Applications of organochalcogen catalysts in C-H amination and substitution reactions

Timothy Maloney

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Reading Committee:

Forrest E. Michael, Chair

Gojko Lalic

Matthew Golder

Program Authorized to Offer Degree:

Department of Chemistry

University of Washington

Abstract

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Timothy Maloney

Chair of the Supervisory Committee:
Forrest E. Michael
Department of Chemistry

The field of C-H activation has been dominated by transition metal catalysis, especially in the formation of new C-N bonds. However, these complexes can be costly, often require arduous syntheses, and can be air and moisture sensitive. Vast amounts of research have been undertaken to elucidate selectivity in these pathways, but there remain regioselectivity and chemoselectivity obstacles to overcome. To avoid the unproductive side reactivity of transition metal complexes, to access structures orthogonal to those available, and to develop more easily tuned catalysts, the Michael Lab has spent tremendous effort in exploring organochalcogen compounds as alternatives to transition metal complexes. During our exploration, we found that in addition to oxidative chemistry, these compounds are competent nucleophiles able to form chalconium salts *in situ*. This observation revolutionized the way our lab thought about phase-transfer catalysis, precluding the need to use premade hygroscopic and difficult to recover salts. This dissertation presents work aimed at advancing the capabilities of organochalcogen species in the context of propargylic C-H amination, directed allylic C-H amination, and -onium salt phase-transfer catalysis.

The first method discussed is the intermolecular propargylic C–H amination of alkynes. This reaction is transition metal-free, instead relying on phosphine selenide catalysts. Terminal, silyl, and internal alkynes bearing a wide range of functional groups can be aminated in high yields. Mechanistic studies revealed that the proposed ene reaction has a transition state that results in substantial partial positive charge development at the carbon atom proximal to the C-H being activated. This allowed inductive and/or hyperconjugative stabilization or destabilization of this positive charge to direct regioselective C-H amination.

Next, a selenium catalyzed allylic C−H amination reaction of vinylsilanes and vinylboranes is discussed. These substrates are ubiquitous in organic synthesis, but direct functionalization of these species without the participation of either the C=C or C−Si/B bonds is rare. Due to the metal-free nature of this protocol, a new C-N bond can be installed without competing transmetallation or alkene addition reactions. In this transformation, the silicon or boron substituent inverts the usual regioselectivity, directing amination to the site distal to that group. Subsequent cross-coupling or demetallation allows access to complementary regioisomeric products.

Finally, organochalcogen-catalyzed phase-transfer reactions are discussed. Contrary to traditional phase-transfer protocols which commonly rely on an exogenous catalyst to affect the solubility of reactants, the relevant ionic species is generated *in situ* via nucleophilic displacement of a variety of alkyl leaving group by chalcogen imidazole compounds. This mode of reactivity was studied in a wide range of non-polar and polar solvents allowing both solid-liquid and liquid-liquid phase transfer reactions with anionic nitrogen, oxygen, and sulfur nucleophiles. The neutral catalyst was easily recovered and recycled in opposition to conventional salts.

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List of Schemes

Acknowledgements

My journey to arrive at and persist through graduate school would not have been possible without the support and influence of many people. First and foremost, I would like to thank Professor Forrest Michael for his mentorship during my time at the University of Washington. His enthusiasm for, encyclopedic knowledge of, and dedication to chemistry cannot be overstated. I thank him for his guidance in shaping my chemical intuition and adaptive mentoring style. Some weeks I would pester Forrest with questions about ideas, papers, or using new reagents, and his door was always open. Other weeks I would just want to put my head down and get things done. I appreciate Forrest's laissez-faire approach, letting me decide what I needed from him, but always being there when I did need something. Finally, I would like to thank Forrest for his patience in both chemistry and personal matters.

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I would not have made it to graduate school, or possibly even into the field of chemistry, if it had not been for my undergraduate research advisor Professor Kristine Nolin. During my first semester at University of Richmond, I remember taking her 6:30 pm organic lab. She was always enthusiastic about the content, but more importantly it was clear her main objective was facilitating the intellectual and personal growth of her students. She made her research lab and the chemistry department a welcoming and enjoyable place to be. Danke DNols.

