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Catalytic Enantioselective Carboannulation with Allylsilanes

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Abstract

The first catalytic asymmetric carboannulation with allylsilanes is presented. The enantioselective [3+2] annulation is catalyzed using a Sc(III)-indapybox complex with tetrakis-[3,5-bis(trifluoromethyl)phenyl]-borate (BArF) to enhance catalytic activity and control stereoselectivity. Functionalized cyclopentanes containing a quaternary carbon are derived from alkylidene oxindole, coumarin, and malonate substrates with high stereoselectivity. The enantioselective 1,4-conjugate addition and enantioselective lactone formation (via trapping of the *β*-silyl carbocation) is also described.

Keywords

asymmetric catalysis; cyclopentane; NaBArF; scandium; conjugate addition

Lewis acid-catalyzed conjugate addition and cyclization reactions of unsaturated carbonyl compounds are important routes for the synthesis of complex heterocycles and carbocycles. Despite significant advances in asymmetric catalysis,[1,2] many conjugate addition and cyclization reactions using unsaturated carbonyl compounds still lack catalytic asymmetric variants. First reported by Knölker in 1990,[3] the cyclopentane annulation of air- and moisture-stable allylsilane nucleophiles with unsaturated carbonyl compounds is a transformation where a catalytic asymmetric variant has eluded development.[4-6] The challenge associated with controlling additions to unsaturated carbonyl compounds is highlighted by the fact that only one method has been reported for a catalytic enantioselective conjugate addition reaction using allylsilanes (Figure 1A).[7] Herein, we report the first catalytic asymmetric annulation of allylsilanes with unsaturated carbonyl compounds (Figure 1B) to access cyclopentanes possessing up to three stereocenters, including a quaternary carbon spirocenter.

The reaction of alkylidene oxindole **1** with allylsilane **2a**[8] offers a platform to study the reactivity and selectivity for the annulation reaction (Table 1). The selective formation of a cyclic product (e.g. **4**) or an allylation (Hosomi-Sakurai) product (e.g. **5**) is determined based on control of the *β*-silyl-stabilized carbocation intermediate (e.g. **3**).[9,10] Selective formation of spirocyclopentane **4**, resulting from rearrangement of the *β*-silyl carbocation intermediate,

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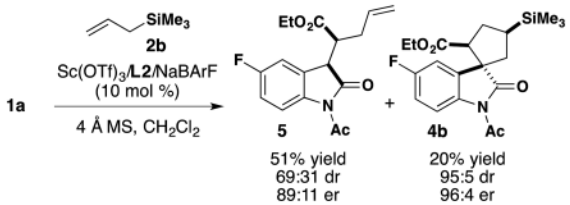
is a critical component of the successful development of this methodology. Our initial studies with chiral tin(IV),[11] copper(II),[7] and scandium(III)[5a,12] complexes afforded only low selectivity and/or low reactivity for the synthesis of spirocyclopentane **4a** (e.g. entries 1-4).[13]

To identify a more effective catalyst, we investigated Sc(III)-pybox complexes with NaBArF [BArF = $B(3,5\text{-}C_6H_3(CF_3)_2)_4$] (Table 1, entries 5-9).[14] A significant activating effect was observed for both $ScCl_3$- and $Sc(OTf)_3$-derived complexes, affording spirocyclopentane **4a**[15] with high yield and up to 97:3 enantioselectivity (entries 5 and 6). Using other counterions such as $NaSbF_6$ and KPF_6, or additives such as TMSCl, did not enhance reactivity (Table S1). The amount of NaBArF was also observed to play a significant effect on the enantioselectivity where increasing the NaBArF from 5 to 50 mol % lowered the rate of the reaction and afforded racemic product **4a** (entry 7). It was also observed that the indapybox ligand plays a critical role in diastereocontrol: in the absence of ligand, the annulation proceeded with low diastereoselectivity (65:35 dr, entry 8). Evaluation of various ligands showed that (*R*,*S*)-indapybox (**L2**) affords with the highest diastereo- and enantioselectivity (Table S1).

