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Lewis Acid Catalyzed (3 + 2)-Annulations of Donor−Acceptor Cyclopropanes and Ynamides

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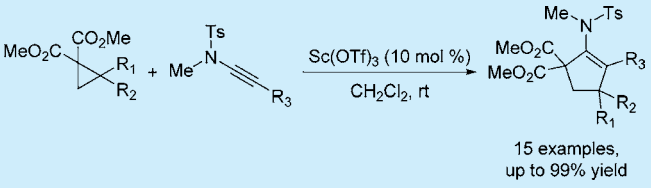
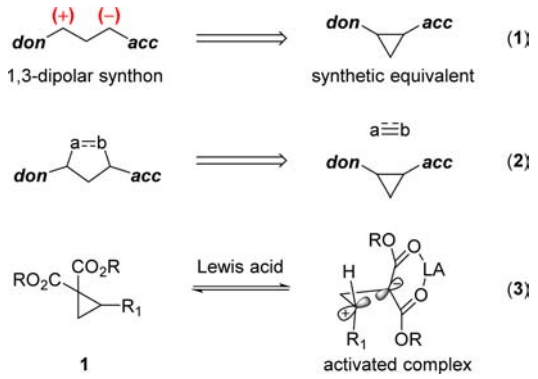
Supporting Information

ABSTRACT: The $Sc(OTf)_3$-catalyzed (3 + 2)-annulation of donor−acceptor cyclopropanes and ynamides is described, providing the corresponding cyclopentene sulfonamides in good to excellent yield. Deprotection and hydrolysis of the resulting ensulfonamides delivers 2,3-substituted cyclopentanones with high diastereoselectivity.



Donor−acceptor (D−A) cyclopropanes continue to receive significant attention as useful synthetic building blocks, particularly for their ability to act as synthetic equivalents to 1,3-dipolar synthons in cycloaddition reactions (eq 1).[1] The



deployment of these carbogenic building blocks has been widespread in the efficient assembly of heterocycles by (3 + *n*)-annulation (eq 2, a or b ≠ carbon),[2] but fewer cases have been described for carbocycle assembly (a, b = carbon).[3−5]

Notable examples of the latter include the annulation between Pd π-allyl activated vinyl D−A cyclopropanes and electron-deficient alkenes.[3a,c,d] Marino and Laborde have achieved silyloxycyclopropane ester activation via fluoride-induced silyl ether cleavage, which enables annulation with activated alkenes to provide cyclopentanes.[3b]

In the realm of Lewis acid activation of the acceptor group, Snider has shown $EtAlCl_2$ to effectively catalyze the annulation between D−A cyclopropanes and methylenecyclohexane derivatives,[4b] providing spiro-bicyclic products with the regioselectivity controlled by the preferential formation of a tertiary carbocation; however, a mixture of regioisomers was observed upon annulation with internal alkenes. Several groups have reported annulations between D−A cyclopropanes and enolsilanes providing cyclopentanes; the products commonly undergo subsequent ring-opening under the reaction conditions to provide linear products.[4k,n] Tang has suppressed the ring-opening byproduct in the annulation between D−A cyclopropanes and enolsilanes through the use of bulky silyl groups (TBDPS) on the enolsilane and ester groups (adamantyl) on the D−A cyclopropane.[4s] The use of allenyl silanes eliminates the potential for subsequent ring opening; however, these trials are complicated by 1,2-silyl migrations, providing a mixture of cyclopentane alkylidene and cyclohexene annulation products.[4f] Ready and Qi have shown ynolsilanes to be effective annulation partners for D−A cyclopropanes under Lewis acidic conditions, providing access to highly substituted cyclopentenones.[4j]

A common embodiment of annulations involving D−A cyclopropanes is the use of a 1,1-cyclopropane diester in conjunction with a Lewis acid activator to create an activated intimate ion pair (eq 3). The site-selective capture of this intimate ion pair by ynamide "dipolarophiles" is the subject of this paper. The preparation of useful functionalized cyclopenten-1-yl sulfonamides by these (3 + 2)-annulations is demonstrated. Deprotection of the ensulfonamide reveals 2,3-substituted cyclopentanones with high levels of diastereoselectivity. This strategy provides access to an important structural motif resembling the products of diastereoselective 1,4-addition to 2-substituted cyclopentenones.