I would like to thank all the members of the Michael Lab whom I overlapped with: Alex Dohoda, Shardon Morrill, Victoria Zottarelli, Ruining Yang, Yuxuan Zhang, Amy Harris, Isaac Knouff, John Tabor, Derek Obenschain, Wei Pin Teh, Tianyi Zhang, Janna Berman, Jesse Spillane, Zackary Stein, Tristan Wine, Nicole Rishwain, Samuel Landing, Blaise Black, Y-Nhi Tran, Dureti Hajikedir, and Halima Bedesco. I would especially like to thank Derek for serving as a mentor to me when I first joined the lab and Isaac for his invaluable contributions to advancing our chemistry. I would also like to thank other professors and faculty, including Professor Matt Golder, Dr. Martin Sadilek, Loch Hickock, and Adrienne Roehrich for their support during my time at UW.

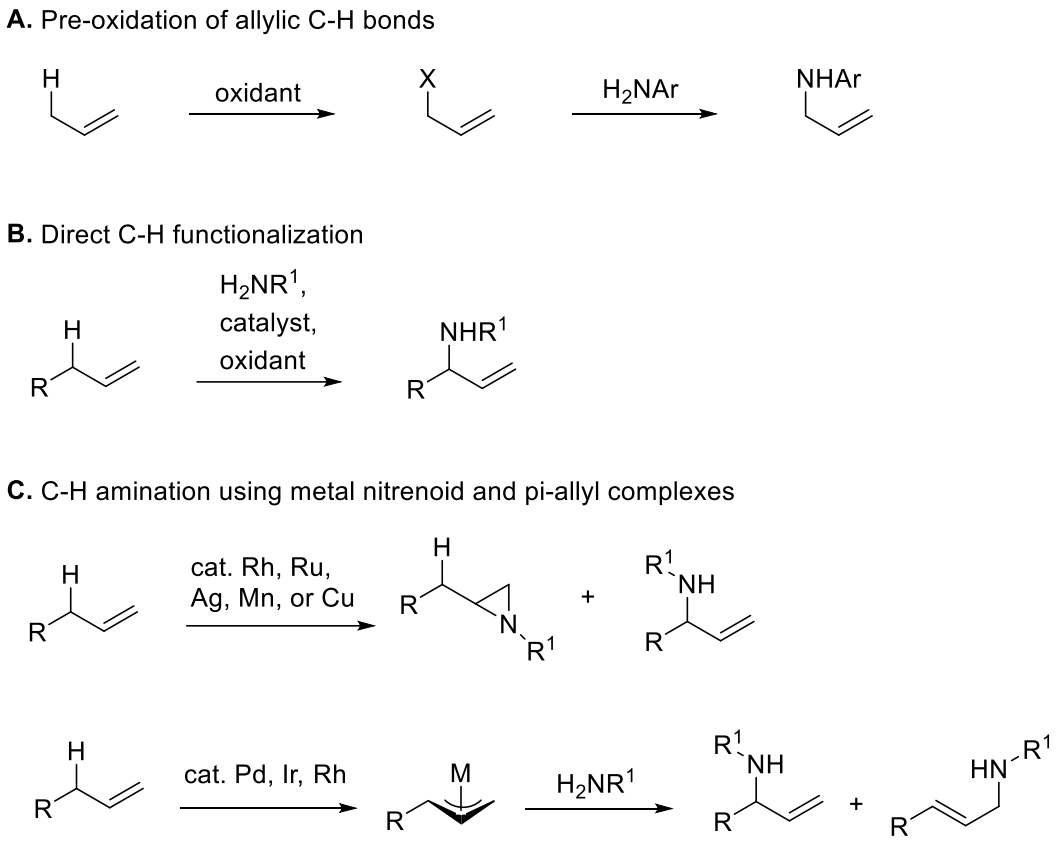
Dedication

To my mom and dad

for their love and support

Chapter 1 – Organoselenium-catalyzed intermolecular propargylic C-H amination of alkynes

