Organocatalysis

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Organocatalytic Enantioselective Nucleophilic Alkynylation of Allyl Fluorides Affording Chiral Skipped Ene-ynes

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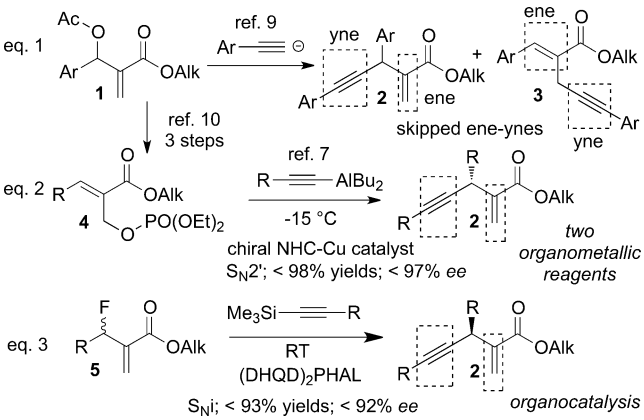
Abstract: *Asymmetric methods for preparation of chiral alkynyl-containing compounds are in extremely high demand in many sectors of chemical research. In this work, we report the discovery of a general organocatalytic enantioselective alkynylation based on the idea of Si/F activation of the allylic C–F bond. This approach features reasonably broad substrate scope, functional group tolerance, and relatively neutral, mild, and operationally convenient reaction conditions; all of which bode well for the synthetic value of the discovered method. In particular, this method provides unique chiral skipped 1,4-ene-ynes having two kinds of versatile functional groups.*

Chiral compounds containing alkynyl moieties directly bonded to a stereogenic center are of great synthetic importance, with a proven relevance for the pharmaceutical industry[1] and for functional materials.[2] Consequently, asymmetric synthesis of alkyne derivatives has been an extremely active area of research.[3] However, the overwhelming majority of the literature methods deal with asymmetric additions of alkynyl groups to unsaturated electrophilic moieties, such as C=O,[4] C=N,[5] and electron-deficient C=C.[6] In sharp contrast, application of alkynyl nucleophiles in catalytic asymmetric substitution reactions is virtually unknown,[7] underscoring a clear void in the current methodology. For example, acetates of Baylis–Hillman adducts **1** (Scheme 1, eq. 1) are excellent carbon electrophiles that easily react with a wide range of nucleophiles.[8] However, their reaction with alkynyl nucleophiles (eq. 1) was shown to proceed with low chemo-selectivity giving, rise to a mixture of S_N2 **2** and S_N2' **3** products,[9] with the latter being the major product under certain reaction conditions. The difficulty in product control is mainly due to the inherent instability of a unique skipped 1,4-ene-yne structure. This property was creatively used by the Hoveyda group in the design of a multistep process based on two consecutive S_N2' substitutions (eq. 2), leading to a formal transformation of **1** to chiral alkynylated products **2**.[10] A key step of this process is the use of Al^{III}-derived alkynyl nucleophiles in the chiral NHC-Cu-catalyzed S_N2' substitutions, which can be conducted with excellent yields and enantioselectivity. Drawing inspiration from these results, we assumed that the development of alkynylation process for the direct transformation of Baylis–Hillman adducts **1** to 1,4-enynes **2**, might be a highly desirable approach, yet mechanistically quite challenging to realize. Herein, we report that analogues of acetates **1**, allyl fluorides **5** (eq. 3), can be directly alkynylated to afford unique chiral 1,4-enynes **2**, that is, chiral skipped ene-ynes, with synthetically attractive stereochemical outcomes. The reactions are conducted under operationally convenient conditions in the presence of catalytic amounts of bis-cinchona-derived $(DHQD)_2PHAL$ and using trimethylsilylated alkynes as alkynylating reagents. This new organocatalytic alkynylation process is the first of its kind and likely to be of significant methodological and synthetic potential.



