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Stereoselective Multiple Functionalization of Pyrylium Salts by Domino Reactions with 2-Silyloxybuta-1,3-dienes**

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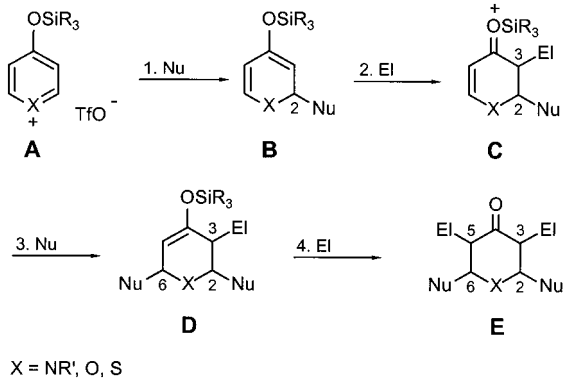
The development of multicomponent domino reactions is particularly attractive as these allow the stereoselective conversion of several simple substrates into complex target molecules, such as annulated or bridged polycycles, in a single step.[1] Pyrylium salts are easily accessible, reactive heteroarenes that react preferably with nucleophiles. Apart from transformations that proceed with conservation of the pyran ring, we are also familiar with reactions in which the primary adducts are stabilized by ring opening or subsequent ring transformation.[2] In contrast, only a few stereoselective reactions that start from pyrylium salts are known to result in complex ring systems. One exception is the 1,3-dipolar cycloadditions of 3-oxidopyrylium salts, which have initially been developed by Sammes et al. and later by Wender, Mascareñas, and Magnus and co-workers to provide an attractive route to various ring systems and natural products.[3]

One concept that may be applied to yield products of a higher complexity in diastereomerically pure form from simple components is the multiple functionalization of positively charged heteroarenes. Here, **A** first reacts regioselectively with a nucleophile at C-2. The resulting enol ether **B** can then react with an electrophile at C-3 forming the Michael acceptor **C**. Subsequent transformation with a nucleophile at C-6 and an electrophile at C-5 yield the trisubstituted **D** and the tetrasubstituted heterocycle **E**, respectively (Scheme 1). Following research on the selective mono- and bisfunctional-



Scheme 1. Multiple functionalization of positively charged heteroarenes.

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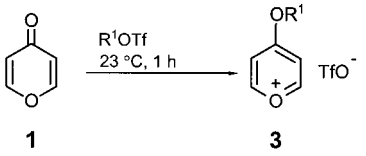
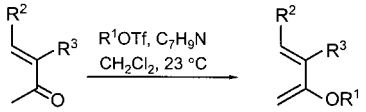
ization of benzannulated systems,[4] we here report on the first selective tris- and tetrafunctionalization of 4-silyloxypyrylium triflates by domino reactions with two equivalents of a 2-silyloxybuta-1,3-diene.

The 4-silyloxypyrylium triflates **3** required as substrates are easily accessible in situ from pyran-4-one (**1**) and silyl triflates R^1OTf under mild conditions [Eq. (1)] and can be reacted with 2-silyloxybuta-1,3-dienes **4** and **9**, respectively. The latter two are also generated in situ in the same flask by the reaction of α,β-unsaturated methyl ketones **2** with silyl triflates in the presence of 2,6-lutidine [Eq. (2)].



(1)

1 **3**

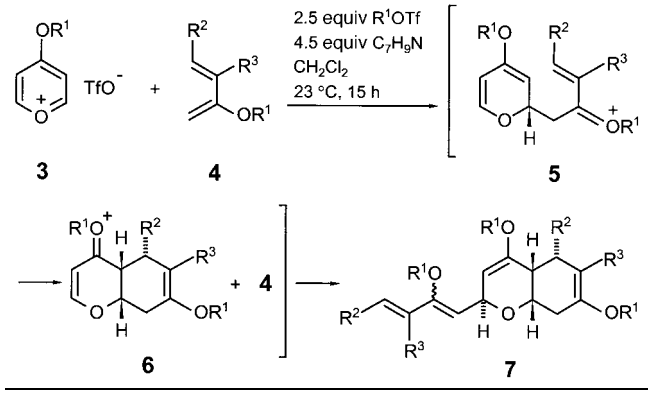


(2)

2 **4,9**

The reactions of **1** (1.0 equiv) and **2** (2.0 equiv) with a total of 4.5 equivalents of various silyl triflates led to the tetrahydro-2*H*-chromenes **7** as their sole products with very good yields in almost all cases. During this trisfunctionalization of pyrylium salts a domino 1,2-/1,4-addition between the 4-silyloxypyrylium triflate **3** and the 2-silyloxybuta-1,3-diene **4** occurs as the first step.[5] The annulated intermediate **6** formed via **5** is then reacted with another molecule **4** under 1,4-addition to give **7** diastereoselectively. In this manner three new C–C bonds and four stereogenic centers can be achieved in a single step (Table 1). Another reason why this new method is quite exciting is that a number of natural products are known to exhibit this ring system.[6]

