Arylation

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An Arylation Strategy to Propargylamines: Catalytic Asymmetric Friedel–Crafts-type Arylation Reactions of C-Alkynyl Imines

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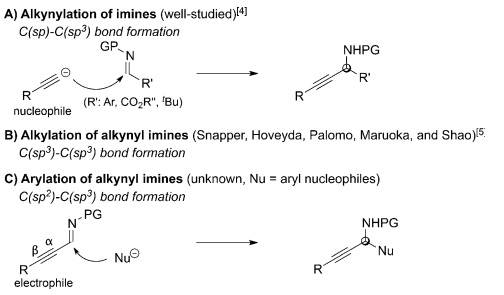
Dedicated to Professor Dieter Enders on the occasion of his 70th birthday

Abstract: *The first arylation strategy for the synthesis of enantioenriched propargylamines is disclosed. This approach, which is complementary to previous alkynylation and alkylation strategies, involves a C(sp^2)–C(sp^3) bond formation, and is based on the first asymmetric Friedel–Crafts-type arylation reaction of C-alkynyl imines. Asymmetric Friedel–Crafts reactions with electron-deficient phenols, a longstanding unsolved challenge, have thus been realized for the first time, enabled by the combination of our recently introduced C-alkynyl N-Boc-protected N,O-acetals as electrophiles and chiral phosphoric acids as catalysts. The synthetic utility of the resulting structurally diverse and polyfunctional chiral propargylamines was demonstrated by a series of selective transformations, including controlled reduction of the alkynyl group and iterative cross-couplings.*

Propargylamines are useful intermediates and versatile building blocks for the synthesis of various polyfunctional amines as well as natural products and biologically active compounds[1] owing to the rich chemistry of the C–C triple bond, which enables its conversion into numerous other functional groups.[2] Propargylamines themselves are also important structural motifs in a number of bioactive compounds.[3] The design and development of new asymmetric methods and strategies for the preparation of chiral propargylamines is thus a critical objective in chemical synthesis. The classic strategy for preparing chiral propargylamines involves the asymmetric nucleophilic alkynylation of imines, thereby creating the chiral propargylic stereocenter in a C-(sp)–C(sp^3) bond-forming event (Scheme 1 A).[4] Recently, several elegant asymmetric syntheses of propargylamines have been developed by utilizing electrophilic alkynyl imines that react with alkyl zinc reagents,[5a] silyl enol ethers,[5b] silyl ketene acetals,[5c,d] enolizable aldehydes,[5e–g] acetylacetone,[5h] β-keto esters,[5i] malonate (thio)esters,[5j] and glycine Schiff bases[5k] as suitable nucleophiles; in these approaches, a C-(sp^3)–C(sp^3) bond formation is involved (Scheme 1 B). However, to the best of our knowledge, chiral propargylamines still have not been synthesized in an arylation approach, which would involve a distinctive and complementary C(sp^2)–C(sp^3) bond formation (Scheme 1 C).



Scheme 1. Strategies for the synthesis of chiral propargylamines through C–C bond formation.

Herein, we report the development of the first arylation strategy for the synthesis of enantioenriched propargylamines. The strategy is based on the first asymmetric aza-Friedel–Crafts-type arylation reaction of alkynyl imines with various aromatic and heteroaromatic compounds as aryl nucleophiles.

The Friedel–Crafts (F-C) reaction is one of the most important C–C bond-forming reactions in organic chemistry.[6] Over the past few decades, the asymmetric F-C reaction has evolved to become a powerful method for the synthesis of various enantioenriched compounds.[7] However, no methods have been reported for the preparation of enantioenriched propargylamines in asymmetric F-C reactions.