Scheme 1. Synthesis of skipped 1,4-ene-ynes by alkynylation of Baylis–Hillman adducts and their derivatives. Literature approaches (eqs. 1 and 2) and the current work (eq. 3).

Recently, we demonstrated that generally unreactive C–F bonds in allyl fluorides **5** can be activated in the presence of Ruppert–Prakash reagent (CF_3-$SiMe_3$), allowing for nucleophilic cleavage of the C–F bond.[11] Taking into account the sterically demanding and electron-withdrawing nature of the CF_3 group,[12] the likelihood of a successful application of other Si–C species for the Si/C–F activation was rather uncertain. In this regard, trimethylsilylated alkynes presented an interesting case, possessing relatively electron-withdrawing but sterically undemanding sp^2 carbons units. To gain an initial idea about the reactivity of silylated alkynes towards allyl fluorides **5**, we conducted a series of reactions (THF,

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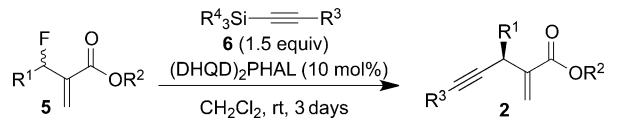
Table 1: Substrate generality study[a]



Entry	R^1	R^2	R^3	R^4	Yield [%][b]	*ee* [%][c]
1	Ph	Me	4-$MeOC_6H_4$	Me	82	92
2	4-MeC_6H_4	Me	4-$MeOC_6H_4$	Me	74	89
3	4-ClC_6H_4	Me	4-$MeOC_6H_4$	Me	93	88
4	4-BrC_6H_4	Me	4-$MeOC_6H_4$	Me	66	88
5[d]	2-MeC_6H_4	Me	4-$MeOC_6H_4$	Me	55	88
6	3-MeC_6H_4	Me	4-$MeOC_6H_4$	Me	71	92
7	*c*-Hex	Me	4-$MeOC_6H_4$	Me	59	85
8	Ph	Me	Ph	Me	82	91
9	Ph	Me	4-MeC_6H_4	Me	78	91
10	Ph	Me	4-BrC_6H_4	Me	56	90
11	Ph	Me	2-$MeOC_6H_4$	Me	91	91
12	Ph	Me	3-$MeOC_6H_4$	Me	68	91
13	Ph	Me	2-naphtyl	Me	60	90
14	Ph	Me	H	Me	91	92
15[d]	Ph	Et	4-$MeOC_6H_4$	Me	77	85
16	Ph	*t*-Bu	4-$MeOC_6H_4$	Me	trace	–
17	Ph	Me	4-$MeOC_6H_4$	Et	35	95
18	Ph	Me	4-$MeOC_6H_4$	*i*Pr	trace	–

[a] The reaction of **5** with **6** (1.5 equiv) was carried out in the presence of $(DHQD)_2PHAL$ (10 mol%) in CH_2Cl_2 (0.2 M) under nitrogen atmosphere at room temperature, unless otherwise noted. [b] Yield of isolated product. [c] Determined by HPLC using a chiral stationary phase. [d] The reaction was carried out for 6 days.

ambient temperature) between methyl 2-[fluoro-(phenyl)methyl]acrylate **5** and 1-methoxy-4-[2-(trimethylsilyl)ethynyl]benzene **6** (Table 1) in the presence of various organocatalysts. Detailed data can be found in Table 1 S of the Supporting Information. The initial results were rather exciting, as they answered the principal question, clearly showing that the target C–F activation/nucleophilic substitutions are possible under very mild organo-catalytic conditions, although the stereochemical outcome required significant optimization. After extensive experimentation, we were able to determine the following key characteristics of these asymmetric alkynylation reactions. First, only binuclear catalysts, such as $(DHQ)_2AQN$, $(DHQ)_2PYR$, and $(DHQ)_2PHAL$ lead to reasonably high levels of enantioselectivity, while mono-nuclear, cinchonine-type bases were markedly ineffective. Second, polar, non-coordinating solvents, such as CH_2Cl_2, provided for higher yields as compared with toluene, THF, or Et_2O. Third, the reactions proceeded at relatively high initial rates until about 50% conversion, noticeably slowing down afterwards. After rather meticulous optimization, we determined that the reaction of **5** with **6** (1.5 equiv), carried out in the presence of $(DHQD)_2PHAL$ (10 mol%) in CH_2Cl_2 (0.2 M) under nitrogen atmosphere at room temperature for three days (72 hrs), provided for the synthetically attractive synthesis of target product **2** (Table 1, entry 1) of 92% *ee* and isolated with 82% yield.

