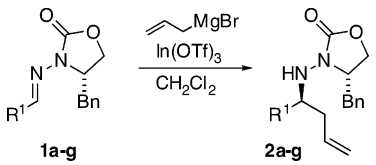
(44) Chelation of SmI_2 by neighboring fluorines increases its reducing power. Prasad, E.; Flowers, R. A., II *J. Am. Chem. Soc.* **2002**, *124*, 6357−6361.

(45) Enantiomeric purities of chiral hydrazines are unchanged during N−N bond cleavage according to this method. See ref 32.

(46) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; pp 353−354.

(47) Addition of allylindium species to imino compounds is known. (a) Jin, S.-J.; Araki, S.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1528−1532. (b) Also see ref 31b and references therein.

TABLE 3. Allyl Addition with Use of a Grignard Reagent in the Presence of $In(OTf)_3$[a]



R^1	hydrazone[b]	allyl adduct[c]	dr[d]
phenyl	**1a**	**2a**, 76%	86:14
p-tolyl	**1b**	**2b**, 53%	82:18
m-nitrophenyl	**1c**	**2c**, 9%	93:7
2-naphthyl	**1d**	**2d**, 65%	80:20
2-furyl	**1e**	**2e**, 56%	93:7
−CH═CHPh	**1f**	**2f**, 64%	86:14
$-CH_2CH_3$	**1g**	**2g**, 28%	63:37

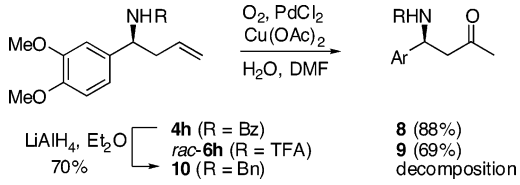
[a] Reaction conditions: see text. [b] Isolated yield. [c] Isolated yields of purified diastereomer mixtures. [d] Diastereomer ratio by HPLC (see Table 1).

such a mixture of $In(OTf)_3$, TBAT, and allylsilane to >12 h prior to combining it with the $In(OTf)_3$−hydrazone complex led to a pronounced diminution of reactivity and selectivity (22% yield, dr 95:5). This suggests that, over time, the $In(OTf)_3$ may react with the active allyl donor, leading either to a less reactive allylindium donor species by a slow transmetalation or to some other decomposition product of the allylsilane. Accordingly, ^1H NMR experiments (500 MHz, CD_2Cl_2, 27 °C) showed that tetraallylsilane is essentially unchanged after 4 h in the presence of TBAT, and when $In(OTf)_3$ is added, consumption of the tetrallylsilane requires at least a further 14 h. These experiments indicate that transmetalation to an allylindium species (if it occurs at all under these conditions) is slow, and even if sufficient time is allowed for complete consumption of the allylsilane, the resulting species does not duplicate the results of Tables 1 and 2.

Next we experimentally tested whether transmetalation, if carried out intentionally by an alternative method, could reproduce the results of allylsilane addition in the presence of TBAT and $In(OTf)_3$. For this purpose, $In(OTf)_3$ was incorporated into the allylmagnesium bromide addition to **1a**, with the intent to reproduce in situ the Mg−In transmetalation reported by Whitesides et al.[48] When a preformed complex of **1a** (1 equiv) and $In(OTf)_3$ (1.3 equiv) was used, allylmagnesium bromide (3 equiv) addition required 2 days to complete and 76% yield of **2a** was obtained, with 86:14 dr (Table 3). This same method was then applied to hydrazones **1b**−**g**. Decomposition of **1c** became a serious side reaction, and the yields and selectivities of the reactions were significantly lower, revealing that these conditions are clearly distinguished from the allylsilane conditions.[49]

For allylmagnesium bromide addition to **1a**, more control experiments on transmetalation were performed. When the order of addition was changed,[48] so that allylmagnesium bromide was allowed to react with $In(OTf)_3$ in CH_2Cl_2 prior to addition of **1a** (either alone or with additional $In(OTf)_3$), there was no reaction observed. The same result was found with use of InI_3 in THF. Again the reactivities observed in the aza-Sakurai reactions of Tables 1 and 2 were not reproduced, adding further evidence against transmetalation and the intermediacy of allylindium species in the allylsilane addition reactions.

SCHEME 6



Two additional observations are inconsistent with the transmetalation hypothesis: The allylsilane addition fails in 10:1 CH_2Cl_2/water, although water is known to be compatible with allylindium addition.[48,50] Also, variation of reactivity and selectivity upon changing the silicon ligands (Table 1) implies the presence of silicon at the transition state.