Ynamides (**2**) have been shown to be excellent partners for (*n* + 2) annulations[6] due to the high regioselectivity with which they react. This selectivity is typically attributed to the major zwitterionic resonance structure. Despite this advantageous reactivity, ynamides have remained unutilized in (3 + 2)-annulations with D−A cyclopropanes (Figure 1); therefore, we initiated investigations to assess the feasibility of applying ynamides in this manifold.

Both the D−A cyclopropanes (**1a−m**)[7] and ynamides (**2a,b**)[8] were prepared in short order according to literature procedures. The monosubstituted cyclopropanes (**1a,b,d−j,m**) were prepared by successive Knoevenagel and Corey−Chaykovsky condensations.[7a] The 2,2-disubstituted cyclo-

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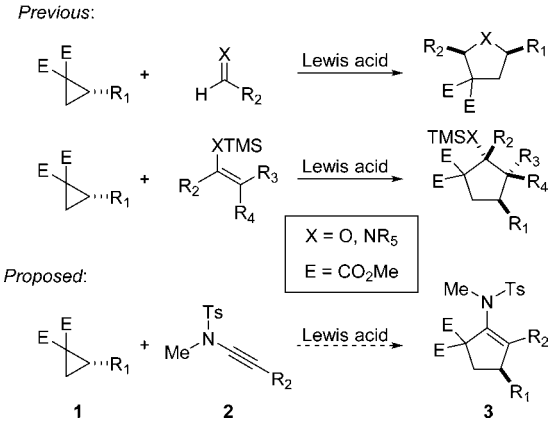


Figure 1. Proposed annulation.

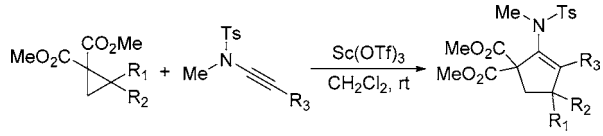
propanes (**1c**,**k**,**l**) were prepared via rhodium-catalyzed (2 + 1)-annulation between dimethyl diazomalonate decomposition and alkenes.[7b] Ynamides (**2a**,**b**) were prepared via copper-catalyzed oxidative cross coupling of TsNHMe and the corresponding terminal alkyne.[8]

Working first with cyclopropane **1b** and ynamide **2a**, we set out to optimize the title transformation. A brief screen of Lewis acids revealed $Sc(OTf)_3$ to be a superior promoter for the reaction, providing complete starting material conversion with catalyst loadings as low as 10 mol %. The efficacy of this particular Lewis acid is congruent with our previously demonstrated (3 + 2)-annulation of D−A cyclopropanes with aldehydes.[9] Attempts to lower the catalyst loading further were met with incomplete consumption of **1b** after 20 h. Two equivalents of the ynamide were required in the annulation to maximize product yields as ynamide hydrolysis was found to be a competitive decomposition pathway (see the Supporting Information).

With the optimized conditions in hand, we began to examine the scope of the annulation (Table 1). The reaction proceeded smoothly for a number of substrates, particularly for cyclopropanes bearing electron-rich aromatic groups (**1a**,**b**,**d**). This observation is in agreement with our previous findings that greater stabilization of the carbenium ion in the zwitterionic indermediate provides faster reaction rates.[9,10] However, there is an apparent limit to the electron releasing ability of the donor group toward promotion of the annulation. *N*,*N*-Dimethylaniline-substituted cyclopropane **1j** (entry 14), the most electron rich of the substrates tested, failed to react after 100 h, presumably due to a marked decrease in electrophilicity at the donor site. This trend may also explain the yield discrepancy between the *p*- and *o*-methoxyphenyl-substituted cyclopropanes (entries 3 and 7).

Decreased yields were also observed for the 2-furyl-substituted cyclopropane (entry 9). This iteration suffered from significant amounts of unidentified side reactions and starting material decomposition. A plausible degradation pathway for **1f** might be the competing Piancatelli rearrangement, which has been previously observed for furyl-substituted D−A cyclopropanes.[11] Cyclopropanes bearing a vinyl donor group (not shown) proceeded in low yields (<30%) upon annulation with **2a** under Lewis acidic conditions. These annulation products were unable to be isolated cleanly, since no conditions that were tested prevented coelution of the amide resulting from the hydrolysis of **2a** from the desired product.

