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Communication

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Diastereodivergent [3+2] Annulation of Aromatic Aldimines with Alkenes via C−H Activation by Half-Sandwich Rare-Earth Catalysts

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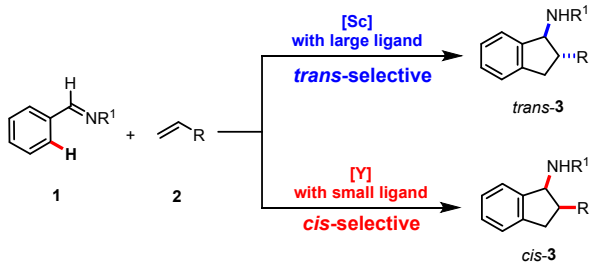
Supporting Information Placeholder

ABSTRACT: Stereodivergent catalysis is of great importance, as it can allow efficient access to all possible stereoisomers of a given product with multiple stereocenters from the same set of starting materials. We report herein the first diastereodivergent [3+2] annulation of aromatic aldimines with alkenes via C−H activation by half-sandwich rare-earth catalysts. This protocol provides an efficient and general route for the selective synthesis of both *trans* and *cis* diastereoisomers of multi-substituted 1-aminoindanes from the same set of aldimines and alkenes, featuring 100% atom efficiency, excellent diastereoselectivity, broad substrate scope, and good functional group compatibility. The diastereodivergence is achieved by fine-tuning the sterics or ligand/metal combination of the half-sandwich rare-earth metal complexes.

Aminoindanes are valuable compounds in biochemical and pharmacological research.[1] In particular, multi-substituted 1-aminoindanes containing contiguous stereogenic centers are important components in a large number of biologically active molecules and pharmaceuticals, in which the absolute and relative configurations are often crucial for the expression of biological activities.[2] Therefore, the development of efficient and selective methods that can provide a full set of all possible diastereoisomers of a given 1-aminoindane compound is of much interest and importance. The catalytic tandem [3+2] annulation of aromatic imines with alkenes, which involves the insertion of an alkene unit into an *ortho*-C−H bond of the aromatic substituent in the imine substrate followed by the intramolecular addition (cyclization) to the imine group, is among the most atom-efficient routes for the synthesis of multi-substituted 1-aminoindanes.[3,4] Obviously, the diastereodivergent catalysis of this transformation would be an ideal route for the efficient synthesis of different diastereomers of the 1-aminoindane products from the same set of imine and alkene starting materials.[5,6] However, such catalyst-controlled diastereodivergent synthesis of 1-aminoindane compounds has not been reported previously despite great interest and extensive studies in this area.[3-6]

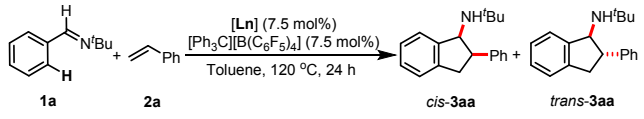
We have recently found that half-sandwich rare-earth alkyl complexes can serve as efficient catalysts for various chemical transformations,[7] including C−H addition to alkenes,[8] copolymerization of polar and non-polar olefins,[9] and diastereodivergent asymmetric carboamination/annulation of cyclopropenes with aminoalkenes.[10] These findings have invoked our interest in exploring the annulation of aldimines with alkenes by rare-earth catalysts. We report here for the first time the diastereodivergent [3+2] annulation of aromatic aldimines with alkenes by half-sandwich rare-earth catalysts with different sterics (Scheme 1). A scandium catalyst bearing the sterically demanding $C_5Me_4SiMe_3$ ligand selectively gave a *trans*-diastereoisomer of the 1-aminoindane, whereas the analogous yttrium complex bearing a smaller C_5Me_4H ligand afforded the *cis*-diastereoisomer. This protocol offers an unprecedented efficient route for the selective synthesis of both *trans* and *cis* diastereoisomers of 1-aminoindane derivatives from the same set of aldimine and alkene starting materials.