Taken together, these results show that the transmetalation is not likely to play a key role in the dual activation method of allylsilane addition to chiral *N*-acylhydrazones. Addition of a hypervalent allylsilicate to the Lewis acid-complexed *N*-acylhydrazone appears to best explain the observations. Stereochemical results are consistent with the chelate structure in Figure 2A, wherein restriction of rotamer populations facilitates steric blocking of the *re* face.

Synthetic Elaborations of the Homoallylic Amines. With the synthetic methodology having been established for allyl addition to chiral *N*-acylhydrazones, it became interesting to consider the most effective approach to broaden the scope of potential applications. For this purpose, oxidation and cross-coupling of the alkene moiety were attractive options, and we briefly explored these transformations to highlight the synthetic utility of the allylsilane addition methodology.

In the course of ongoing synthetic objectives, we had occasion to attempt conversion of homoallylic amines to the corresponding methyl ketones by Wacker oxidation.[51] Amide **4h**, obtained in 78% yield from **2h** by the two-step procedure of Scheme 3, was oxidized successfully to afford 88% of the desired methyl ketone **8** under modified Wacker oxidation conditions[52] employing 20 mol % of $PdCl_2$ (Scheme 6). Similarly, Wacker oxidation of racemic TFA-amide *rac*-**6h**[53] furnished methyl ketone **9** in 69% yield. Although free base **10** was oxidized to the methyl ketone, elimination of the amino substituent consumed the desired product.[54] Acylated β-aminoketones **8** and **9** did not suffer this decomposition, and were easily isolated and purified.

We also sought to couple our homoallylic amine synthesis with the ubiquitous olefin metathesis,[55] a strategic intersection

(48) Whitesides et al. have reported that allylmagnesium bromide and $InCl_3$ gives allylindium(III) dichloride. Kim, E.; Gordon, D. M.; Schid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500−5507.

(49) The allylmagnesium bromide additions in the presence of $In(OTf)_3$ are also clearly distinguished from known allylindium addition reactions. Stereoselectivity is low in the former, while Cook's allylindium addition to these chiral *N*-acylhydrazones was fast (3 h) and highly diastereoselective (>99: 1 dr, see ref 31b).

(50) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149−11176. Kumar, H. M. S.; Anjaneyulu, S.; Reddy, E. J.; Yadav, J. S. *Tetrahedron Lett.* **2000**, *41*, 9311−9314. Chan, T. H.; Lu, W. *Tetrahedron Lett.* **1998**, *39*, 8605−8608.

(51) Reviews: Takacs, J. M.; Jiang, X.-T. *Curr. Org. Chem.* **2003**, *7*, 369−396. Tsuji, J. *Synthesis* **1984**, 369−384.

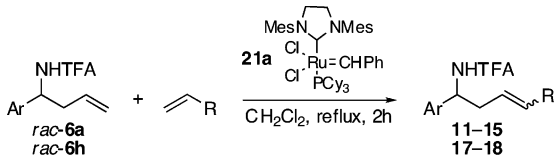
(52) Smith, A. B., III; Cho, Y.-S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765−8768.

(53) Racemic homoallylic amine was readily prepared by a convenient catalytic allylsilane addition procedure: see ref 24.

(54) Benzylamine **10** was oxidized to a complex mixture containing the known alkene ArCH═CHCOCH$_3$ (Ar = 3,4-dimethoxyphenyl). Jitoe, A.; Masuda, T.; Nakatani, N. *Phytochemistry* **1993**, *32*, 357−364.

(55) For reviews of olefin metathesis, see: (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199−2238.

TABLE 4. Cross Metathesis of Homoallylic Trifluoroacetamides



Ar	R	Yield %	E/Z
Ph	$SiMe_3$	80 (**11**)	2:1
Ph	OH	68 (**12**)	7:1
Ph	CO_2Me	86 (**13**)	4.5:1
Ph	O	72 (**14**)	4.5:1
Ph	OH (**16**)	61 (**15**)	>10:1[a]
veratryl[b]	CO_2Me	98 (**17**)	5:1
veratryl[b]	OTBS, OH (**19**)	30 (**18**)	>10:1[a]

[a] Mixture of alcohol diastereomers was obtained (dr 3:2). [b] Veratryl = 3,4-dimethoxyphenyl.

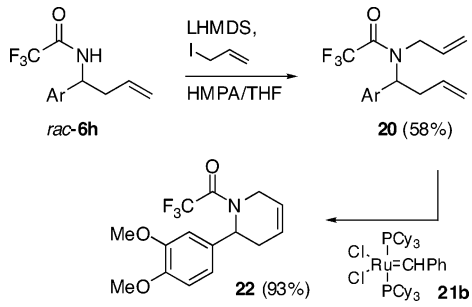
that would offer greatly expanded synthetic potential. Exploiting this tactic, a wide range of homoallylic amines could be easily prepared from the parent homoallylic trifluoroacetamide, offering potential access to numerous highly functionalized building blocks for synthesis. Whereas ring-closing metathesis had been reported with trifluoroacetamide precursors in a few isolated cases,[56] it was a surprise to find that cross-metathesis reactions of *N*-TFA-protected homoallylic amines had not been previously reported.