The primary activating effect of NaBArF is attributed to formation of the cationic scandium complex.[12] Formation of a cationic $Sc(OTf)_2BArF$•(*R*,*S*)-indapybox complex is supported by isolation of NaOTf from the precipitate (63% yield based on FAAS and ^{19}F NMR analysis).[16] The erosion of enantioselectivity with increasing NaBArF may be due to formation of $Sc(BArF)_3$ or $Sc(BArF)_2X$ species; however, investigation of a preformed $Sc(BArF)_3$ species did not show comparable erosion (entry 9).[17] Analysis of the $Sc(OTf)_2BArF$•(*R*,*S*)-indapybox complex using ^1H, ^{19}F and ^{45}Sc NMR spectroscopy indicates a dynamic catalyst complex that is rapid and reversible on the NMR time scale. Based on literature precedent for carbocation stabilization, we also hypothesize that NaBArF can play a secondary role to facilitate formation of the transient *β*-silyl carbocation (e.g. **3**).[18]

The Sc(III)-pybox/NaBArF system is also effective for the catalytic enantioselective 1,4-conjugate addition of allyltrimethyl-silane (**2b**) to afford allylation product **5** (eq 1). Even using a small silyl group such as TMS, these conditions still afford spirocyclopentane **4b**, which suggests that conditions using NaBArF suppress silyl elimination and/or promote 1,2-silyl migration of the *β*-silyl carbocation.



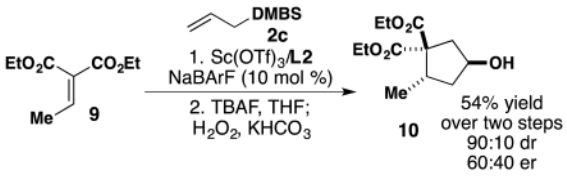
(1)

With this optimal catalyst system, we demonstrated that the spirocyclopentane annulation proceeds with excellent yields, diastereo- and enantioselectivity for a variety of alkylidene oxindole substrates (Table 2). Various ester (**1c**-**1g**) and nitrile (**1h**) substrates proceed efficiently. Phenyl-substituted alkylidene **1i** required higher catalyst loading and extended reaction times, affording spirocycle **4i** with high diastereoselectivity and moderate enantioselectivity. Chelating oxindoles containing urea and Cbz groups (**1j** and **1k**) also afford product **4** in excellent yield and enantioselectivity.[19]

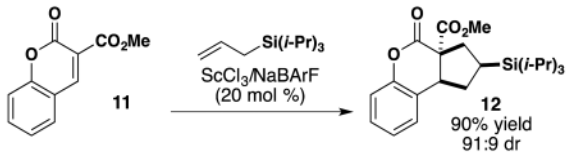
The NH spirooxindoles, such as **4l** and **4m**, can be accessed by simple deprotection of the N-Acyl oxindoles with $KHCO_3$ and H_2O_2 in high yield (80-88% yield over two steps). The silyl-substituted spirooxindoles can be oxidized using modified Tamao-Fleming conditions to generate hydroxy-substituted spirooxindoles (e.g. **6n**) with retention of stereochemistry.[21]

Rate enhancement observed with ester-substituted alkylidene **1d** compared to phenyl-substituted alkylidene **1i** (45 min vs 4 d) suggests that the reaction is promoted by coordination of the proximal ester group with the transient *β*-silyl carbocation (e.g. **7**, Table 3). Using *tert*-butyl substituted oxindole **1f** leads to trapping of the transient *β*-silyl carbocation and isolation of lactone **8f**.[15,22] The yield of lactone **8** is influenced by the use of chloride vs triflate salt (53 vs 18% yield, Table 3), which is attributed to Lewis acid initiated deprotection of the *tert*-butyl ester. The reaction of **1f** using excess NaBArF (60 mol %) promotes formation of allylation product **5f** with 95% conversion (in 48 h).

The enhanced catalytic activity with NaBArF and the reactivity trends observed with alkylidene oxindoles translate to malonate- and coumarin-derived electrophiles **9** and **11**, which broadens access to functionalized carbocycles containing a quaternary carbon (eqs 2 and 3).[23] Allylsilane annulation followed by oxidation afforded carbocycle **10** in high diastereoselectivity, but with low enantioselectivity (eq 2). Coumarin-derived cyclopentane **11**, a carbocycle not previously accessed using [3+2] annulation methodology, can also be accessed with high diastereoselectivity (eq 3). While oxindole derivatives are highly enantioselective, malonate and coumarin derivatives eluded asymmetric induction.



(2)



(3)

In summary, we have developed the first catalytic asymmetric [3+2] annulation of unsaturated carbonyl compounds with allylsilanes, giving spirocyclopentane core structures in high yields, diastereo- and enantioselectivities. Significant ligand and counterion effects are observed to control the path of the transient β-silyl carbocation (annulation vs allylation vs lactone), as well as the diastereo- and enantioselectivity. The annulation methodology can be applied to malonate- and coumarin-derived electrophiles with high yields and diastereoselectivities. More detailed mechanistic and computational studies are underway to elucidate the factors controlling the stereoselectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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15.

