

Catalytic Enantioselective Carboannulation with Allylsilanes**

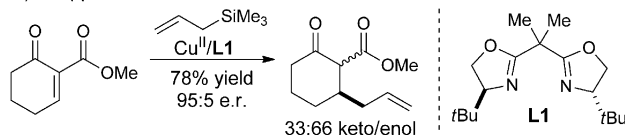
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Abstract: The first catalytic asymmetric carboannulation with allylsilanes is presented. The enantioselective [3+2] annulation is catalyzed using a scandium(III)/indapybox complex with tetrakis-[3,5-bis(trifluoromethyl)phenyl]-borate (BArF) to enhance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

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 et al. 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 (Scheme 1 A).^[7] Herein, we report the first catalytic asymmetric annulation of allylsilanes with unsaturated carbonyl compounds (Scheme 1 B) to access cyclopentanes possessing up to three stereocenters, including a quaternary carbon spirocenter.

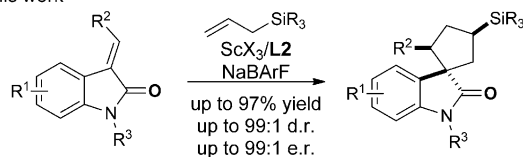
The reaction of the alkylidene oxindole **1a** with allylsilane **2a**^[8] offers a platform to study the reactivity and selectivity for the annulation reaction (Table 1). The selective formation of a cyclic product (**4**) or an allylation (Hosomi–Sakurai)

A) Snapper, 2008



only report of a catalytic asymmetric Hosomi–Sakurai conjugate addition

B) This work



first catalytic asymmetric [3+2] carboannulation with allylsilane

Scheme 1. Catalytic asymmetric additions of allylsilanes to α,β -unsaturated carbonyl compounds. BArF = tetrakis-[3,5-bis(trifluoromethyl)-phenyl]borate.

Table 1: Optimization of the allylsilane annulation with alkylidene oxindoles.^[a]

Entry	Conditions	Yield [%] ^[b]	d.r. ^[c]	e.r. ^[d]
1	SnCl ₄ /(S)-binol (20 mol %), 24 h	75 ^[e]	50:50 ^[e]	70:30
2	Cu(OTf) ₂ /(S)-PhBox/NaBARF (10 mol %), 168 h	< 5	n.d.	n.d.
3	ScCl ₃ /L2/NaSbF ₆ (10 mol %), 72 h	< 5	n.d.	n.d.
4	ScCl ₃ /L2/NaSbF ₆ , TMSCl ^[f]	< 10 ^[e]	n.d.	n.d.
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 ^[e]	65:35	–
9	Sc(BArF) ₃ /L2 (20 mol %)	99 ^[e]	95:5	84:16

[a] All reactions performed under argon with 3.0 equiv of allylsilane in a 1:1.1:1 ratio of [ScCl₃(thf)₃], (R,S)-indapybox, and NaBARF for 1 h at a 5 mol % catalyst loading (unless otherwise noted). [b] Yield of isolated product. [c] Determined using ¹H NMR spectroscopy. [d] Determined using chiral-phase HPLC. [e] Allylation product **5** was also observed. [f] Used 3 equiv of TMSCl. binol = 2,2'-dihydroxy-1,1'-binaphthyl, M.S. = molecular sieves, Tf = trifluoromethanesulfonyl, thf = tetrahydrofuran, TMS = trimethylsilyl.

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product **5**; for structure see Eq. (1)] is determined based on control of the β -silyl-stabilized carbocation intermediate **3**.^[9,10] Selective formation of **4**, resulting from rearrangement of the β -silyl carbocation intermediate, 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 **4a** (entries 1–4).^[13]

To identify a more effective catalyst, we investigated scandium(III)/pybox complexes with NaBARF [BARF = B-(3,5-C₆H₃(CF₃)₂)₄] (Table 1, entries 5–9).^[14] A significant activating effect was observed for both ScCl₃- and Sc(OTf)₃-derived complexes, thus affording **4a**^[15] with high yield and up to 97:3 enantioselectivity (entries 5 and 6). Using other counterions such as NaSbF₆ and KPF₆, or additives such as TMSCl, did not enhance reactivity (see Table S1 in the Supporting Information). The amount of NaBARF was also observed to have a significant effect on the enantioselectivity where increasing the NaBARF from 5 to 50 mol % lowered the rate of the reaction and afforded racemic **4a** (Table 1, 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 (entry 8). Evaluation of various ligands showed that (*R,S*)-indapybox (**L2**) affords the highest diastereo- and enantioselectivity (Table S1).

The primary activating effect of NaBARF is attributed to the formation of a 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 ¹⁹F NMR analysis).^[16] The erosion of enantioselectivity with increasing amounts of NaBARF may be due to generation of Sc(BARF)₃ or Sc(BARF)₂X species. However, investigation of a preformed Sc(BARF)₃ species did not show comparable erosion (Table 1, entry 9).^[17] Analysis of the Sc(OTf)₂BARF·(*R,S*)-indapybox complex using ¹H, ¹⁹F, and ⁴⁵Sc NMR spectroscopy indicates that formation of a dynamic catalyst complex 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 (**3**).^[18]

The scandium(III)/pybox/NaBARF system is also effective for the catalytic enantioselective 1,4-conjugate addition of allyltrimethylsilane (**2b**) to afford the allylation product **5** [Eq. (1)]. Even when using a small silyl group such as TMS, these reaction conditions still afford **4b**, which suggests that reaction conditions using NaBARF suppress silyl elimination and/or promote 1,2-silyl migration.