Cross-metathesis reactions of TFA-protected homoallylic amines were examined by using 5% mol of second generation Grubbs catalyst (**21a**) in refluxing methylene chloride (Table 4). These reactions proved to be no exception to precedent. Under these conditions, cross-metathesis between the protected homoallylic amine *rac*-**6a** or *rac*-**6h** and a number of functionalized alkenes proceeded effectively. Allyltrimethylsilane was coupled with *rac*-**6a** to afford **11** in good yield; further elaboration with the allylic silane moiety can be envisioned. Cross-metathesis with various oxygen-containing alkenes including alcohol, ketone, and ester functionality was also effective; methyl acrylate gave excellent yields of α,β-unsaturated δ-aminoesters **13** and **17**. Racemic allylic alcohols **16** and **19** were employed in the cross-metathesis with *rac*-**6a** and *rac*-**6h**, respectively, affording **15** and **18** as inseparable diastereomeric mixtures. Together, these functionalized cross-metathesis partners yield products with broad synthetic potential.

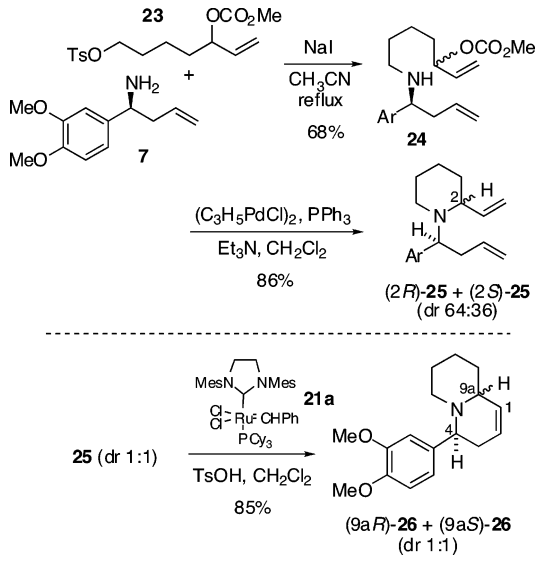
Piperidine and quinolizidine alkaloids may be constructed through a tactic combining allylic amination (i.e., *N*-allylation) with metathesis. For example, *N*-allylation of trifluoroacetamide *rac*-**6h** (Scheme 7) and ring-closing metathesis of the resulting diene **20** with the first-generation Grubbs catalyst (**21b**) smoothly provided unsaturated piperidine **22** in 54% yield for two steps.

For the quinolizidine skeleton, a simple nucleophilic substitution with tosylate **23** delivers secondary amine **24** in 68% yield

SCHEME 7



SCHEME 8



from **7** (Scheme 8). Subjection of this material to intramolecular Pd-catalyzed allylic amination[57] gave piperidine **25** in high yield. With triphenylphosphine as the ligand, the α-vinyl diastereomer (2*R*)-**25** was preferred.[58]

A preformed TsOH salt[5] of the tertiary amine **25** (dr 1:1) was treated with second-generation Grubbs catalyst (**21a**) to afford ring-closing metathesis product **26** (dr 1:1) as an easily separated mixture of diastereomers in 85% yield (Scheme 8). This established the quinolizidine framework, wherein the relative configuration was determined by observation of Bohlmann bands[59] in the infrared spectrum of (9a*S*)-**26**.

Conclusions

Highly stereoselective allylsilane addition to chiral *N*-acylhydrazones occurs in the presence of stoichiometric amounts of easily handled, air-stable TBAT and $In(OTf)_3$. To our knowledge these are the first examples of useful auxiliary acyclic stereocontrol in allylsilane addition to stable, isolable imino derivatives. Diastereomer ratios ranged upward from 95:5 for

(56) (a) Fu, G. C.; Nguyen, S. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857. (b) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1979−1980. (c) Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376−2378. (d) Maier, M. E.; Lapeva, T. *Synlett* **1998**, 891−893.

(57) Trost, B. M.; Calkins, T. L.; Oertelt, C.; Zambrano, J. *Tetrahedron Lett.* **1998**, *39*, 1713−1716. Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3671−3686.

(58) Improvement in the diastereoselectivity of this allylic amination step was briefly examined, substituting PPh_3 with the (+)- or (−)-enantiomer of Trost's *N*,*N*′-bis(2′-diphenylphosphinobenzoyl)-1,2-diaminocyclohexane ligand, or its naphthoyl-substituted analogue. These reactions were all nonselective (dr 1:1), despite the general utility of these important ligands. Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327−9343. Trost, B. M.; Bunt, R. C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 99−102.