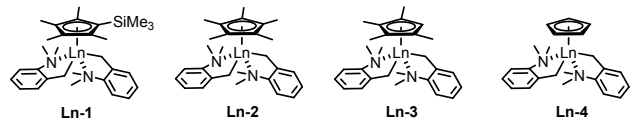
Scheme 1. Diastereodivergent [3+2] Annulation of Aldimines with Alkenes via C−H Activation by Rare-Earth Catalysts



At first, we examined the reaction of *N*-*tert*-butyl benzaldimine (**1a**) with styrene (**2a**) by using a series of half-sandwich scandium complexes bearing different Cp ligands.[11] In the presence of $[Ph_3C][B(C_6F_5)_4]$ as a cocatalyst, the $C_5Me_4SiMe_3$-ligated scandium complex **Sc-1** showed high activity and high stereoselectivity at 120 °C, quantitatively affording the [3+2] annulation product *trans*-**3aa** with excellent *trans*-diastereoselectivity (d.r. > 19:1) (Table 1, entry 1). When a less sterically demanding C_5Me_5-ligated scandium complex **Sc-2** was used, the diastereoselectivity was significantly deteriorated, yielding a 3.5:1 mixture of *trans*-**3aa** and *cis*-**3aa** (Table 1, entry 2). Intriguingly, the use of a further smaller C_5Me_4H-ligated complex **Sc-3** reversed the diastereoselectivity, giving a *cis*-rich diastereoisomer mixture although the selectivity was low (*trans*-**3aa**/*cis*-**3aa** = 1:1.5) (Table 1, entry 3). When the smallest C_5H_5-ligated complex **Sc-4** was employed, the *cis*-selectivity was greatly increased to *trans*-**3aa**/*cis*-**3aa** = 1:19, albeit in relatively low yields (37-45%) (Table 1, entries 4 and 5).[12]

Table 1. Catalyst Screening for [3+2] Annulation of Benzaldimine 1a with Styrene[a]





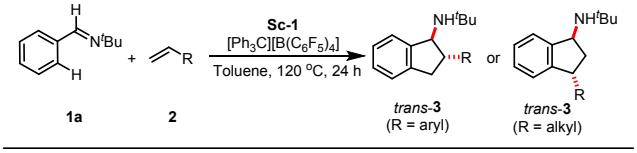
Entry	[Ln]	Yield (%)[b]	d.r. (*trans* : *cis*)[c]
1	**Sc-1**	99	> 19 : 1
2	**Sc-2**	99	3.5 : 1
3	**Sc-3**	99	1 : 1.5
4	**Sc-4**	37	1 : 19
5[d]	**Sc-4**	45	1 : 19
6[d,e]	**Y-1**	90	1 : 4
7[d,e]	**Y-2**	97	1 : 8
8[d,e]	**Y-3**	95	< 1 : 19
9[d,e]	**Y-4**	50	< 1 : 19

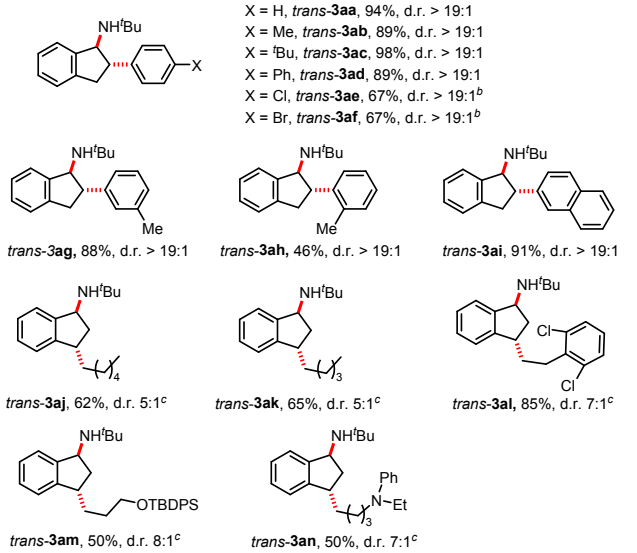
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.8 mmol), **[Ln]** (7.5 mol %), $[Ph_3C][B(C_6F_5)_4]$ (7.5 mol %), toluene (2 mL), 120 °C, 24 h, unless otherwise noted. [b] Combined NMR yield of both diastereomers. [c] Determined by NMR analysis. [d] **[Ln]** (10 mol %), $[Ph_3C][B(C_6F_5)_4]$ (10 mol %). [e] **2a** (0.6 mmol).