Section 1: Introduction

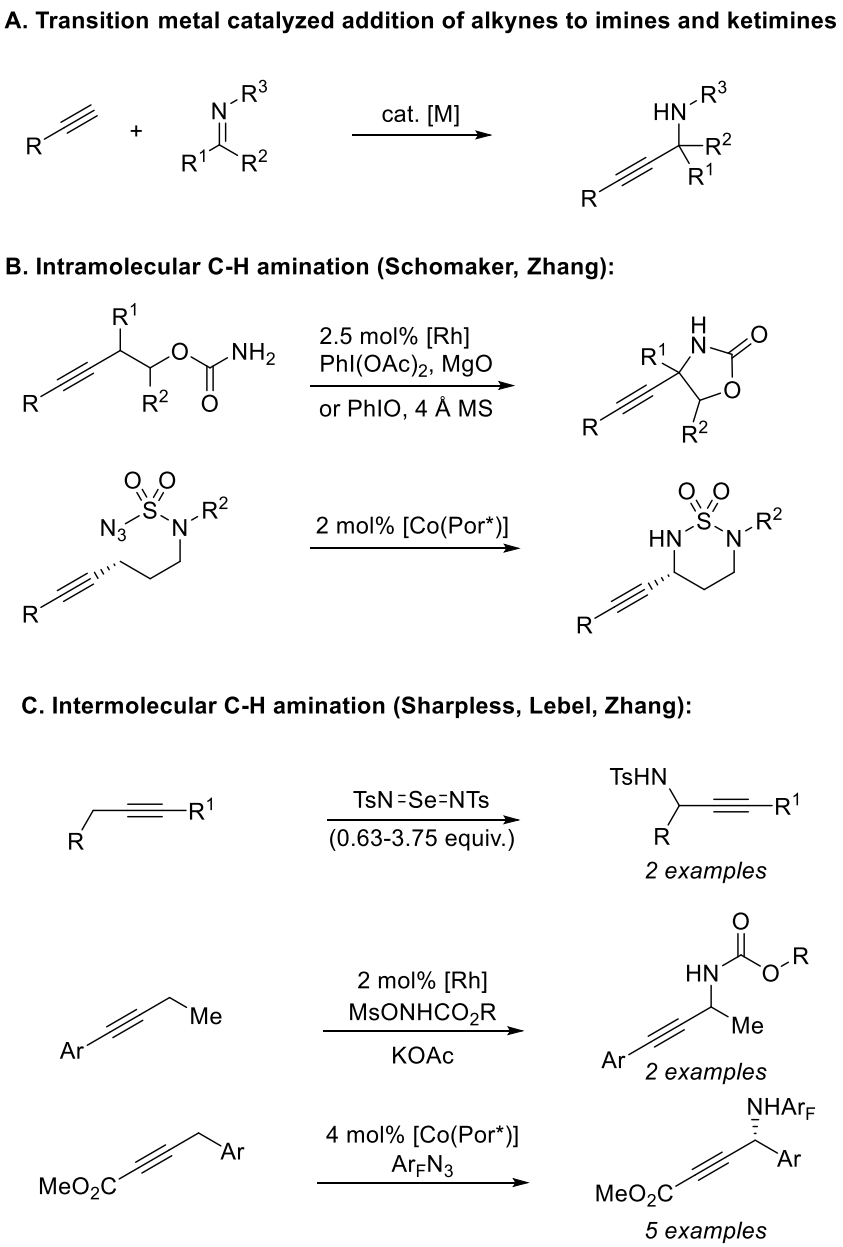


Scheme 1: Common routes for accessing allylic amines.

Carbon nitrogen bonds are abundant in biologically active compounds and serve as synthetic intermediates for the construction of more complex molecules. Traditional methods of installing nitrogen containing groups in the allylic or propargylic position usually rely on leveraging the reactivity of pre-oxidized starting materials, e.g. reductive amination or nucleophilic attack (Scheme 1A). Direct C-H amination methods avoid this need to prefunctionalize the starting material and have the potential to access orthogonal reactivity due to catalyst control over the process (Scheme 1B). However, regio- and chemoselectivity issues plague the direct amination of these allylic and propargylic C-H bonds in existing protocols. Common

methods include Rh or Ru catalyzed nitrenoid insertions into C-H bonds, but aziridination often competes with insertion (Scheme 1C).[1] Displacement of Pd or Rh π-allyl complexes with nitrogen nucleophiles are also an alternative method, but terminal or styrenyl allylamines are often selectively formed (Scheme 1C).[2] Thus, a general catalytic method that chemoselectively oxidizes one C-H bond to give a predictable regioisomer of the aminated product is highly desirable.