The structure and absolute stereochemistry of **4m** was assigned and confirmed based on X-ray crystallography (anomalous dispersion method). The relative stereochemistry of lactone **8f** was assigned by X-ray analysis. Absolute stereochemistry of **8f** was assigned by analogy to structure **4m**. CCDC 958776 (**4m**) and CCDC 961076 (**8f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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18.

For an example of NaBArF promoting formation of β-silyl carbocations, see: Lambert JB, Zhao Y, Wu H. J Org Chem. 1999; 64:2729. [PubMed: 11674342] . For an example of NaBArF allowing carbocation isolation, see: Bahr SR, Boudjouk P. J Org Chem. 1992; 57:5545..

19.

A chelating electrophile is required for enantiocontrol: *N*-methyl substrate **4o** afforded racemic product in 60% conversion.

20.

See Table S7 for details of deprotection conditions.

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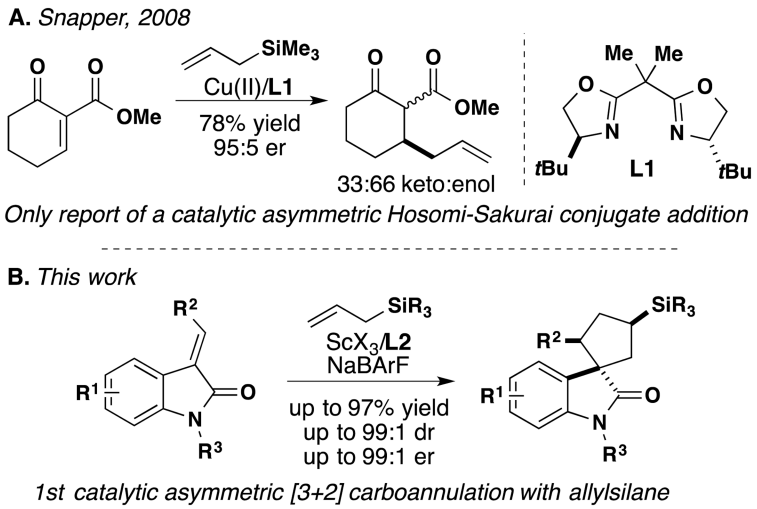
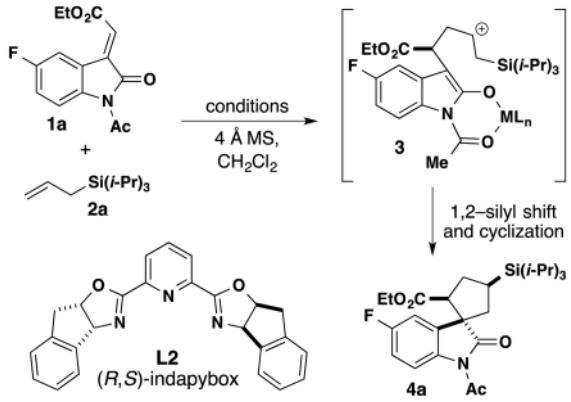


Figure 1. Catalytic asymmetric additions of allylsilanes to α,β-unsaturated carbonyl compounds

Table 1

Optimization of the allylsilane annulation with alkylidene oxindoles



entry	conditions	yield (%)[a]	dr[b]	er[c]
1	$SnCl_4$/(*S*)-BINOL (20 mol %), 24h	75[b]	50:50[d]	70:30
2	$Cu(OTf)_2$/(*S*)-PhBox/NaBArF (10 mol %), 168h	<5	nd	nd
3	$ScCl_3$/**L2**/$NaSbF_6$ (10 mol %), 72h	<5	nd	nd
4	$ScCl_3$/**L2**/$NaSbF_6$, TMSCl[e]	<10[b]	nd	nd
5	**$ScCl_3$/L2/NaBArF**	**99**	**99:1**	**97:3**
6	$Sc(OTf)_3$/**L2**/NaBArF	94	95:5	92:8
7	$ScCl_3$/**L2** with 50 mol % NaBArF	73	95:5	56:44
8	$ScCl_3$/NaBArF	95[b]	65:35	--
9	$Sc(BArF)_3$/**L2** (20 mol %)	100[b]	95:5	84:16

All reactions performed under argon with 3.0 equiv of allylsilane in a 1:1.1:1 ratio of $ScCl_3(THF)_3$, (*R*,*S*)-indapybox, and NaBArF for 1h at 5 mol % catalyst loading (unless otherwise noted).