In sharp contrast with the exclusive formation of *trans*-**3aa** by **Sc-1**, the $C_5Me_4SiMe_3$-ligated yttrium analog **Y-1** afforded the *cis*-**3aa** as a major product (1:4 d.r.) (Table 1, entry 6).[13–15] In line with the trend observed above, the less hindered C_5Me_5-ligated yttrium complex **Y-2** showed a higher *cis*-diastereoselectivity (1:8 d.r.) (Table 1, entry 7). Remarkably, the even smaller C_5Me_4H-ligated complex **Y-3** exclusively afforded *cis*-**3aa** (< 1:19 d.r.) in 95% yield (Table 1, entry 8). The C_5H_5-ligated yttrium complex **Y-4** also gave *cis*-**3aa** with high diastereoselectivity, but in a lower yield similar to what was observed in the case of the analogous **Sc-4** (Table 1, entry 9).

Having established the catalyst-controlled diastereodivergent [3+2] annulation of **1a** with **2a** as shown above, we then examined the substrate scope of this transformation by using **Sc-1** and **Y-3**. Table 2 summarizes the *trans*-selective annulation of **1a** with various alkenes catalyzed by **Sc-1**. *Para*-substituted styrenes with either alkyl or aryl substituents worked well with **1a**, exclusively affording the corresponding 1-amino-2-aryl-*trans*-substituted indane derivatives *trans*-**3ab**–**3ad** with high yields (89–98%) and excellent diastereoselectivity (d.r. > 19:1). Chloro and bromo substituents were compatible (*trans*-**3ae** and *trans*-**3af**). *Meta*- and *ortho*-methyl-substituted styrenes also reacted with **1a** in a *trans*-diastereoselective fashion to give *trans*-**3ag** and *trans*-**3ah** with d.r. > 19:1, although a lower yield was observed in the case of *ortho*-methylstyrene probably due steric influence. 2-Vinylnaphthalene was also suitable for this reaction, giving the desired product *trans*-**3ai** in high yield and high diastereoselectivity (d.r. > 19:1). The [3+2] annulation of aliphatic alkenes with **1a** afforded the corresponding 1-amino-3-alkyl-*trans*-substituted indane derivatives *trans*-**3aj**–**3an** with d.r. in a range of 5:1 to 8:1.[16] Notably, the OTBDPS and NPhEt functional groups were compatible. No reaction between **1a** and vinyltrimethylsilane was observed, probably due to steric hindrance.

Table 2. *Trans*-Diastereoselective [3+2] Annulation of Aldimine 1a with Various Alkenes by Sc-1[a]