To fill this gap, we became interested in the previously unreported asymmetric aza-F-C reaction of alkynyl imines with aryl nucleophiles, a new reaction type in alkynyl imine chemistry. We hypothesized that this methodological study could benefit significantly from the use of phenols (ArOH) as aryl nucleophiles because they are readily available, inexpensive, and versatile chemical feedstocks and building blocks for synthesis owing to their diverse transformations and intriguing chemistry, and they are important structural motifs widely found in natural products, bioactive molecules, and lignin.[8] However, only naphthols and/or electron-rich phenols could be used as ArOH nucleophiles in previously reported asymmetric F-C reactions.[9,10] To date, asymmetric F-C reactions with much less nucleophilic but synthetically more useful electron-deficient phenols have not been reported. Furthermore, the use of electron-neutral phenol in the asymmetric F-C reaction has also remained elusive owing to its lower nucleophilicity compared to naphthols and electron-rich phenols and additional site-selectivity issues as

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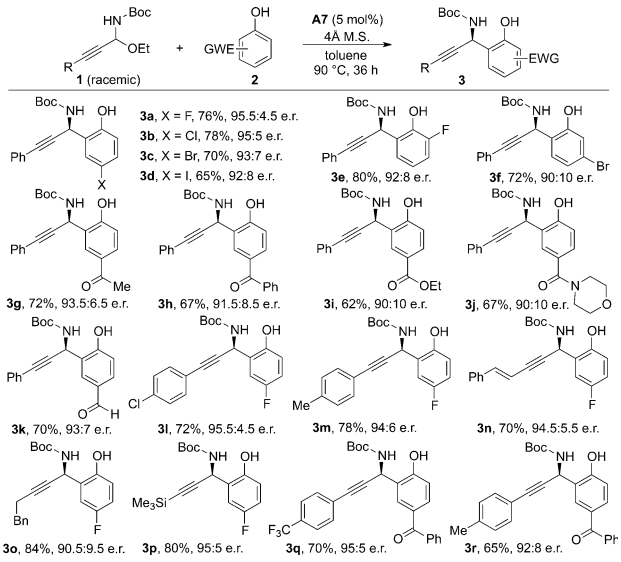
the reaction could occur at two different reaction sites (*ortho* and *para* position). We envisaged that the strategic and innovative use of C-alkynyl N-Boc-protected N,O-acetals, recently introduced by us[5j] as tailor-made electrophiles for F-C reactions, may provide a previously unrecognized opportunity for the realization of all of these challenges to develop an aza-Friedel–Crafts-type arylation strategy for the synthesis of synthetically and biologically important chiral propargylamines.

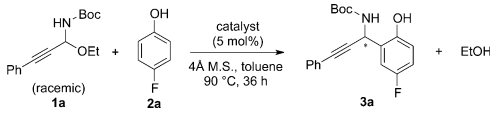
We began our studies by examining the F-C-type reaction of C-alkynyl N-Boc-protected N,O-acetal **1a** with electron-deficient phenol **2a**. Unfortunately, the use of chiral bifunctional base catalysts, which have been shown to be efficient in the enantioselective tandem in situ generation of C-alkynyl imines/Mannich-type reaction of **1a** with malonate (thio)esters,[5j] failed to produce the desired product even at high temperature. This result prompted us to identify an alternative organocatalyst that must be capable of both catalytically generating challenging N-Boc-protected C-alkynyl imines from C-alkynyl N-Boc-protected N,O-acetals and promoting the subsequent aza-F-C arylation reaction with high enantioselectivity. After extensive investigations, we found that chiral phosphoric acids are effective catalysts for the tandem process combining the in situ generation of C-alkynyl imines and aza-F-C-type arylation. In the presence of chiral phosphoric acid catalyst **A7** ((*R*)-TRIP)[11] and 4 Å molecular sieves (employed to scavenge the ethanol generated during the formation of the C-alkynyl imine), the reaction between **1a** and **2a** took place smoothly to provide the desired 1,2-addition aza-F-C product **3a** in 76% yield with 95.5:4.5 e.r. (Table 1, entry 7). Notably, the 1,4-addition product was not observed.[12] Although chiral phosphoric acids have been shown to be highly enantioselective organocatalysts in numerous reactions,[13] the use of this class of organocatalysts in aza-F-C reactions of phenols with high enantiocontrol has remained elusive.

The generality of this new method is shown in Scheme 2. A broad range of electron-deficient phenols **2** reacted with C-alkynyl N-Boc-protected N,O-acetals **1** to give the desired functionalized propargylamines in good yields with high enantioselectivities (**3a**–**3r**).