Table 1. Substrate Scope[a,b]



entry	R_1	R_2	R_3	pdt	yield[c] (%)
1	4-MePh	H (**1a**)	C_5H_{11}	**3a**	>99
2	4-MePh	H (**1a**)	Ph	**3b**	>99
3	4-OMePh	H (**1b**)	C_5H_{11}	**3c**	89 (86)[d]
4	4-OMePh	H (**1b**)	Ph	**3d**	>99
5	4-OMePh	Me (**1c**)	C_5H_{11}	**3e**	64
6	4-OMePh	Me (**1c**)	Ph	**3f**	53
7	2-OMePh	H (**1d**)	C_5H_{11}	**3g**	>99
8	2,3-(CH_2O_2)Ph	H (**1e**)	C_5H_{11}	**3h**	64
9	2-furyl	H (**1f**)	C_5H_{11}	**3i**	46
10	2-thienyl	H (**1g**)	C_5H_{11}	**3j**	84
11	2-thienyl	H (**1g**)	Ph	**3k**	93
12	(*E*)-CH=CHPh	H (**1h**)	C_5H_{11}	**3l**	69
13	4-ClPh	H (**1i**)	C_5H_{11}	**3m**	NR[e]
14	4-NMe_2Ph	H (**1j**)	C_5H_{11}	**3n**	NR[e]
15	Ph	Me (**1k**)	C_5H_{11}	**3o**	59 (90)[f]
16	Ph	C≡CH (**1l**)	C_5H_{11}	**3p**	63
17	Ph	H (**1m**)	C_5H_{11}	**3q**	82

[a]Reactions performed with 1.0 equiv of **1** and 2.0 equiv of **2** in dry CH_2Cl_2 (0.1 M) with 0.10 equiv of $Sc(OTf)_3$. [b]Reactions were run for 18 h. [c]Isolated yield. [d]Run on 20 mmol scale of **1b**. [e]No reaction observed after 100 h. [f]Run with 3.0 equiv of **2a** and 0.15 equiv of $Sc(OTf)_3$.

2,2-Disubstituted cyclopropanes (entries 5, 6, 15, and 16) all suffered from diminished yields under the standard reaction conditions, presumably due to a slower rate of annulation. Since in situ ynamide hydrolysis is competitive with the annulation, at extended reaction times the availability of the ynamide is compromised. In these cases, the addition of 3 equiv of ynamide (entry 15) resulted in dramatically increased yields of **3o**. The alkynyl moiety, which has been shown to be an effective donor for (3 + 2)-annulations between D−A cyclopropanes and aldehydes,[12] (entry 16) also functions as an effective donor in the annulation with ynamides, providing **3p** in 63% yield.

Our group has shown previously[2d,9] that enantioenriched D−A cyclopropanes transfer chirality to their annulation products with high fidelity, undergoing complete inversion at the donor site stereogenic center. As shown in Figure 2, this mechanistic feature is also observed in the case of annulation with ynamides. Stereospecific back-side capture of the intimate ion pair (eq 3) would account for this finding.[9]

We then began to examine the feasilibity of performnig a dynamic kinetic asymmetric transformation (DYKAT)[13] of

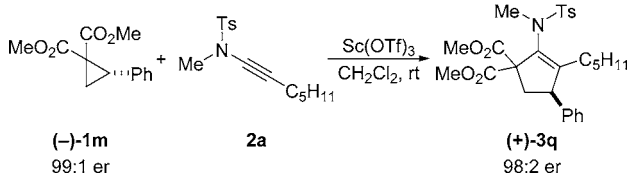


Figure 2. Chirality transfer study.