(59) Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157−2167.

all unsaturated hydrazones examined, while propionaldehyde hydrazone gave a ratio of 82:18. All evidence is consistent with a mechanism involving dual activation in which the nucleophilic component is a hypervalent allylfluorosilicate and the electrophilic component is a chiral *N*-acylhydrazone−In(III) chelate.

A trifluoroacetyl substituent enables clean and efficient reductive cleavage of the N−N bond in the adducts with SmI_2 in the presence of MeOH, conditions which are compatible with alkene functionality. These reactions furnish chiral homoallylic amines which bear a convenient TFA protecting group. Synthetic potential is demonstrated in combination with Wacker oxidation[60] and metathesis transformations. Considering the synthetic versatility of the allyl group, the allylsilane addition described here offers potentially useful methodology for highly stereoselective access to complex targets.

Experimental Section[61]

Representative Procedure for the Preparation of Enantiopure *N*-Acylhydrazones (1a−h): (*S*)-3-(Benzylidene)amino-4-phenylmethyl-2-oxazolidinone (1a). A procedure based on the literature method[34] was employed. To a solution of (*S*)-3-amino-4-phenylmethyl-2-oxazolidinone (60 mg, 0.31 mmol) in toluene (10 mL) was added anhydrous $MgSO_4$ (200 mg), a catalytic amount of *p*-TsOH (ca. 5 mol %), and benzaldehyde (0.05 mL, 0.49 mmol). After the solution was heated at reflux for 10 min, concentration and flash chromatography (5:1 hexane/ethyl acetate) gave **1a** (70 mg, 81%) as a colorless solid, the properties of which matched the published data.[26]

Representative Procedure for Addition with Tetraallylsilane and TBAT (2a−h): (4*S*,1′*S*)-3-(1′-Allyl-1′-phenylmethylamino)-4-phenylmethyl-2-oxazolidinone (2a). A mixture of **1a** (56 mg, 0.2 mmol) and indium triflate (0.26 mmol) in CH_2Cl_2 (2.2 mL) was stirred at room temperature. Meanwhile, a mixture of TBAT (0.6 mmol) and tetraallylsilane (0.6 mmol) in CH_2Cl_2 (0.8 mL) was stirred in another flask. After 4 h, the TBAT mixture was added to the hydrazone mixture. The resulting reaction mixture was stirred at room temperature for 2 d, and then 2 mL of water was added. The organic phase was separated, dried over anhydrous $MgSO_4$, concentrated and purified by flash chromatography to give **2a** (50 mg, 78%) as a colorless oil: $[\alpha]^{23}_D$ −19.5 (*c* 0.43, $CHCl_3$); IR (film) 3290, 3028, 2927, 1754, 1699, 1653, 1558, 1497, 1456, 1399, 1093, 918 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.13 (m, 8H), 6.91 (dd, J = 7.2 Hz, 2H), 5.74 (dddd, J = 10.2, 10.2, 7.8, 6.1 Hz, 1H), 5.13 (dd, J = 17.1, 1.4 Hz, 1H), 5.05 (dd, J = 10.3, 1.0 Hz, 1H), 4.43 (s, 1H), 4.23 (ddd, J = 7.9, 1.3, 1.3 Hz, 1H), 3.77−3.70 (m, 2H), 3.16 (dd, J = 13.4, 3.4 Hz, 1H), 3.06−3.04 (m, 1H), 2.45−2.40 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 142.1, 135.99, 135.98, 134.2, 129.1, 128.8, 128.5, 127.98, 127.93, 126.9, 118.4, 65.8, 62.9, 58.2, 40.3, 36.8; MS (EI) *m*/*z* (rel intensity) 323 ([M + H]$^+$, 40%); Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.40; H, 6.89; N, 8.59. Diastereomer ratios of **2a**−**h** were determined by HPLC comparison with authentic mixtures (see the Supporting Information).