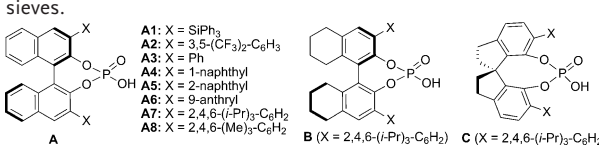
Scheme 2. Asymmetric Friedel–Crafts-type arylations of C-alkynyl N-Boc-protected N,O-acetals **1** with electron-deficient phenols **2**. EWG = electron-withdrawing group.

Table 1: Optimization of the asymmetric Friedel–Crafts-type arylation of **1a** with electron-deficient phenol **2a**.[a]



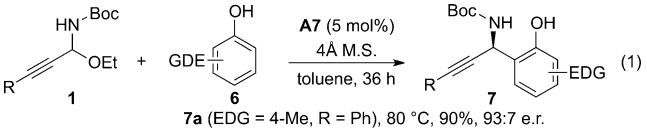
Entry	Catalyst	Yield [%][b]	e.r.[c]
1	**A1**	40	58:42
2	**A2**	63	53.5:46.5
3	**A3**	57	61.5:38.5
4	**A4**	50	77:23
5	**A5**	30	60.5:39.5
6	**A6**	69	83.5:16.5
7	**A7**	**76**	**95.5:4.5**
8	**A8**	75	82:18
9	**B**	68	93:7
10	**C**	47	80:20

[a] General reaction conditions: **1a** (0.075 mmol), **2a** (0.05 mmol), catalyst (5 mol%), and 4 Å M.S. (40 mg) in toluene (1 mL) for 36 h. [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. Boc = *tert*-butoxycarbonyl, M.S. = molecular sieves.



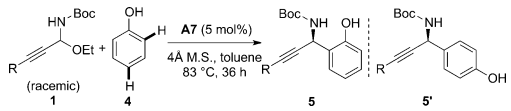
Next, we turned our attention to the aza-F-C-type arylation reaction of C-alkynyl N-Boc-protected N,O-acetals **1** with electron-neutral phenol (**4**). Interestingly, in contrast to the rare example of an asymmetric F-C reaction with electron-neutral phenol (**4**), which required a highly activated trifluoropyruvate as the electrophile, a chiral base as the catalyst, and furnished the *para*-functionalized product (one chiral alcohol),[14] unactivated racemic C-alkynyl N-Boc-protected N,O-acetals **1** as electrophiles reacted with electron-neutral phenol **4** in the presence of the chiral phosphoric acid catalyst to provide the *ortho*-functionalized products (various chiral propargylamines **5**) in good yields with high enantioselectivities (Table 2).

Electron-rich phenols **6** and 1- and 2-naphthol **8** and **9** were also used as substrates in the F-C-type arylation reaction for propargylamine synthesis [Eqs. (1)–(3)].



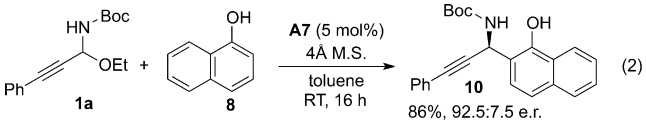
(1)

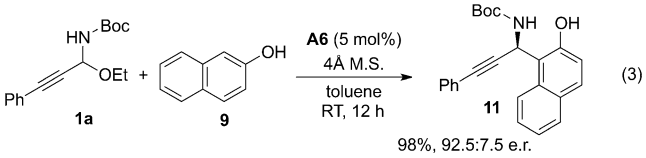
Table 2: Asymmetric Friedel–Crafts-type arylation of C-alkynyl N,O-acetals **1** with phenol (**4**).[a]