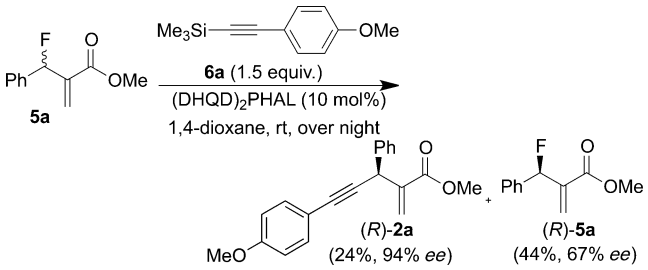
Having optimized the reaction conditions, we were in position to focus on the substrate generality study of this organo-catalytic enantioselective alkynylation procedure. As shown in Table 1, we briefly assessed the effect of substituents at all four possible sites of variation, including major structural groups R^1 and R^3 directly bonded to the C–F and acetylene moieties, as well as alkyl groups R^2 and R^4 on the ester and silicon functions, correspondingly. All reactions were conducted under the same standard conditions and, for the purpose of comparison, were not optimized. Thus, using *p*-MeO-substituted trimethylsilyl-ethynyl-benzene as a model reagent, variation of the substituent R^1 on the starting allyl fluorides **5** revealed that synthetically useful levels of the stereochemical outcome can be maintained for substrates with a phenyl-bearing electron-withdrawing and -donating groups in various positions on the aromatic ring (entries 1–6). In particular, excellent enantioselectivity (88–92% *ee*) was observed in all of the cases studied, with chemical yields ranging from 55 to 92%. The lowest yield was recorded for the *o*-Me-substituted substrate (entry 5), while the highest (92%) was obtained for the *p*-ClC_6H_4 derivative (entry 3). Considering other results in this series (entries 1–6), it appears that electron-withdrawing substituents tend to afford products (*R*)-**2** with higher chemical yields, while the presence of electron-donating groups render somewhat slower reaction rates and lower isolated yields. Preparation of starting allyl fluorides **5** bearing R^1 alkyl groups is limited as compared to that of aromatic derivatives. Therefore, this type of substitution is presented by one example given in entry 7. Under the standard conditions, the reaction of *c*-hexyl containing allyl fluoride **5** proceeded rather slowly, and after three days was not fully complete. Nevertheless, the expected product of 85% *ee* was isolated with 59% yield; no other by-products were detected in the crude reaction mixture.

Another series of experiments was conducted to explore the structural generality of trimethylsilyl-ethynyl-benzene reagents **6** (entries 8–13). Once again, the major feature revealed by these reactions was the consistently excellent level of enantioselectivity, which is not influenced by the nature of substituents on the phenyl ring. On the other hand, the chemical yields were less consistent, ranging from 56 (entry 10) to 91% (entry 11). It should be noted that all of the reactions were rather clean, by-product-free, and leave room for further optimization of the reaction conditions. Of particular importance is the result obtained in the reaction of phenyl-substituted allyl fluoride **5** (entry 14) with unsubstituted trimethyl-silyl-acetylene **6**. The target nucleophilic substitution took place at a relatively high rate, affording product (*S*)-**2** with excellent stereochemical outcome (91% yield, 92% *ee*). The structural generality of these reactions, which allow preparation of products with unprotected acetylene C–H functional groups, is quite remarkable. Such structural tolerance is extremely rare and can be realized only under very mild conditions of this organocatalytic process. On the other hand, the substrates **6**, containing electron-withdrawing groups, failed to deliver the expected products **2**, most likely due to the increased C–H acidity of the stereogenic carbon.

