Synthetic Methods

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Catalytic Enantioselective Carboannulation with Allylsilanes**

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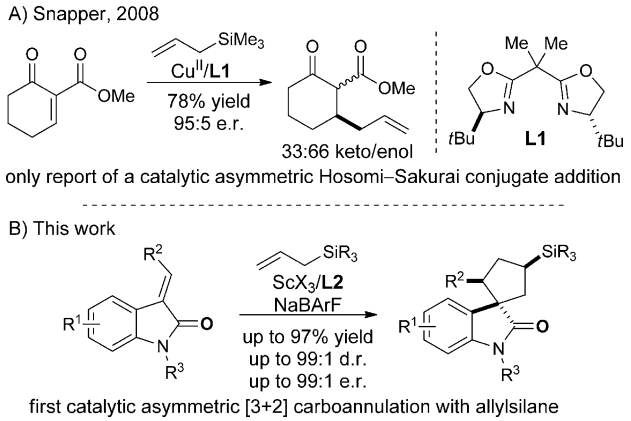
Abstract: *The first catalytic asymmetric carboannulation with allylsilanes is presented. The enantioselective [3+2] annulation is catalyzed using a scandium(III)/indapybox complex with tetrakis-[3,5-bis(trifluoromethyl)phenyl]-borate (BArF) to enhance catalytic activity and control stereoselectivity. 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.*

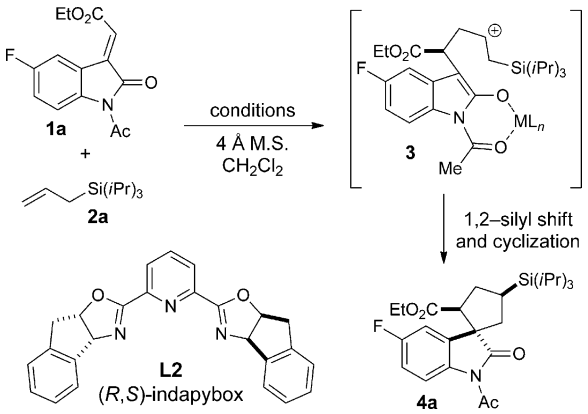
Lewis acid catalyzed conjugate addition and cyclization reactions of unsaturated carbonyl compounds are important routes for the synthesis of complex heterocycles and carbocycles. Despite significant advances in asymmetric catalysis,[1,2] many conjugate addition and cyclization reactions using unsaturated 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)



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[c]	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[c]	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[c]	65:35	–
9	$Sc(BArF)_3$/**L2** (20 mol%)	99[c]	95:5	84:16

[a] 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 1 h at a 5 mol% catalyst loading (unless otherwise noted). [b] Yield of isolated product. [c] Determined using ^{1}H 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-$C_6H_3(CF_3)_2)_4$] (Table 1, entries 5–9).[14] A significant activating effect was observed for both $ScCl_3$- and $Sc(OTf)_3$-derived complexes, thus affording **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 (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 $Sc(OTf)_2$BArF·(*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 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 $Sc(OTf)_2$BArF·(*R*,*S*)-indapybox complex using ^1H, ^{19}F, and ^{45}Sc 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.

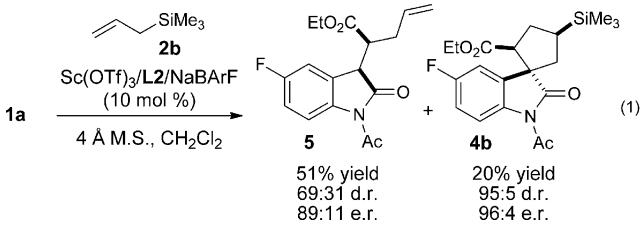
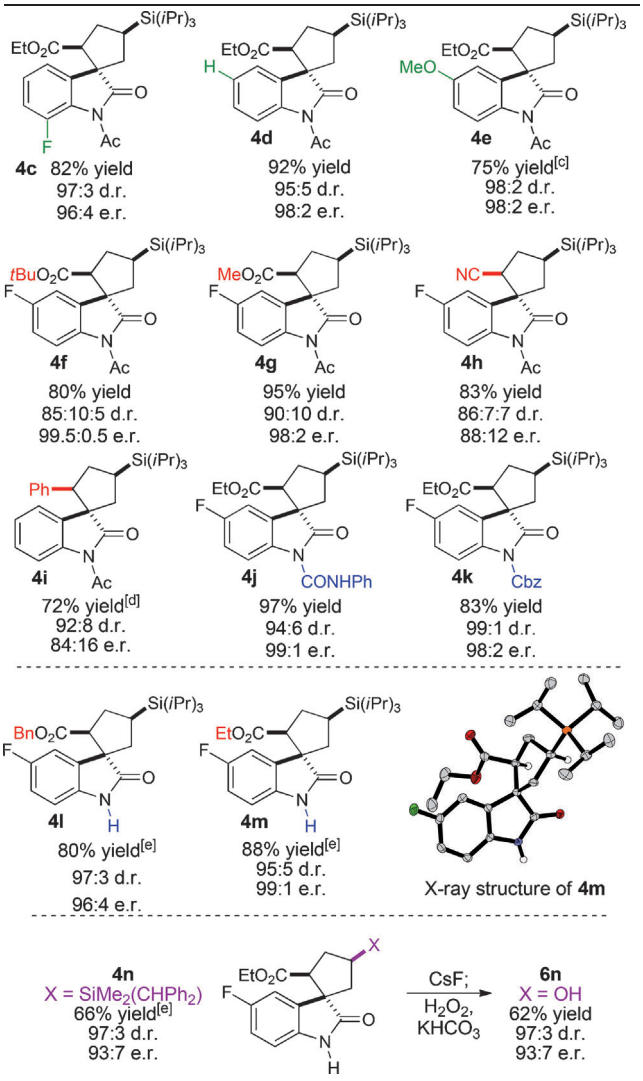