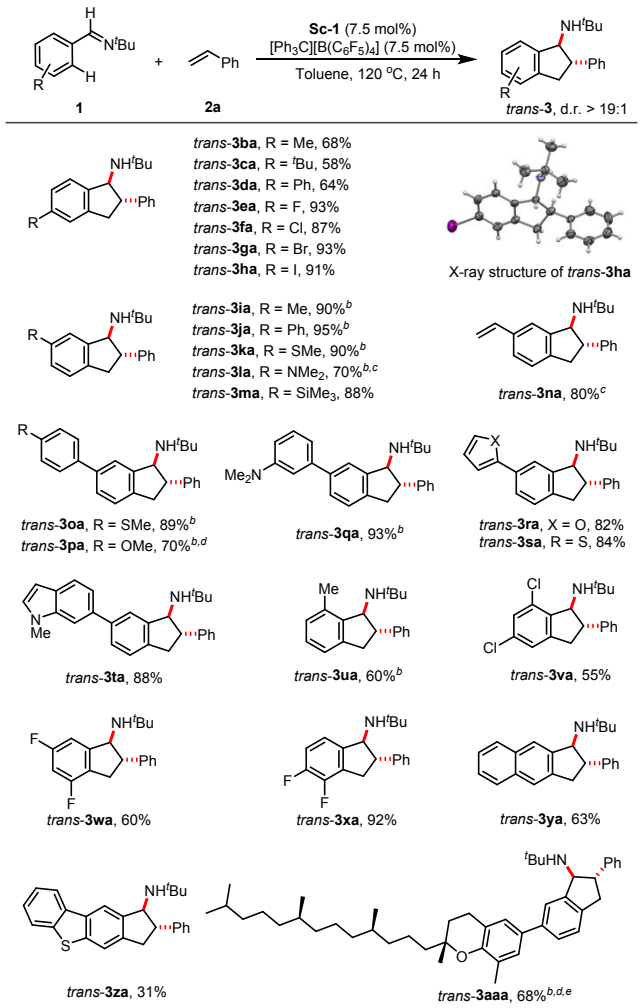




[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.8 mmol), **Sc-1** (7.5 mol%), $[Ph_3C][B(C_6F_5)_4]$ (7.5 mol%), toluene (2 mL), 120 °C, 24 h, isolated yields of *trans*-isomers, d.r. determined by NMR analysis of the crude product, unless otherwise noted. [b] **Sc-1** (12 mol%), $[Ph_3C][B(C_6F_5)_4]$ (12 mol%). [c] **Sc-1** (10 mol%), $[Ph_3C][B(C_6F_5)_4]$ (10 mol%).

The reactions of various *N*-*tert*-butyl aromatic aldimines with styrene catalyzed by **Sc-1** are shown in Table 3. Alkyl (**3ba**, **3ca**, **3ia**, **3ua**)- and aryl (**3da**, **3ja**, **3oa**–**3ta**)-substituted benzaldimines were all suitable for the *trans*-selective annulation with styrene, affording the corresponding *trans*-diastereoselective products in 58–95% yields with excellent d.r. (> 19:1). Functional groups such as halides (F, Cl, Br, I) (**3ea**–**3ha**, **3va**–**3xa**), $SiMe_3$ (**3ma**), NMe_2 (**3la**, **3qa**), SMe (**3ka**, **3oa**), OMe (**3pa**), vinyl (**3na**), and aromatic heterocycles (**3ra**–**3ta**) were compatible, thus offering more opportunities for further elaboration of the aminoindane products. In the case of *meta*-substituted benzaldimines (**3ia**–**3ta**), the reaction selectively occurred at the C–H bond *para* to the substituent probably due to steric influence. 2-Naphthyl aldimine was also suitable for this reaction, affording *trans*-**3ya** in 63% yield with excellent *trans*-diastereoselectivity (> 19:1 d.r.). The reaction of thiofluorenyl aldimine with styrene gave *trans*-**3za** (>19:1 d.r.) in 31% yield together a considerable amount of an unpurified amino-free indene product probably formed by the deamination of *trans*-**3za**.[4b,17] Remarkably, the reaction of a (+)-*δ*-tocopherol-derived aldimine with styrene also efficiently afforded the targeted *trans*-annulation product *trans*-**3aaa** in 68% yield with excellent diastereoselectivity at the indane ring (> 19:1 d.r.), demonstrating the useful potential of this protocol in the synthesis of aminoindane derivatives bearing naturally occurring structures. The configuration of *trans*-**3ha** was unequivocally determined by the X-ray crystallographic analysis.

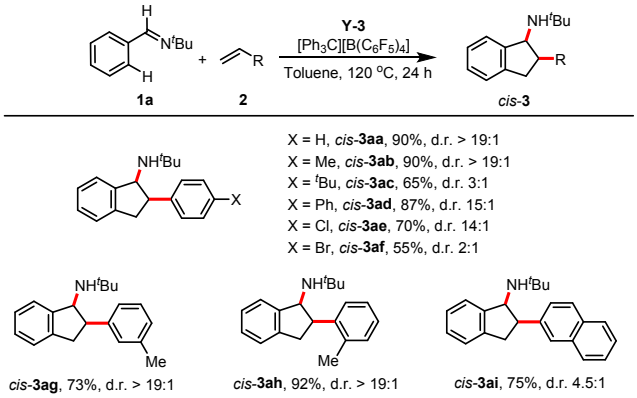
Table 3. *Trans*-Diastereoselective [3+2] Annulation of Various Aldimines with Styrene by Sc-1[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.8 mmol), **Sc-1** (7.5 mol%), $[Ph_3C][B(C_6F_5)_4]$ (7.5 mol%), toluene (2 mL), 120 °C, 24 h, isolated yields of *trans*-isomers, d.r. > 19:1 in all cases as shown by NMR analysis of the crude product, unless otherwise noted. [b] **Sc-1** (10 mol%), $[Ph_3C][B(C_6F_5)_4]$ (10 mol%). [c] 36 h. [d] 40 h. [e] 1:1 d.r. based on original chiral centers of the substrate.