An additional set of experiments was designed to investigate the effect of substituents on the ester function in allyl fluorides **5** (entries 15, 16) and trialkyl-silyl group (entries 17, 18). Quite interestingly, we found that increasing steric bulk at both positions severely hindered the reaction progress. For

example, while the reaction of methyl and ethyl esters **5** (entries 9 and 15) gave fairly comparable results, the application of *t*-butyl ester (entry 16) did not yield the expected product, and the starting compounds **5** and **6** were recovered chemically intact. Similar modes of reactivity was observed in the reactions of TES- and TIPS-derived reagents **6**. Thus, the presence of the TES slowed the reaction rate, but afforded product **2** in excellent enantiomeric purity (95% *ee*), isolated with 35% yield (entry 17). On the other hand, acetylene **6**, bearing a TIPS group, did not react with allyl fluoride **5** at all (entry 18). We believe the data presented in Table 1 effectively outline the major aspects of reactivity, synthetic potential, and limitations of the reactions under study, as well as providing some mechanistic insights.

Taking advantage of the data published by the Hoveyda group, the absolute stereochemistry of product **2** (Table 1, using $(DHQD)_2PHAL$) was unambiguously determined to be *R* by a comparison of the spectral and chiroptical properties with the reported values and HPLC retention times. To gain mechanistic insight regarding the stereochemical progression of these organo-catalytic alkynylations, we decided to investigate the enantiomeric composition of the reaction components. To this end, the reaction presented in Scheme 2 was



Scheme 2. Dynamic kinetic resolution of allyl fluoride **5** during the course of enantioselective organo-catalytic alkynylation.

stopped and worked up well before its completion. The result was rather intriguing as it clearly showed a case of significant dynamic kinetic resolution producing product (*R*)-**2** of excellent enantiomeric purity (94% *ee*) and unreactive, partially racemized enantiomer (*R*)-**5a** of 67% *ee*.

These data can be rationalized assuming that the (*R*)-enantiomer of starting allyl fluoride **5** undergoes relatively fast S_Ni substitution with trimethyl-silyl-acetylene **6** to give alkylated product (*R*)-**2** with retention of the absolute configuration. Furthermore, enantiomer (*R*)-**5** does not react with **6**, undergoing instead a rate-limiting racemization, producing the reactive enantiomer (*S*)-**5**, and thus driving the reaction to completion. In support of this proposal was a consistent observation that about 50% conversion of the reaction products was usually observed after the first 12 hrs, while the completion and optimal chemical yields required a much longer period of time (three days). While the deduction of the precise mechanistic details will require further study beyond the scope of this report, we can suggest that the corresponding S_Ni substitution might proceed via TA-**A** (Figure 1) featuring molecules of starting compounds **5** and **6**, as well as the organo-catalyst **B**. Constructing TS-**A** we

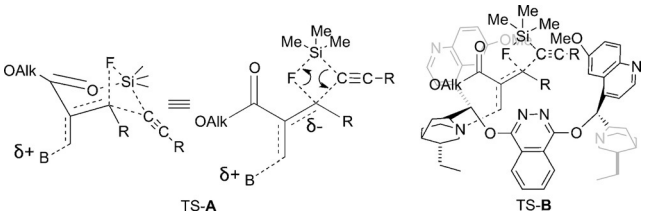
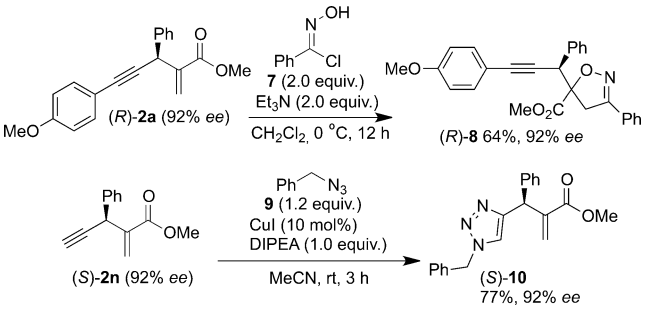