Table 2: Optimization of the allylsilane annulation with alkylidene oxindoles.[a,b]

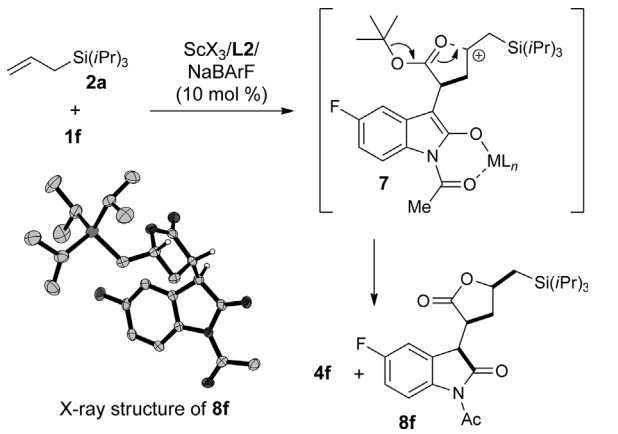


[a] Reaction conditions: See Table 1, entry 5 (10 mol%). Yield of isolated product. [b] Diastereomeric and enantiomeric ratios determined as in Table 1. [c] Using 20 mol% catalyst. [d] Reaction run for 4 days using 20 mol% catalyst with 20 mol% TfOH. [e] Yield over two steps (see Table S7).[20] Thermal 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 $KHCO_3$ and H_2O_2 in high yield (80–88% yield over two steps). The silyl-substituted spirooxindoles can be oxidized

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



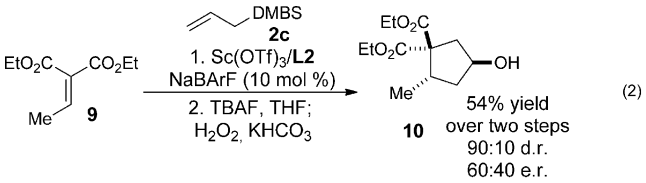
X	Ratio (**8 f**/**4 f**)[a]	Yield [%][b]	d.r.[c]	e.r.[d]
OTf	63:37	53	44:17:19:20	85:15
Cl	19:81	18	21:47:23:9	94:6

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

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

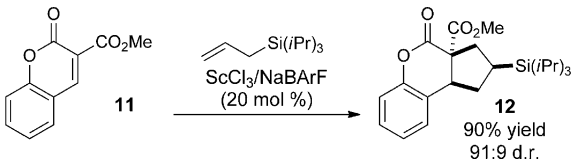
Rate enhancement observed with the ester-substituted alkylidene **1 d** compared to that of the phenyl-substituted alkylidene **1 i** (45 min versus 4 d) suggests that the reaction is promoted by coordination of the proximal ester group with the transient β-silyl carbocation (e.g. **7**; Table 3). Using the *tert*-butyl-substituted oxindole **1 f** leads to trapping of the transient β-silyl carbocation and isolation of the lactone **8 f**.[15,22] The yield of **8 f** 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 **1 f** 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



(2)

(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



(3)