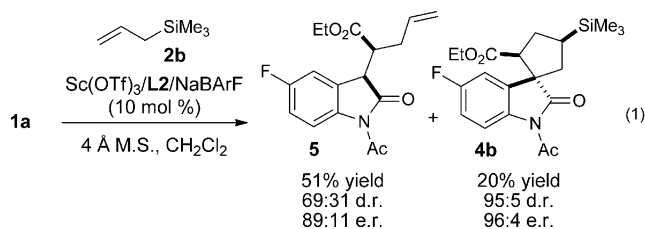


Table 2: Optimization of the allylsilane annulation with alkylidene oxindoles.^[a,b]

4c 82% yield 97:3 d.r. 96:4 e.r.	4d 92% yield 95:5 d.r. 98:2 e.r.	4e 75% yield^[c] 98:2 d.r. 98:2 e.r.
4f 80% yield 85:10:5 d.r. 99.5:0.5 e.r.	4g 95% yield 90:10 d.r. 98:2 e.r.	4h 83% yield 86:7:7 d.r. 88:12 e.r.
4i 72% yield^[d] 92:8 d.r. 84:16 e.r.	4j 97% yield 94:6 d.r. 99:1 e.r.	4k 83% yield 99:1 d.r. 98:2 e.r.
4l 80% yield^[e] 97:3 d.r. 96:4 e.r.	4m 88% yield^[e] 95:5 d.r. 99:1 e.r.	X-ray structure of 4m
4n X = SiMe₂(CHPh₂) 66% yield^[e] 97:3 d.r. 93:7 e.r.	6n X = OH 62% yield 97:3 d.r. 93:7 e.r.	

[a] Reaction conditions: See Table 1, entry 5 (10 mol %). Yield of isolated product. [b] Diastereomeric and enantiomeric ratios determined as in Table 1. [c] Using 20 mol % catalyst. [d] Reaction run for 4 days using 20 mol % catalyst with 20 mol % TFOH. [e] Yield over two steps (see Table S7).^[20] Thermal ellipsoids shown at 50% probability.

With this optimal catalyst system, we demonstrated that the spirocyclopentane annulation proceeds with excellent yields, and diastereo- and enantioselectivity for a variety of alkylidene oxindole substrates (Table 2). Various ester (**1c–g**) and nitrile (**1h**) substrates proceed efficiently. The phenyl-substituted alkylidene **1i** required higher catalyst loading and extended reaction times, thus affording the spirocycle **4i** with high diastereoselectivity and moderate enantioselectivity. Chelating oxindoles containing urea and Cbz groups (**1j** and **1k**) also afford the products **4j** and **4k**, respectively, 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 KHCO₃ and H₂O₂ in high yield (80–88 % yield over two steps). The silyl-substituted spirooxindoles can be oxidized

Table 3: Formation of the lactone **8f** by trapping of a β -silyl carbocation.

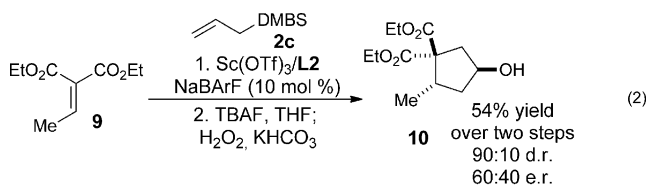
X	Ratio (8f / 4f) ^[a]	Yield [%] ^[b]	d.r. ^[c]	e.r. ^[d]
OTf	63:37	53	44:17:19:20	85:15
Cl	19:81	18	21:47:23:9	94:6

[a] Based on mass recovery. [b] Yield of isolated product. [c] Determined using ^1H NMR spectroscopy. [d] Determined using chiral-phase HPLC. Thermal ellipsoids shown at 30% probability.

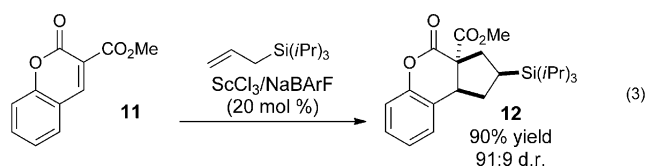
using modified Tamao–Fleming conditions to generate hydroxy-substituted spirooxindoles (**6n**) with retention of stereochemistry.^[21]

Rate enhancement observed with the ester-substituted alkylidene **1d** compared to that of the phenyl-substituted alkylidene **1i** (45 min versus 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 the *tert*-butyl-substituted oxindole **1f** leads to trapping of the transient β -silyl carbocation and isolation of the lactone **8f**.^[15,22] The yield of **8f** is influenced by the use of chloride versus triflate salt (53 versus 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 allylation with 95% conversion (in 48 h).

The enhanced catalytic activity with NaBARF and the reactivity trends observed with alkylidene oxindoles translate to the malonate- and coumarin-derived electrophiles **9** and **11**, respectively, which broadens access to functionalized carbocycles containing a quaternary carbon center [Eqs. (2) and



(3); DMBS = dimethylbenzhydrylsilane, TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran).^[23] Allylsilane annulation followed by oxidation afforded the carbocycle **10** in high diastereoselectivity, but with low enantioselectivity [Eq. (2)]. The 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.

In summary, we have developed the first catalytic asymmetric [3+2] annulation of unsaturated carbonyl compounds with allylsilanes, thus giving spirocyclopentane core structures in high yields, and diastereo- and enantioselectivities. Significant ligand and counterion effects are observed to control the path of the transient β -silyl carbocation (annulation versus allylation versus 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.

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