Figure 1. Plausible translon states TS-**A** and TS-**B** in the enantioselective organo-catalytic alkynylations under study.

considered the following key points: i) activation of C–F bond by simultaneous Si/F and base/allylic system interactions; ii) no formation of fully charged species; and iii) shielding of one of the TS-**A** faces and rendering one enantiomer inaccessible for the substitution. These mechanistic considerations are fully consistent with the corresponding experimentally observed data, such as: the presence of both trimethyl-silyl-acetylene and base are necessary for the reactions to take place; very mild, ambient temperature, neutral pH reaction conditions; and only binuclear organo-catalysts show reasonably high level of enantioselectivity. To account for the latter, we attempted to build TS-**B** showing the mode of substrate activation and blocking one of the faces for incoming trimethyl-silyl-acetylene. Furthermore, sterically congested structures of TS-**A** and TS-**B** are fully consistent with the strong steric effects discussed above, in particular, the bulk of alkyl groups on the silyl moiety in **6**.

As should be routinely done in any research on catalytic asymmetric synthesis,[13] we conducted SDE (self-disproportionation of enantiomers) tests using achiral chromatography[14] and sublimation.[15] Among the products (*R*)-**2**, we selected compound (*R*)-**2a** as a model substrate to carry out the SDE tests. Both sublimation and achiral chromatography tests gave negative results, suggesting that the isolation of compounds (*R*)-**2** by routine column chromatography and their drying in high vacuum are safe and do not alter the original enantiomeric composition.

Finally, we felt it essential to demonstrate the synthetic potential of chiral chiral skipped ene-ynes **2** by examples of chemo-selective elaboration of both the alkene and acetylene functional groups. To this end, we conducted the cyclization reaction presented in Scheme 3. In particular, base-catalyzed [2 + 3]-cycloaddition[16] of the alkene group in (*R*)-**2a** with



Scheme 3. Chemo-selective elaboration of the alkenyl and alkynyl groups in skipped ene-ynes 2. Synthesis of isoxazole (*R*)-**8** and 1,2,3-triazole (*S*)-**10**.

imidoyl chloride **7** took place quite readily, affording the target product (*R*)-**8** without any loss of the original enantiomeric purity (92% *ee*). In another example, to use the chemistry of the acetylene group in (*S*)-**2n**, we synthesized 1,2,3-triazole (*S*)-**10** by the reaction with benzylazide **9** in the presence of a catalytic amount of CuI and 1.0 equiv of DIPEA.[17] Triazole (*S*)-**10** was isolated with excellent yield and, again, with uncompromised enantiomeric purity of 92% *ee*.

To conclude, the results reported in this communication clearly demonstrate that organo-catalytic enantioselective nucleophilic alkynylation can be realized based on the Si/F activation of the allylic C–F bond. Formation of reactive, chiral skipped 1,4-ene-ynes **2** can be very nicely controlled from Baylis–Hillman adducts under metal-free, mild organocatalytic conditions for the first time, while Hoveyda's work requires designed starting materials with two organometallic reagents of Al and Cu. Our approach displays reasonably broad substrate scope and functional group compatibility under mild conditions. Furthermore, mechanistic complexity, likely including dynamic kinetic resolution and S_Ni substitution, suggest promise for effective tuning of the substrate reactivity. Additionally, the operationally convenient conditions coupled with good yields and excellent enantioselectivity bode well for widespread synthetic application of this method.

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