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racemic D−A cyclopropanes and ynamides based on our previous work in the cases of tetrahydrofurans[2h] and pyrrolidines.[2i] However, we found this tactic to be ineffective in the case of the title reaction, as the reactivity of **1b** and **2a** were significantly hindered by the application of the MgI_2(pybox) catalyst system (Figure 3). Varying the electronic

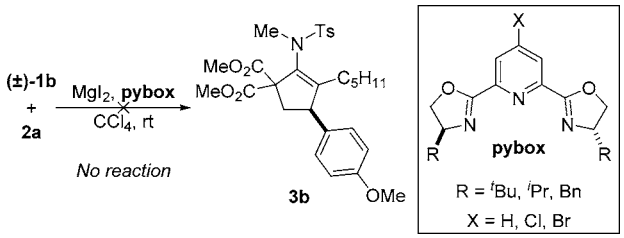

Figure 3. Proposed DYKAT.

profile of the pybox ligand by introducing halogens at the 4-position (X = Cl, Br) had no effect on the annulation. In addition, variation of the reaction solvent or temperature showed no promise for increasing starting material conversion. For example, treatment of **1b** with **2a** in refluxing CCl_4 for 2 d resulted in only trace degradation (<5%) of **1b**. Notably, no degradation of the ynamide was observed. This lack of reactivity was attributed to unfavorable steric interactions between the chiral ligand (R = ^{t}Bu) and the approaching ynamide. In an attempt to minimize this strain, less sterically demanding pybox ligands (R = ^{i}Pr, Bn) were evaluated, neither of which was successful in promoting the annulation.

In an effort to provide synthetically attractive cyclopentanones from the enamide products **3**, the sulfonyl group was first cleaved via single-electron reduction using sodium naphthalenide. The resultant enamine was then hydrolyzed under acidic conditions to provide cyclopentanones **4a−d** as single diastereomers (Figure 4).

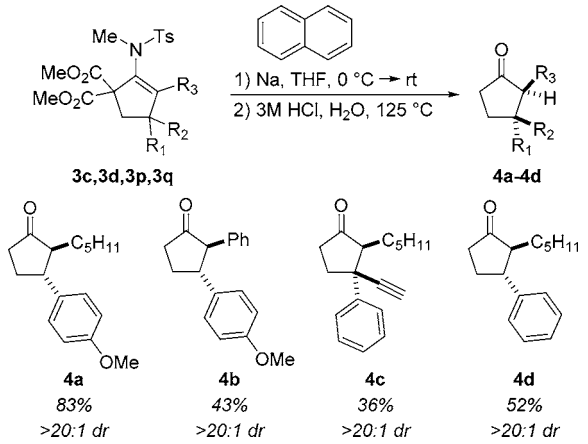

Figure 4. Tosyl reduction and hydrolysis. (a) Isolated yield of **4** over two steps. (b) Diastereomeric ratio (dr) determined by ^{1}H NMR of isolated product.

The *gem*-diester moiety was also removed during the hydrolysis. NOESY analysis of the cyclopentanone products **4** confirmed an *anti* relationship between the R_1 and R_3 substituents (Figure 5). These 3,3-disubstituted cyclopentanones are of particular note, as they represent an expedient synthesis of formal conjugate addition products of 2,3-disubsituted cyclopentenones.

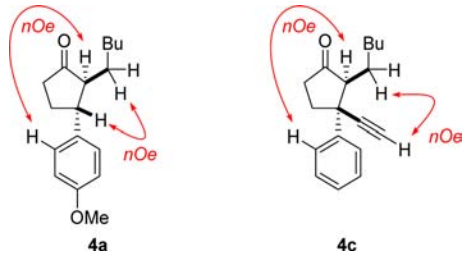

Figure 5. NOE observations.

Unsubstituted ynamides (R_3 = H) were not tested in the annulation with D−A cyclopropanes, since the resultant cyclopentanones **4** that would be accessed from these substrates are analogous to the products of 1,4-addition to cyclopentenone or the 1,4-reduction of *β*-substituted cyclopentenones. There are already several excellent reports of enantioselective variants of these reactions.[14,15]

In conclusion, we have shown ynamides to be suitable partners in (3 + 2)-annulation with D−A cyclopropanes, providing cyclopentene sulfonamide products. Subsequent deprotection provides 2,3-substituted cyclopentanone products with high stereoselectivity. Studies into the further development of D−A cyclopropane annnulations are underway in our group and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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