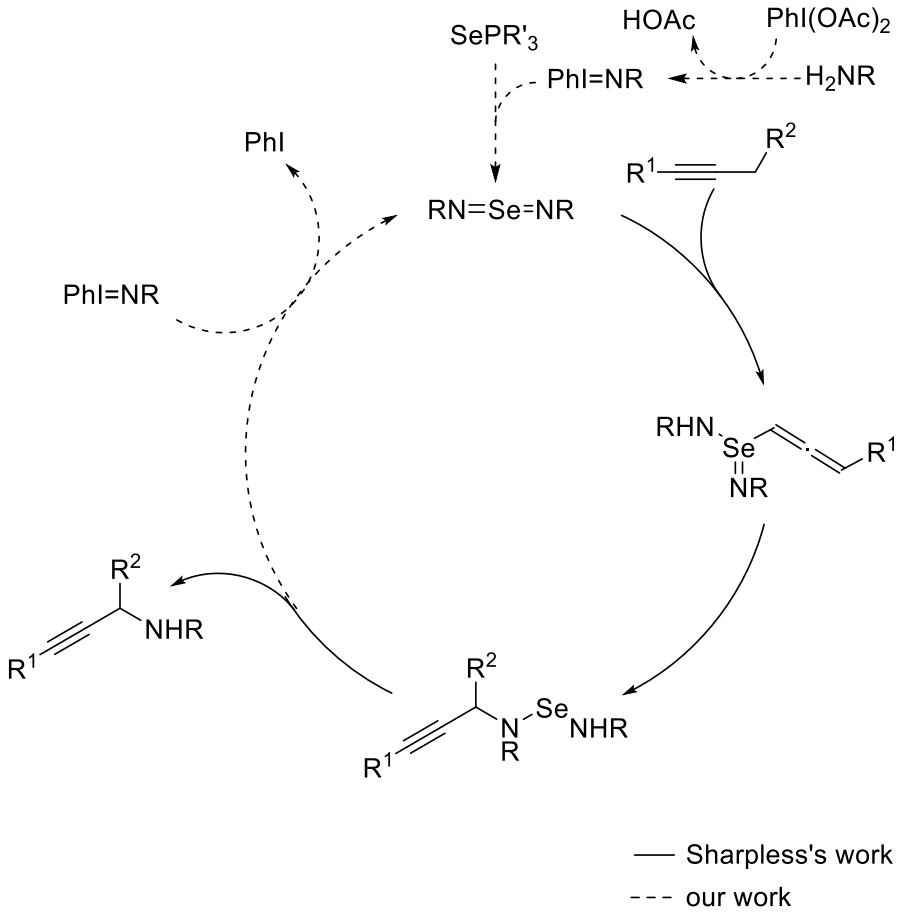
At the time of exploration and to the best of our knowledge, very few examples of catalytic, propargylic C-H aminations had been reported. Several methods to achieve this propargylic C-H amination relieved on using metal nitrenoids and a tethered nucleophile, which fundamentally limited their generality.[3-10] Schomaker reported the intramolecular Rh-catalyzed C-H amination of homopropargylic carbamates to give cyclic propargylic carbamates (Scheme 2B).[3] This method was only shown to be tolerant of cyano- and trifluoromethyl substituted aryl alkynes, as well as alkyl substitution at the homopropargylic position. Zhang reported an enantioselective intramolecular amination of sp^3 C-H bonds using Co(II)-based metalloradical catalysis to activate sulfamoyl azides as nucleophiles (Scheme 2B).[8] However, only secondary propargylic C-H bonds were shown to undergo the reaction, potentially explosive azides must be handled, and the Co(II)-porphyrin complex was made in four steps. Even fewer intermolecular examples of propargylic C-H aminations had been reported, several with very examples demonstrated and poor generality.[11-16] Zhang demonstrated intermolecular propargylic C-H amination by extension of this Co(II)-porphyrin system, however the generality of this method was severely limited to aryltetrolate esters using fluoroarylazides as nitrogen sources (Scheme 2C).[14] Lebel reported the stereoselective Rh-catalyzed C-H amination of two 4-arylbut-1-ynes using a chiral *N*-mesyloxycarbamate nucleophile (Scheme 2C).[15]



Scheme 2: Common routes to propargylic amines.

Although intermolecular in nature, this method was low yielding and very limited in scope. A more practical and general alternative to these transition-metal catalyzed aminations was missing in the literature.