(4*S*,1′*S*)-3-(1′-(3,4-Dimethoxyphenyl)but-3′-enylamino)-4-phenylmethyl-2-oxazolidinone (2h). With use of the procedure described above for the preparation of **2a**, from **1h** (1.53 g, 4.5 mmol) was obtained **2h** (920 mg, dr 96:4, 54% yield) as a colorless oil. Major diastereomer (1′*S*)-**2h**: $[\alpha]^{23}_D$ −75 (*c* 0.08, $CHCl_3$); IR (film) 3286, 2934, 2835, 1753, 1593, 1516, 1455, 1262, 1237, 1141, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25−7.18 (m, 7H), 6.83 (d, J = 8.1 Hz, 1H), 5.81−5.75 (m, 1H), 5.17 (d, J = 17.0 Hz, 1H), 5.10 (d, J = 10.2 Hz, 1H), 4.45 (br s, 1H), 4.24 (dd, J = 7.1, 7.1 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.80−3.79 (m, 2H), 3.21−3.15 (m, 2H), 2.51 (dd, J = 13.1, 9.5 Hz, 1H), 2.46−2.43 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 149.1, 148.7, 135.9, 134.5, 134.3, 129.0, 128.8, 126.9, 120.3, 118.3, 111.1, 110.8, 65.8, 62.4, 58.1, 56.0, 55.9, 40.3, 36.8; MS (APCI) *m*/*z* (rel intensity) 383 ([M + H]$^+$, 7%). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.10; H, 6.85; N, 7.32. Found: C, 68.91; H, 6.75; N, 7.30. Minor diastereomer (1′*R*)-**2h**: colorless oil; $[\alpha]^{23}_D$ +28 (*c* 0.1, $CHCl_3$); IR (film) 3281, 2934, 2836, 1754, 1593, 1516, 1455, 1419, 1263, 1141, 1092, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.27−7.03 (m, 5H), 6.95 (d, J = 1.9 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.71 (dddd, J = 16.3, 13.8, 7.3, 6.1 Hz, 1H), 5.14−5.12 (m, 1H), 5.07−5.02 (m, 1H), 4.40−4.25 (br, 1H), 4.20 (dd, J = 7.0, 7.0 Hz, 1H), 4.01 (dd, J = 7.3, 7.3 Hz, 1H), 3.88−3.82 (m, 2H), 3.87 (s, 3H), 3.84 (s, 3H), 3.00 (dd, J = 13.9, 3.8 Hz, 1H), 2.52−2.43 (m, 2H), 2.14 (dd, J = 13.0, 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 149.0, 148.8, 136.0, 134.6, 133.4, 128.9, 128.8, 127.0, 120.5, 117.9, 111.3, 111.0, 66.4, 62.5, 58.9, 56.0, 55.9, 39.7, 37.6; MS (APCI) *m*/*z* (rel intensity) 341 ([M − allyl]$^+$, 100%). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.10; H, 6.85; N, 7.32. Found: C, 68.83; H, 6.84; N, 7.08.

Representative Procedure for Wacker Oxidation (8 and 9): (*S*)-*N*-[1-(3,4-Dimethoxyphenyl)-3-oxobutyl]benzamide (8). A mixture of benzamide **4h** (622 mg, 2.0 mmol), $PdCl_2$ (72 mg, 0.40 mmol), and $Cu(OAc)_2$ (148 mg, 0.80 mmol) in H_2O/DMF (1:7, 16 mL) was stirred under oxygen (1 atm) for 2 d. To the brownish mixture was added 1% HCl solution. The resulting clear solution was extracted with CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$ solution and brine. It was dried over anhydrous $MgSO_4$, concentrated, and purified by flash chromatography (1:1 hexanes−EtOAc). Methyl ketone **8** (576 mg, 88%) was obtained as a colorless solid: mp 139−140 °C; $[\alpha]^{21}_D$ −9.5 (*c* 0.39, $CHCl_3$); IR (film) 3329, 3064, 2997, 2940, 2837, 1715, 1636, 1516, 1462, 1418, 1359, 1261, 1142, 1026 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 7.0 Hz, 2H), 7.50−7.40 (m, 3H), 7.29 (d, J = 7.8 Hz, 1H), 6.88−6.80 (m, 3H), 5.55−5.49 (m, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.20 (d, J = 16.5 Hz, 1H), 3.00 (d, J = 16.5 Hz, 1H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1, 166.6, 149.3, 148.1, 134.3, 133.6, 131.6, 128.6, 127.0, 118.4, 111.4, 110.4, 56.0, 55.9, 50.0, 48.1, 31.0; MS (APCI) *m*/*z* (rel intensity) 327 ([M + 1]$^+$, 46%). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.51; H, 6.36; N, 4.17.