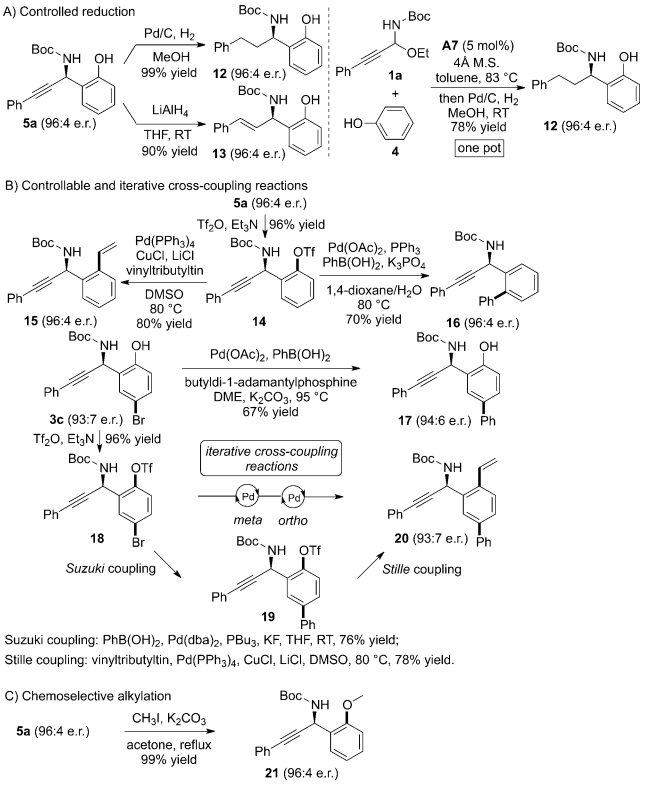
Entry	R	Product	Yield [%][b]	e.r.[c]
1	C_6H_5	**5a**	76	96:4
2	2-Me-C_6H_4	**5b**	76	96:4
3	3-Me-C_6H_4	**5c**	72	96:4
4	4-Me-C_6H_4	**5d**	70	95:5
5	4-MeO-C_6H_4	**5e**	83	91:9
6	4-Br-C_6H_4	**5f**	79	91.5:8.5
7	4-Cl-C_6H_4	**5g**	80	94.5:5.5
8	4-CF_3-C_6H_4	**5h**	80	94:6
9	2-thienyl	**5i**	74	91.5:8.5
10	PhCH=CH	**5j**	72	95.5:4.5
11	1-cyclohexenyl	**5k**	75	94:6
12[d]	$PhCH_2CH_2$	**5l**	72	90.5:9.5
13[d]	*n*Bu	**5m**	65	90:10
14[d]	cyclohexyl	**5n**	70	91:9
15[d]	cyclopropyl	**5o**	60	90:10
16[d]	trimethylsilyl	**5p**	94	92:8

[a] General reaction conditions: **1** (0.075 mmol), **4** (0.05 mmol), **A7** (5 mol%), and 4 Å M.S. (40 mg) in toluene (1 mL) for 36 h. [b] Yields of isolated products. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At 90 °C.





The alkynyl groups on the chiral propargylamines were readily converted into the corresponding alkyl and alkenyl groups by controlled reduction (Scheme 3 A). Treatment of **5a** with Pd/C under H_2 atmosphere led quantitatively to the alkyl-substituted product **12**,[15] which corresponds to the F-C product of an alkyl-substituted *N*-Boc imine, which was previously difficult to access. Notably, product **12** could also be obtained in a one-pot reaction combining two effective atom-economic catalytic processes. The present method of using the N-Boc-protected C-alkynyl imine precursor instead of the *N*-Boc C-alkyl imine itself, which is generally labile and difficult to isolate and readily isomerizes to the corresponding ene carbamate, is a convenient, efficient, and strategically advantageous alternative. When the reduction of **5a** was carried out with $LiAlH_4$, the alkynyl group was cleanly reduced to give *E*-alkenyl-substituted product **13**, which is formally derived from the unknown F-C reaction of the *N*-Boc imine with an *E*-alkenyl substituent.



Scheme 3. Diverse transformations of the obtained propargylamines.

The phenolic hydroxy group offers more possibilities for further transformations (Scheme 3 B). For example, triflate **14** could be easily prepared in 96% yield, and furnished compounds **15** and **16** in good yields upon metal-catalyzed Stille and Suzuki coupling reactions, respectively. Notably, we also developed an iterative cross-coupling process. Starting from **3c**, *meta*-phenylation delivered monosubstituted **17** in 67% yield. Compound **18**, which is also derived from **3c**, first underwent *meta*-selective phenylation to **19**. The second iteration with a tin reagent resulted in *ortho* vinylation and led to the formation of differentially disubstituted product **20**.