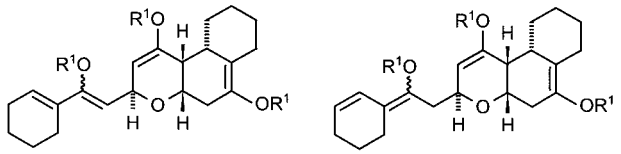
Table 1. Tetrahydro-2*H*-chromenes **7** by domino reactions of **3** and **4**.[a]



3	R^1	**4**	R^2	R^3	**7**	Yield [%]	*E*/*Z*
a	TBDMS	**a**	Ph	H	**a**	96	4.0:1.0
b	TES	**b**	Ph	H	**b**	98	4.1:1.0
c	TDMS	**c**	Ph	H	**c**	90	3.8:1.0
a	TBDMS	**d**	*p*-C_6H_4CN	H	**d**	80	11.0:1.0
a	TBDMS	**e**	*p*-C_6H_4Cl	H	**e**	35	1.3:1.0
a	TBDMS	**f**	$(CH_2)_4$		**f**	86	[b]
b	TES	**g**	$(CH_2)_4$		**g**	98	[b]
d	TIPS	**h**	$(CH_2)_4$		**h**	99	[b]
e	TMS	**i**	*p*-$C_6H_4CO_2Me$	H	**i**	62	3.4:1.0
e	TMS	**j**	*p*-$C_6H_4NO_2$	H	**j**	56	only *E*

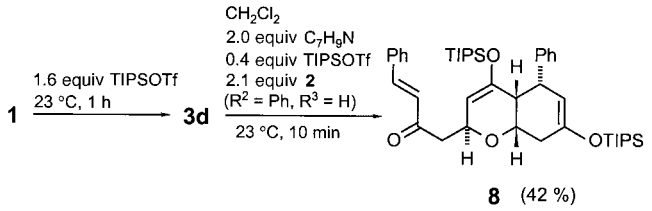
[a] TBDMS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TDMS = thexyldimethylsilyl, TIPS = triisopropylsilyl, TMS = trimethylsilyl. [b] The products **7f–h** were isolated as a mixture of two constitutional isomers.

Taking the reaction of pyran-4-one (**1**) with benzalacetone (**2**; R^2 = Ph, R^3 = H) and triisopropylsilyl triflate (TIPSOTf) as an example, we were able to show that the amount of the



7f–h

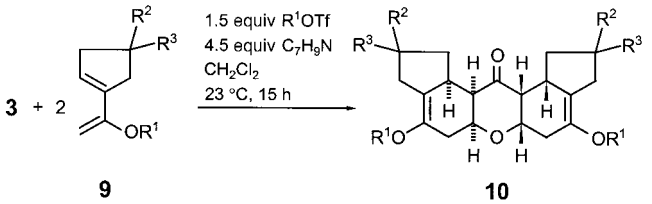
silyl triflate has a significant influence on product formation: for instance, reaction of one equivalent of **1**, 2.1 equivalents of **2** (R^2 = Ph, R^3 = H), and just two equivalents of TIPSOTf gives exclusively **8** (Scheme 2). Evidently, the reactivity of the systems giving **7** or **8** is not sufficient to bring about the second ring closure. In order to direct the reactions in this way, we increased both the reactivity of the 2-silyloxybuta-1,3-diene and of the silyl triflate.



Scheme 2. Influence of the amount of silyl triflate applied.

The importance of the reactivity of the 2-silyloxy-buta-1,3-dienes is revealed in reactions of **3** with the silyl enol ethers **9** of different 1-acetylcyclopentenes. With these highly reactive reagents the second ring closure occurs readily to give dicyclopenta[*a,j*]octahydroxanthen-9-ones **10** exclusively (Table 2). We assume that they derive from a sequential domino 1,2-/1,4-addition and a domino 1,4-/1,4-addition between **3** and two equivalents of **9**. In these cases we were able to isolate just

Table 2. Dicyclopenta[*a,j*]octahydroxanthen-9-ones **10** by domino reactions between **3** and **9**.