Representative Procedure for Cross Metathesis (11−15, 17−18): (*E*)-2,2,2-Trifluoro-*N*-(1-phenyl-4-trimethylsilylbut-3-enyl)-acetamide (11). To a Schlenk tube containing *rac*-**6a** (40 mg, 0.164 mmol) was added CH_2Cl_2 (2.7 mL), allyltrimethylsilane (80 μL, 0.492 mmol), and second-generation Grubbs catalyst **21a** (5% mol) under argon, then the mixture was heated at reflux. When the reaction was complete (TLC, ca. 3 h), the mixture was concentrated and passed through a short plug of silica gel, eluting with EtOAc. Concentration and purification by flash chromatography gave **11** as a mixture of alkene isomers (43 mg, 80%, *E*/*Z* = 2:1). Further chromatography (20:1 petroleum ether−methyl *tert*-butyl ether) gave (*E*)-**11** as a colorless oil: IR (film) 3309, 3085, 3036, 2947, 2907, 1715, 1698, 1653, 1557, 1539, 1453, 1416, 1317, 1248, 1183 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 6.47 (br s, 1H), 5.53 (ddd, J = 16.2, 8.1, 8.1 Hz, 1H), 5.10−5.05 (m, 1H), 4.98 (ddd, J = 7.0, 7.0, 7.0 Hz, 1H), 2.60−2.55 (m, 2H), 1.41 (d, J = 8.1 Hz, 1H), −0.06 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4 ($^2J_{CF}$ = 36.9 Hz), 139.6, 132.1, 128.9, 128.0, 126.4, 122.0, 115.9 ($^1J_{CF}$ = 286.4 Hz), 53.8, 39.1, 23.1, −2.1; MS (MALDI) *m*/*z* (rel intensity) 330 ([M + 1]$^+$, 8%); HRMS-CI (*m*/*z*) [M + H]$^+$ calcd for $C_{16}H_{23}F_3NOSi$, 330.1501, found 330.1500.

(*S*)-2,2,2-Trifluoro-*N*-allyl-*N*-(1-(3,4-dimethoxyphenyl)-1-butenyl)acetamide (20). To a solution of trifluoroacetamide *rac*-**6h** (53 mg, 0.175 mmol) in THF (1 mL) was added lithium hexamethyldisilazide (0.18 mL, 1 M in THF, 0.87 mmol) and allyl iodide (0.02 mL, 0.2 mmol). Monitoring by TLC showed no

(60) During preparation of this manuscript a related homoallylic amide Wacker oxidation approach was reported in a total synthesis of quinolizidine alkaloid abresoline. Atobe, M.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **2005**, *46*, 2669−2673.

(61) A statement of general experimental procedures is provided in the Supporting Information.

reaction. Additional allyl iodide (0.2 mL, 2 mmol) and HMPA (0.1 mL) were added at ambient temperature, and the mixture was stirred in the dark for 16 h. Concentration and flash chromatography gave *N*-allyl product **20** (35 mg, 58%) as a colorless liquid followed by unreacted **6h** (17 mg, 32%). Complicated NMR spectra were observed for **20** as a result of hindered rotation. IR (film) 3056, 2982, 2939, 2834, 2300, 1686, 1604, 1521, 1477, 1265, 1208, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92−6.80 (m, 3H), 5.79−5.66 (m, 2.5H), 5.60−5.48 (m, 4.5H), 3.93−3.67 (m, 8H), 2.93−2.61 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4 ($^2J_{CF}$ = 35.3 Hz), 149.1, 134.2, 134.0, 133.1, 132.2, 129.8, 128.8, 120.7, 120.1, 118.8, 118.0, 117.8, 116.6 ($^1J_{CF}$ = 287 Hz), 112.0, 111.5, 110.8, 110.7, 59.5, 59.4, 55.9, 55.8, 47.3, 46.1, 35.9, 35.2; MS (EI) *m*/*z* (rel intensity) 343.01 ($[M]^+$, 14%). Anal. Calcd for $C_{17}H_{20}F_3NO_3$: C, 59.47; H, 5.87; N, 4.08. Found: C, 59.49; H, 5.90; N, 4.03.

(*S*)-2-(3,4-Dimethoxyphenyl)-*N*-2,2,2-trifluoroacetyl-1,2,3,6-tetrahydropyridine (22). To a solution of *N*-allyltrifluoroacetamide **20** (25 mg, 0.072 mmol) in CH_2Cl_2 (36 mL) was added Grubbs catalyst **21b** (5.9 mg, 0.0072 mmol). After 16 h at ambient temperature, concentration and flash chromatography gave **22** (21 mg, 92.5%) as a colorless liquid. Complicated NMR spectra were observed for **22** as a result of hindered rotation (two rotamers, ratio 3:2). IR (film) 2929, 2851, 1687, 1518, 1451, 1257, 1188, 1143, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90−6.78 (m, 3H), 6.06−5.90 (m, 1H), 5.98 (d, J = 6.6 Hz, 0.6H), 5.66−5.61 (m, 1H), 5.30 (d, J = 5.7 Hz, 0.4H), 4.61 (br d, J = 18.1 Hz, 0.4H), 4.14 (br d, J = 17.8 Hz, 0.6H), 3.86 (s, 3H), 3.83 (s, 3H), 3.56−3.49 (m, 0.6H), 3.24 (br d, J = 18.9 Hz, 0.4H), 2.78−2.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2 ($^2J_{CF}$ = 35.3 Hz), 155.7 (J = 35.5 Hz), 149.1, 148.8, 130.6, 129.8, 124.7, 123.9, 123.4, 122.7, 119.5, 119.2, 116.7 ($^1J_{CF}$ = 286 Hz), 111.0, 110.9, 110.1, 56.0, 55.9, 53.5, 50.1, 40.9, 39.7, 28.2, 26.9; MS (EI) *m*/*z* (rel intensity) 315.2 ($[M]^+$, 42%). Anal. Calcd for $C_{15}H_{16}F_3NO_3$: C, 57.14; H, 5.12; N, 4.44. Found: C, 57.32; H, 5.09; N, 4.40.