[a] isolated yield.

[b] Determined using ^{1}H NMR spectroscopy.

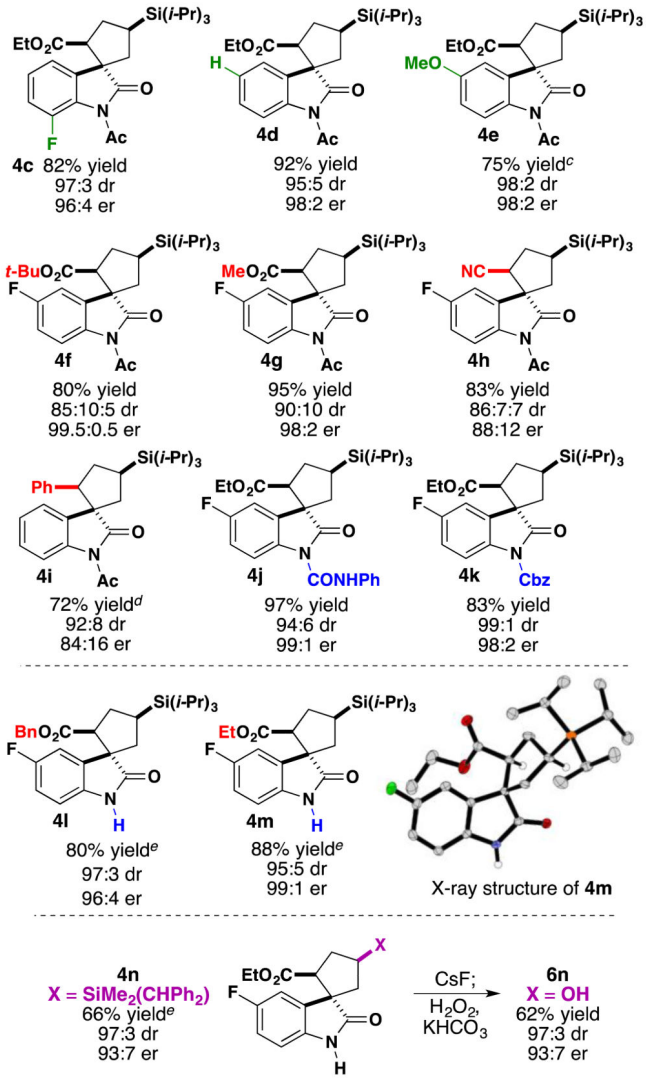
[c] Determined using chiral-phase HPLC.

[d] Allylation product **5** was also observed.

[e] 3 equivalents of TMSCl were used.

Table 2

Optimization of the allylsilane annulation with alkylidene oxindoles



Conditions: See Table 1, entry 5 (10 mol %).

[a] Isolated yield.

[b] Diastereo-meric and enantiomeric ratios determined as in Table 1.

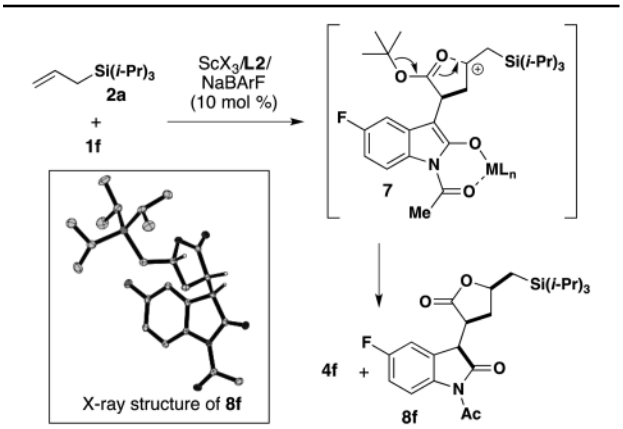
[c] Using 20 mol % catalyst.

[d] Reaction run for 4 d using 20 mol % catalyst with 20 mol % TfOH.

[e] Yield over two steps (See Table S7).[20]

Table 3

Formation of lactone 8f via trapping of β-silyl carbocation



X	ratio (8f:4f)[a]	yield of 8f (%)[b]	dr of 8f[c]	er of 8f[d]
OTf	63:37	53	44:17:19:20	85:15
Cl	19:81	18	21:47:23:9	94:6

[a] Based on mass recovery.

[b] Isolated yield.

[c] Determined using ^{1}H NMR spectroscopy.

[d] Determined using chiral-phase HPLC.