3	R^1	**9**	R^2	R^3	**10**	Yield [%]
a	TBDMS	**a**	H	H	**a**	85
e	TMS	**b**	H	H	**b**	75
d	TIPS	**c**	H	H	**c**	33
a	TBDMS	**d**	CO_2Me	CO_2Me	**d**	58
e	TMS	**e**	CO_2Me	CO_2Me	**e**	51
a	TBDMS	**f**	$=CH(CH_3)_2$		**f**	31
a	TBDMS	**g**	$CH(CH_3)_2$	H	**g**	61

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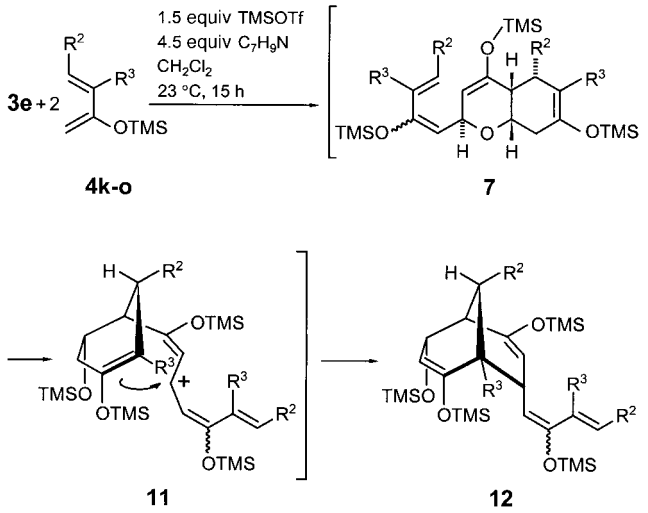
one of the 32 possible diastereomers. The relative configuration follows from the analysis of the NMR spectra, which is made a lot easier by the C_2 symmetry of the compounds. The structural assignments are corroborated by X-ray structural analysis of **10d**.[7]

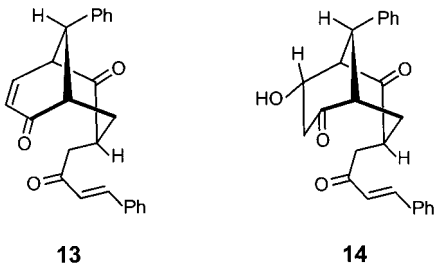
Product formation could also be governed by the reactivity of the silyl triflate, although the direction taken was somewhat unexpected: It came as a surprise that the reactions of the trimethylsilyloxypyrylium triflate **3e** with two equivalents of the 2-trimethylsilyloxybuta-1,3-dienes **4k–o** in the presence of the highly reactive TMSOTf selectively yielded the bicyclo[3.3.1]nona-2,6-dienes **12** (Table 3). We assume that cleavage of the pyran ring occurs in this three-component reaction after the formation of **7** by TMSOTf that then generates the bisallyl cations **11**, which are rearranged in an

Table 3. Bicyclo[3.3.1]nona-2,6-dienes **12** by domino reactions between 4-trimethylsilyloxypyrylium triflate **3e** and 2-trimethylsilyloxybuta-1,3-dienes **4k–o**



3	R^1	4	R^2	R^3	12	Yield [%]
e	TMS	**k**	Ph	H	**a**	94
e	TMS	**l**	*p*-C_6H_4OMe	H	**b**	51
e	TMS	**m**	*p*-C_6H_4Cl	H	**c**	80
e	TMS	**n**	*p*-C_6H_4CN	H	**d**	54
e	TMS	**o**	$(CH_2)_4$		**e**	96

intramolecular and stereocontrolled fashion to give the end products **12**. Four new C–C bonds and five stereogenic centers are formed when these highly functionalized bridged systems are established in a single step. This is all the more interesting as there are a number of bioactive natural products with a bicyclo[3.3.1]nonane framework, but with hardly any stereoselective routes available that lead to this particular ring system.[8] The structure of the products was determined by NMR analysis of compounds **13** and **14** resulting from derivatization or hydrolysis, respectively, of **12a**.[9] An X-ray structural analysis for **13** is also available.[7] Only **4i,j** and **9b,e** deviate from this reactivity pattern in that they exclusively yield **7i,j** and **10b,e**, respectively.



Experimental Section

Pyran-4-one (**1**) (1.00 mmol) was treated with silyl triflate (4.50 mmol) under argon and left at room temperature for 1 h. Then dichloromethane (3 mL), 2,6-lutidine (4.50 mmol), and a solution of the α,β-unsaturated ketone **2** (2.0 mmol) in dichloromethane (2 mL) were added and the mixture was stirred for 15 h at room temperature. The reaction mixture was treated with a solution of saturated sodium hydrogen carbonate (10 mL) and extracted with dichloromethane (3×10 mL). After the combined organic layers had been dried over sodium sulfate, the solvent was removed in vacuo. The workup was performed under argon, and purification of the crude products was accomplished by flash chromatography on silica gel.

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[9] Compound **13** was isolated from the reaction of **12a** with 10% H_2SO_4 in THF (RT, 1 h) in 35% yield. Compound **14** was accessible in 80% yield by reaction of **12a** with two equivalents of tetrabutylammonium fluoride in THF (0 °C, 10 min).

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