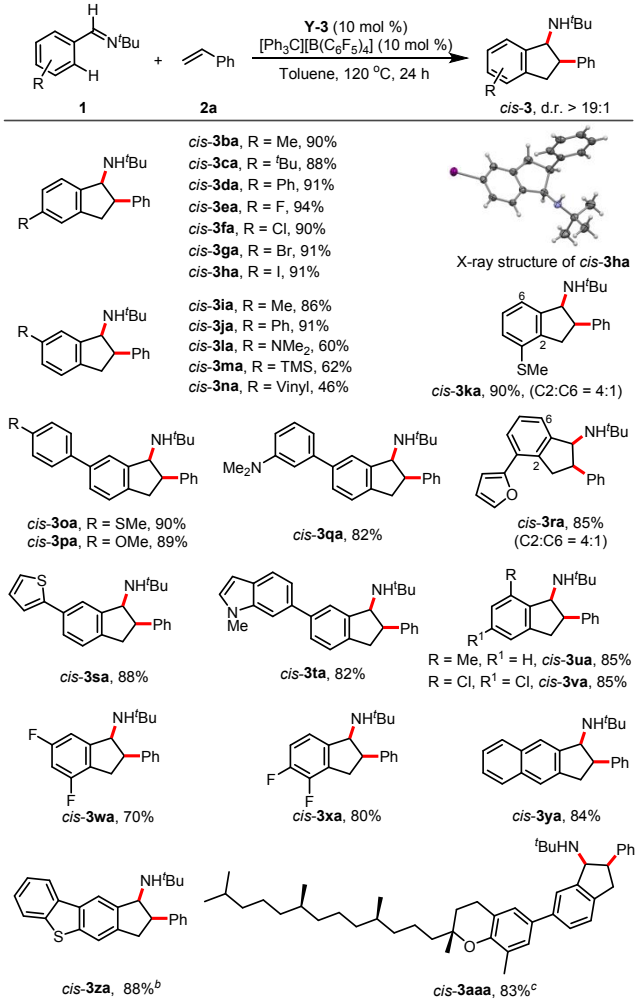
The *cis*-selective annulations of **1a** with various styrenes catalyzed by **Y-3** are shown in Table 4. *Para*-methyl-, phenyl-, and chloro-substituted styrenes all showed high *cis*-selectivity to give the corresponding *cis*-annulation products *cis*-**3ab**, *cis*-**3ad**, and *cis*-**3ae** in 70-90% yields with high d.r. (14:1 to >19:1). ^{t}Bu- and Br-substituted styrenes were less selective possibly due to steric influence.[18] *Meta*- and *ortho*-methyl-substituted styrenes also worked well with **1a**, affording the *cis*-selective products *cis*-**3ag** and *cis*-**3ah**, respectively with excellent diastereoselectivity (> 19:1). 2-Vinylnaphthalene showed relatively lower diastereoselectivity, giving *cis*-**3ai** in 75% yield with 4.5:1 d.r. The annulation reaction of aliphatic alkenes with **1a** by **Y-3** did not take place under the similar conditions, in agreement with the metal influences observed previously in olefin polymerization.[19]

Table 4. *Cis*-Diastereoselective [3+2] Annulation of Aldimine 1a with Various Styrenes by Y-3[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), **Y-3** (10 mol%), $[Ph_3C][B(C_6F_5)_4]$ (10 mol%), toluene (2 mL), 120 °C, 24 h, isolated yields of *cis*-isomers, d.r. determined by NMR analysis of the crude product.

Table 5. *Cis*-Diastereoselective [3+2] Annulation of Various Aldimines with Styrene by Y-3[a]

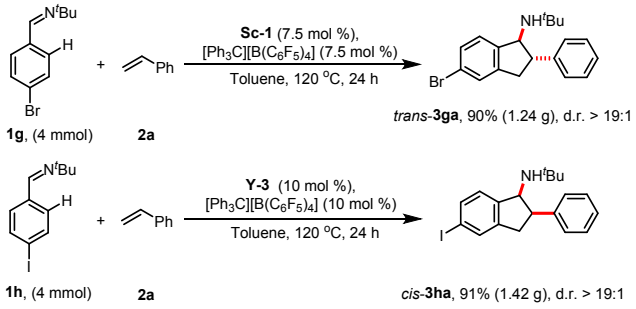


[a]Reaction Conditions: **1** (0.2 mmol), **2a** (0.6 mmol), **Y-3** (10 mol%), $[Ph_3C][B(C_6F_5)_4]$ (10 mol%), toluene (2 mL), 120 °C, 24 h, isolated yields of *cis*-isomers, d.r. > 19:1 in all cases as shown by NMR

analysis of the crude product, unless otherwise noted.. [b] 16:1 d.r. (*cis*/*trans*). [c] 1:1 d.r. based on original chiral centers of the substrate.