7-((*S*)-1-(3,4-Dimethoxyphenyl)but-3-enylamino)hept-1-en-3-yl Methyl Carbonate (24). To a solution of amine **7** (187 mg, 0.903 mmol), tosylate **23**[62] (257 mg, 0.750 mmol), and Et_3N (0.11 mL, 0.825 mmol) in acetonitrile (9.0 mL) was added sodium iodide (169 mg, 1.12 mmol) in one portion under argon. The resulting white suspension was refluxed for 4 d. Basic brine (2 M NaOH saturated with NaCl) was added to the cooled reaction mixture and the mixture was extracted with CH_2Cl_2 and dried over anhydrous $MgSO_4$. Concentration and flash chromatography (1:1 hexanes−EtOAc to 30:1 CH_2Cl_2−MeOH to 5:1 CH_2Cl_2−MeOH) afforded unreacted amine **7** (48 mg) and **24** (183 mg, 65%, dr 1:1) as a pale yellow oil. IR (film) 3427, 3243, 3049, 2985, 2929, 1724, 1652, 1537, 1483, 1455, 1385, 1355, 1334, 1150, 907 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.80−6.77 (m, 2H), 5.77−5.63 (m, 2H), 5.23 (d, J = 17.0 Hz, 1H), 5.15 (d, J = 10.5 Hz, 1H), 5.09−4.96 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.72 (s, 3H), 3.53 (dd, J = 7.5, 6.0 Hz, 1H), 2.44−2.27 (m, 4H), 1.68−1.22 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 149.1, 148.0, 136.8, 136.0, 135.6, 119.4, 117.4 (2C), 111.0, 110.0, 79.0, 78.97, 62.4, 55.9, 54.6, 47.4, 43.2, 34.1, 29.9, 22.7. Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.82; H, 8.26; N, 3.91.

(*R*)-1-((*S*)-1-(3,4-Dimethoxyphenyl)but-3-enyl)-2-vinylpiperidine (2*R*-25) and (*S*)-1-((*S*)-1-(3,4-Dimethoxyphenyl)but-3-enyl)-2-vinylpiperidine (2*S*-25). To a solution of amine **24** (dr 1:1, 84.0 mg, 0.22 mmol), triphenylphosphine (35 mg, 0.13 mmol), and allylpalladium chloride dimer (13 mg, 0.036 mmol) was added Et_3N (80 μL, 0.57 mmol) via a microsyringe. The resulting solution was stirred at room temperature for 3 d, then concentrated. The residue was taken up by 3:1 hexanes−EtOAc and filtered. The filtrate was concentrated and purified by flash chromatography (5:1 to 1:1 hexanes−EtOAc) to give **25** (60 mg, 89%, (2*R*):(2*S*) = 1.6:1) as a pale yellow oil. The mixture was used in the next step without separation. Pure diastereomers were obtained by further flash chromatography. (2*R*)-**25**: pale yellow oil; $[\alpha]^{22}_D$ +1.2 (*c* 0.6, $CHCl_3$); IR (film) 3074, 2931, 2851, 2795, 1639, 1590, 1514, 1463, 1416, 1322, 1255, 1235, 1145, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.95 (s, 1H), 6.89−6.75 (m, 2H), 5.93 (ddd, J = 18.0, 9.5, 9.5 Hz, 1H), 5.65 (dddd, J = 17.0, 10.0, 6.5, 6.5 Hz, 1H), 5.21 (d, J = 17.5 Hz, 1H), 5.10 (d, J = 10.0 Hz, 1H), 4.98 (dd, J = 17.0, 1.5 Hz, 1H), 4.90 (d, J = 10.0 Hz, 1H), 3.96−3.90 (m, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.19 (dd, J = 6.5, 6.5 Hz, 1H), 2.63−2.41 (m, 3H), 2.16 (dd, J = 10.0, 10.0 Hz, 1H), 1.80−1.15 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 147.7, 141.6, 137.0, 135.2, 120.7, 115.9, 115.4, 112.6, 110.4, 62.8, 62.7, 55.92, 55.87, 45.2, 34.0, 30.4, 26.2, 23.7; MS (APCI) *m*/*z* (rel intensity) 302 ($[M + 1]^+$, 48%). Anal. Calcd for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03; N, 4.65. Found: C, 75.84; H, 9.17; N, 4.34. (2*S*)-**25**: pale yellow oil; $[\alpha]^{22}_D$ +20 (*c* 0.15, $CHCl_3$); IR (film) 3073, 2931, 2835, 2801, 2713, 1734, 1640, 1589, 1514, 1463, 1418, 1261, 1146, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85−6.70 (m, 3H), 5.88 (ddd, J = 17.5, 8.5, 8.5 Hz, 1H), 5.74 (dddd, J = 17.0, 10.5, 7.0, 7.0 Hz, 1H), 5.19−5.11 (m, 2H), 4.98 (dd, J = 17.0, 1.5 Hz, 1H), 4.94−4.88 (m, 1H), 3.98 (dd, J = 7.5, 7.5 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.93−2.84 (m, 1H), 2.72−2.46 (m, 2H), 1.85−1.02 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.1, 147.7, 143.8, 136.9, 130.3, 121.1, 115.5, 115.1, 112.9, 110.4, 63.7, 62.7, 55.9, 55.8, 45.5, 37.2, 34.8, 26.3, 24.1; MS (MALDI) *m*/*z* (rel intensity) 302 ($[M + 1]^+$, 27%); HRMS-CI (*m*/*z*) $[M + H]^+$ calcd for $C_{19}H_{28}NO_2$ 302.2107, found 302.2112.