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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[1] G. P. Howell, *Org. Process Res. Dev.* **2012**, *16*, 1258.
[2] a) J. Christoffers, G. Koripelly, A. Rosiak, M. Rössle, *Synthesis* **2007**, 1279; b) D. A. Evans, T. Rovis, J. S. Johnson, *Pure Appl. Chem.* **1999**, *71*, 1407.
[3] H.-J. Knölker, P. G. Jones, J.-B. Pannek, *Synlett* **1990**, 429.
[4] For diastereoselective examples, see: a) R. L. Danheiser, B. R. Dixon, R. W. Gleason, *J. Org. Chem.* **1992**, *57*, 6094; b) J. S. Panek, N. F. Jain, *J. Org. Chem.* **1993**, *58*, 2345; c) H.-J. Knölker, N. Foitzik, O. Schmitt, *Tetrahedron Lett.* **1999**, *40*, 3557; d) H. J. Knölker, P. G. Jones, R. Graf, *Synlett* **1996**, 1155.
[5] a) For the catalytic asymmetric allylsilane [3+2] annulation with isatins, see: N. V. Hanhan, N. R. Ball-Jones, N. T. Tran, A. K. Franz, *Angew. Chem.* **2012**, *124*, 1013; *Angew. Chem. Int. Ed.* **2012**, *51*, 989; b) During review of this manuscript, the first catalytic asymmetric allylsilane [4+2] annulation with β,γ-unsaturated α-ketoesters was reported. See: Y. Matsumura, T. Suzuki, A. Sakakura, K. Ishihara, *Angew. Chem.* **2014**, *126*, 6245; *Angew. Chem. Int. Ed.* **2014**, *53*, 6131.
[6] Allylsilane precursors have been used to generate trimethylenemethane nucleophiles. See: B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396.
[7] M. Shizuka, M. L. Snapper, *Angew. Chem.* **2008**, *120*, 5127; *Angew. Chem. Int. Ed.* **2008**, *47*, 5049.
[8] M. G. Organ, V. Dragan, M. Miller, R. D. J. Froese, J. D. Goddard, *J. Org. Chem.* **2000**, *65*, 3666.
[9] M. A. Brook in *Silicon in Organic, Organometallic, and Polymer Chemistry*, Wiley, New York, **2000**, pp. 521 – 523.
[10] For reviews on allylsilane reactivity, see: a) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, *95*, 1293; b) L. Chabaud, P. James, Y. Landais, *Eur. J. Org. Chem.* **2004**, 3173; c) A. W. Schmidt, H.-J. Knölker, *Synlett* **2010**, 2207.
[11] M. E. Kieffer, L. M. Repka, S. E. Reisman, *J. Am. Chem. Soc.* **2012**, *134*, 5131.

[12] a) D. A. Evans, J. Wu, C. E. Masse, D. W. C. MacMillan, *Org. Lett.* **2002**, *4*, 3379; b) D. A. Evans, K. R. Fandrick, H.-J. Song, K. A. Scheidt, R. Xu, *J. Am. Chem. Soc.* **2007**, *129*, 10029.

[13] Other Lewis-acidic metal complexes (e.g. In, Bi, Zn, Cu) are ineffective as catalysts. See Tables S1–S4 in the Supporting Information.

[14] a) H. Nishida, N. Takada, M. Yoshimura, T. Sonoda, H. Kobayashi, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2600; b) I. Krossing, I. Raabe, *Angew. Chem.* **2004**, *116*, 2116; *Angew. Chem. Int. Ed.* **2004**, *43*, 2066.

[15] The structure and absolute stereochemistry of **4m** was assigned based on X-ray crystallography (anomalous dispersion method). The relative stereochemistry of **8f** was assigned by X-ray analysis. Absolute stereochemistry of **8f** was assigned by analogy to the structure of **4m**. CCDC 958776 (**4m**) and 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.

[16] a) M. Brookhart, B. Grant, J. Volpe, *Organometallics* **1992**, *11*, 3920; b) B. A. Arndtsen, R. G. Bergman, *Science* **1995**, *270*, 1970.

[17] See Table S5 for details. Also see: S. France, M. H. Shah, A. Weatherwax, H. Wack, J. P. Roth, T. Lectka, *J. Am. Chem. Soc.* **2005**, *127*, 1206.

[18] For an example of NaBArF promoting formation of β-silyl carbocations, see: a) J. B. Lambert, Y. Zhao, H. Wu, *J. Org. Chem.* **1999**, *64*, 2729. For an example of NaBArF allowing carbocation isolation, see: b) S. R. Bahr, P. Boudjouk, *J. Org. Chem.* **1992**, *57*, 5545.

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

[20] See Table **S7** for details of deprotection conditions.

[21] a) Z. H. Peng, K. A. Woerpel, *Org. Lett.* **2001**, *3*, 675; b) Z. H. Peng, K. A. Woerpel, *Org. Lett.* **2000**, *2*, 1379.

[22] For examples of heterocycle formation by trapping of carbocations, see: a) S. Yamazaki, K. Ohmitsu, K. Ohi, T. Otsubo, K. Moriyama, *Org. Lett.* **2005**, *7*, 759; b) B. H. Shupe, E. E. Allen, J. P. MacDonald, S. O. Wilson, A. K. Franz, *Org. Lett.* **2013**, *15*, 3218; c) T. Ollevier, Z. Li, *Adv. Synth. Catal.* **2009**, *351*, 3251.

[23] The relative stereochemistry of **10** and **12** was assigned by analogy to literature reports. See: H.-J. Knölker, N. Foitzik, H. Goesmann, R. Graf, P. G. Jones, G. Wanzl, *Chem. Eur. J.* **1997**, *3*, 538.