The aldimine substrate scope for the *cis*-diastereoselective [3+2] annulation with styrene by **Y-3** is shown in Table 5. It is generally similar to that for the *trans*-diastereoselective reactions catalyzed by **Sc-1**. Alkyl, aryl, vinyl, silyl, halogen, and heteroatom substituents were all compatible, affording the corresponding *cis*-diastereoselective annulation products in good yields with high d.r. (16:1 to > 19:1 d.r.). The configuration of *cis*-**3ha** was unequivocally determined by the X-ray crystallographic analysis. In the case of 3-thiomethyl- and 3-furyl-substituted benzaldimines, the C–H activation occurred at both the C2 and C6 positions to give the regioisomers with a ratio of C2/C6 = 4:1 in high *cis*-diastereoselectivity (see *cis*-**3ka** and *cis*-**3ra**). The preference of C−H activation at the C2 position was probably due to an interaction of the thiomethyl/furyl groups in the aldimines with the yttrium atom in **Y-3**. Such C2–H activation was not observed in the case of **Sc-1** (see *trans*-**3ka** and *trans*-**3ra**, Table 3) probably because of the steric hindrance of the $C_5Me_4SiMe_3$ ligand.

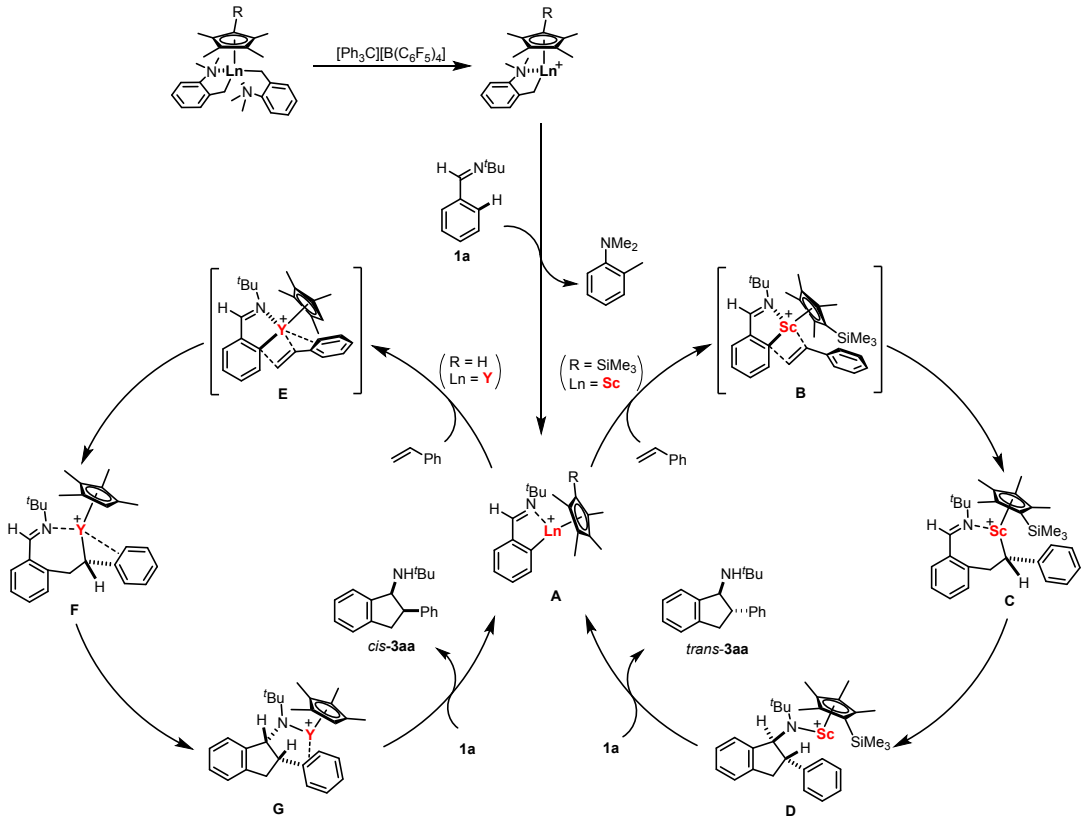
Scheme 2. Gram Scale Reactions



Scheme 2 shows two examples of gram-scale reactions catalyzed by **Sc-1** and **Y-3**, respectively, which gave the corresponding diastereoselective annulation products in excellent yields and excellent d.r., demonstrating again the synthetic usefulness of this protocol.[20,21]