A reaction model is proposed in Figure 1. The chiral phosphoric acid can simultaneously activate both the phenol and the in situ generated C-alkynyl imine through hydrogen-bonding interactions. This creates a chiral environment where the phenol preferentially attacks the *Re* face of the C=N group of the alkynyl imine.

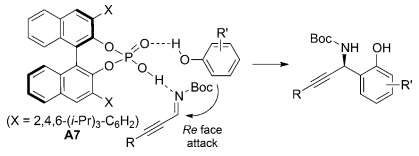
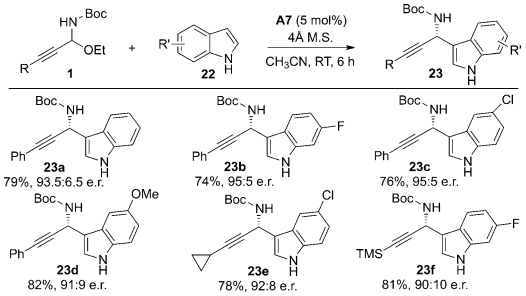


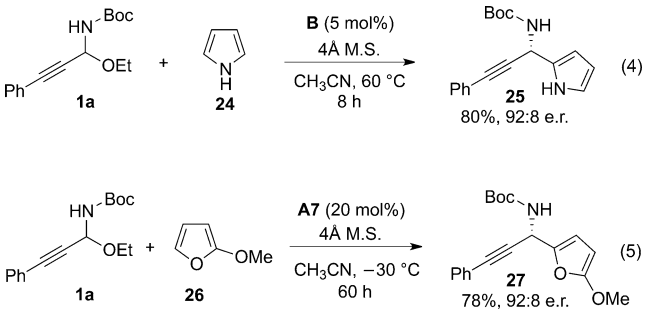
Figure 1. Proposed reaction model.

To increase the generality of our aza-F-C-type arylation for the synthesis of structurally diverse propargylamines and considering the fact that indole-containing compounds are versatile synthetic building blocks and privileged structural

motifs in numerous natural products and biologically active molecules, we also explored the previously unreported reaction of C-alkynyl N-Boc-protected N,O-acetals with indoles. As shown in Scheme 4, this new tandem arylation proceeded smoothly to furnish the desired (3-indolyl)methanamines substituted with a synthetically flexible alkyne group in good yields with high enantioselectivities, which is a good complement to previous methods for preparing (3-indolyl)-methanamines substituted with either an aromatic or aliphatic group.[16,17] To the best of our knowledge, there are no other approaches for the asymmetric synthesis of α-indole-substituted propargylamines **23**. This new tandem F-C-type arylation propargylamine synthesis was also applicable to other types of heteroarenes, such as pyrrole[18] and 2-methoxyfuran[19] [Eqs. (4) and (5)].



Scheme 4. Friedel–Crafts-type arylations of C-alkynyl N,O-acetals **1** with indoles **22**.



In summary, we have developed the first arylation strategy for the asymmetric synthesis of synthetically and biologically important propargylamines. This approach, which is complementary to previous alkynylation and alkylation strategies, involves a $C(sp^2)$–$C(sp^3)$ bond formation and is based on the first asymmetric Friedel–Crafts-type arylation reaction of in situ generated N-Boc-protected C-alkynyl imines. Remarkably, highly enantioselective asymmetric Friedel–Crafts reactions of electron-deficient phenols were thus realized for the first time, enabled by the optimal combination of electrophile and catalyst. By employing our recently introduced C-alkynyl N-Boc-protected N,O-acetals as electrophiles and chiral phosphoric acids as catalysts, unprecedented asymmetric Friedel–Crafts reactions with electron-deficient, -neutral, and -rich phenols as well as 1- and 2-naphthols have also been achieved, providing structurally diverse and densely functionalized propargylamines, which are versatile precursors to other useful chiral molecules. Moreover, the arylation strategy can be further extended to heteroarenes, such as indoles, pyrrole, and 2-methoxyfuran, and furnished novel scaffolds of pharmaceutical and biological importance.

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Keywords: alkynyl imines · arylation · Brønsted acids · Friedel–Crafts reaction · propargylamines

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