(1*S*,2*S*)-6-(3,4-Dimethoxyphenyl)-1,3,4,6,6,7,9a-hexahydro-2*H*-quinolizine (26). A diastereomeric mixture of 2-vinylpiperidines (2*R*)-**25** and (2*S*)-**25** (114 mg, 0.378 mmol, dr = 1:1) and $TsOH\cdot H_2O$ (78 mg, 0.40 mmol) in CH_2Cl_2 (170 mL) was stirred at ambient temperature for 3 h. Second-generation Grubbs catalyst **21b** (50 mg, 0.0588 mmol) was added in one portion under argon. After 2 d at ambient temperature, a second portion of **21b** (20 mg, 0.024 mmol) was added. After another 36 h, the mixture was concentrated, acidified with 2 M HCl, and washed with EtOAc to remove the catalyst. The acidic aqueous phase was adjusted to pH 10 (2 M NaOH), extracted with CH_2Cl_2, and concentrated to afford **26** as a diastereomeric mixture (dr 1:1). Flash chromatography (2:1 hexanes−EtOAc to 20:1 EtOAc−MeOH to 8:1 EtOAc−MeOH) furnished the two separated diastereomers (88 mg in total, 85%) (9a*R*)-**26** and (9a*S*)-**26**. (9a*R*)-**26**: pale yellow oil; $[\alpha]^{25}_D$ −60 (*c* 0.8, $CHCl_3$); IR (film) 2927, 2850, 2739, 1589, 1511, 1460, 1323, 1260, 1144, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.82−6.74 (m, 2H), 5.90−5.84 (m, 1H), 5.57 (dd, J = 10.0, 1.5 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.88−2.79 (m, 1H), 2.72 (d, J = 11.5 Hz, 1H), 2.66 (d, J = 11.0 Hz, 1H), 2.26 (dd, J = 18.0, 1.5 Hz, 1H), 2.12−1.08 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 148.1, 138.4, 130.9, 124.2, 121.1, 111.8, 110.4, 61.0, 55.88, 55.82, 54.6, 52.5, 32.2, 31.9, 25.3, 24.7; HRMS-EI (*m*/*z*) $[M]^+$ calcd for $C_{17}H_{23}NO_2$ 273.1729, found 273.1724. (9a*S*)-**26**: pale yellow oil; $[\alpha]^{25}_D$ −58 (*c* 0.42, $CHCl_3$); IR (film) 2930, 2878, 2783 and 2728 (Bohlmann bands), 1698, 1648, 1516, 1260, 1233, 1134, 1029 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.83−6.75 (m, 2H), 5.76−5.69 (m, 1H), 5.88 (d, J = 9.5 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.22 (dd, J = 10.5, 3.5 Hz, 1H), 2.67 (d, J = 11.0 Hz, 2H), 2.45−2.38 (m, 1H), 2.25−1.15 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 148.1, 136.3, 130.7, 124.6, 120.4, 110.8, 110.6, 66.1, 63.21, 56.1, 55.9, 52.5, 36.5, 32.7, 26.3, 25.1; MS (APCI) *m*/*z* (rel intensity) 274 ($[M + 1]^+$, 100%); HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{24}NO_2$,274.1807, found 274.1804.

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Supporting Information Available: Characterization data and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(62) For preparation of **23**, see the Supporting Information.