A possible mechanism for the diastereodivergent annulations of aldimine **1a** with styrene **2a** by **Sc-1** and **Y-3** is shown in Scheme 3. The coordination of the nitrogen atom of **1a** to the metal atom of the cationic alkyl species, which was generated by the reaction of **Sc-1** or **Y-3** with $[Ph_3C][B(C_6F_5)_4]$,[11] followed by *ortho*-C−H activation (deprotonation) of the phenyl group in **1a** with the metal alkyl species would give a five-membered metallacycle intermediate like **A**. In the case of **Sc-1**, the 2,1-insertion of styrene into the Sc−aryl bond in **A** via a transition state like **B** should afford **C**, in which an interaction between the Sc atom and the phenyl group in the styrene unit might be difficult because of steric repulsion with the $C_5Me_4SiMe_3$ and N^{t}Bu groups. The intramolecular nucleophilic addition of the resulting Sc−C bond to the C=N unit in **C** would give the cyclization product **D** with a sterically favored *trans* configuration. The C−H activation (deprotonation) of **1a** by the Sc−N bond in **D** should release *trans*-**3aa** and regenerate the catalyst species **A**.[22] In the case of **Y-3**, the interaction between the Y atom and both the C=C double bond and the phenyl group in styrene could be possible to give a transition state like **E**, because the metal size of Y is larger than that of Sc and the C_5Me_4H ligand in **E** is much smaller than the $C_5Me_4SiMe_3$ ligand in **B**.[14,23] An Y---phenyl interaction could remain in the styrene insertion product **F**, which upon cyclization should yield the *cis* product **G** because of the amino---phenyl chelation to the Y atom. Finally, the acid-base reaction between **G** and **1a** releases *cis*-**3aa** and regenerates the catalyst species **A**.

Scheme 3. Proposed Reaction Mechanism of Diastereodivergent [3+2] Annulation of Aldimine1a with Styrene 2a



In summary, we have achieved for the first time the diastereodivergent [3+2] annulation of aromatic aldimines with alkenes via C−H activation by fine-tuning the metal/ligand combination or steric environment of a series of half-sandwich rare-earth metal catalysts. The combination of a sterically demanding ligand such as $C_5Me_4SiMe_3$ with scandium (**Sc-1**), which is the smallest metal in the rare-earth series, preferably affords the annulation products in a *trans*-selective fashion. In contrast, the analogous catalyst with a smaller ligand such as C_5Me_4H and a larger metal ion such as Y (**Y-3**) enables the selective formation of the *cis*-diastereoisomers. This protocol features broad substrate scope, high regio- and diastereoselectivity, and good functional group compatibility, offering an efficient route for the selective synthesis of both *cis* and *trans* diastereomers of a new family of multi-substituted 1-aminoindance derivatives from the same set of aldimine and alkene starting materials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Synthetic procedures, characterization data for all new compounds (PDF).

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Notes

The authors declare no competing financial interests.

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(22) For the formation of 1-amino-3-alkyl-*trans*-substituted indane derivatives in the case of aliphatic alkenes through a 1,2-insertion mechanism (Table 2, ***trans*-3aj**–**3an**), see Supporting Information (Figure S3).

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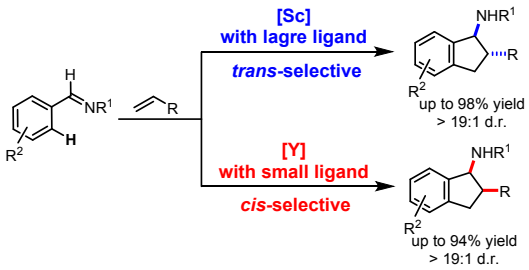
[Sc]
with lagre ligand
trans-selective
up to 98% yield
> 19:1 d.r.
[Y]
with small ligand
cis-selective
up to 94% yield
> 19:1 d.r.