In 1976, Sharpless reported the stoichiometric intermolecular amination of propargylic and allylic C-H bonds using preformed bisimidoselenide reagents (Scheme 2C).[17] The proposed active species was formed via mixing Se metal and two equivalents of anhydrous Chloramine-T to give a "white-gray slurry," which, upon treatment with an alkyne or alkene, yielded the allylically or

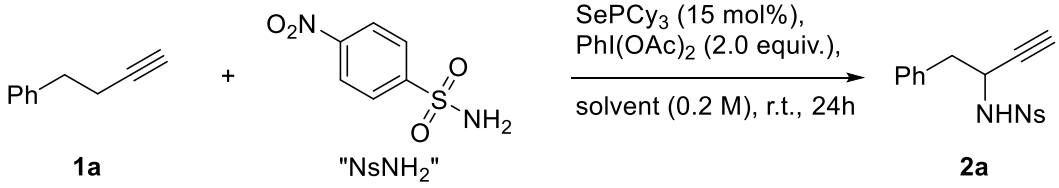


Scheme 3: Proposed catalytic cycle for propargylic C-H amination.

rearrangement and deselenation generated the propargylic or allylic amine (Scheme 3). With a suitable selenium source, oxidant, and nitrogen source, one can envision oxidatively closing this catalytic cycle. Our lab successfully closed this cycle using phosphine selenides, hypervalent iodine oxidants, and sulfonamides or sulfamates, and we applied this selenium catalyzed direct C-H amination to alkenes in a chemo- and regioselective manner.[19] Herein, we discuss the extension of this method to propargylic C-H bonds and an electronic effect that allowed regioselective C-H activation (Scheme 2D).[20]

Section 2: Results and Discussion

To begin optimization, the model substrate 4-phenyl-1-butyne, compound **1a**, was subjected to the previously reported allylic amination conditions using 4- nitrobenzenesulfonamide ($NsNH_2$), diacetoxyiodobenzene ($PhI(OAc)_2$), and tricyclohexylphosphine selenide ($SePCy_3$) to afford a 55% yield of propargyl sulfonamide **2a** (Scheme 4, entry 3). Attempts to determine what side reactions were consuming the other 45% of starting material were unsuccessful. Optimization of these initial conditions began with a solvent screen. Non-polar solvents such as hexanes and cyclohexane gave no conversion to the desired product (entry 1), however toluene and benzene gave 76% and 78% yield, respectively (entry 2). The more polar solvents acetone and ethyl acetate generated moderate conversions to **2a** (entries 9-10). Surprisingly, 73% yield was observed in dimethyl sulfoxide (DMSO), indicating the reaction might not be as water sensitive as first assumed (entry 12). However, when water was tested as a solvent, no product was observed (entry 13). Ultimately, dioxane proved to be the optimal solvent for this substrate, giving an 85% yield of **2a** (entry 16). The reaction proved to be robust to concentration changes, as 88% and 81% yield was observed for 0.1 and 0.4 M in dioxane, respectively (entries 17-18).



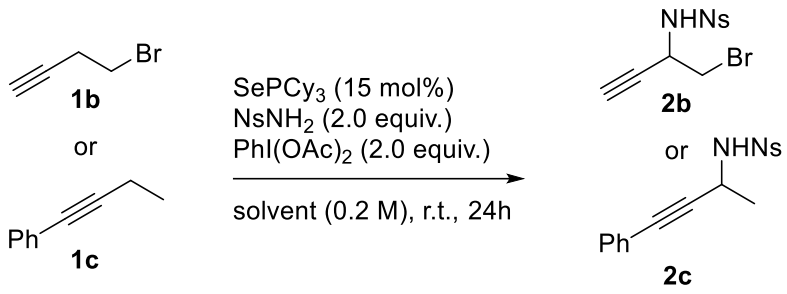
1a "$NsNH_2$" **2a**

entry	solvent	yield (%)[a]	SM (%)
1	cyclohexane	-	>99
2	hexanes	-	92
3	benzene	76	-
4	toluene	78	-
5	DCM	55	-
6	DCE	43	15
7	$CHCl_3$	72	-
8	MeCN	35	23
9	acetone	64	23
10	EtOAc	62	-
11	DMF	-	91
12	DMSO	73	-
13	H_2O	-	40
14	Et_2O	29	36
15	THF	37	22
16	dioxane	85	-
17	dioxane (0.1 M)	88	-
18	dioxane (0.4 M)	81	-

[a] ^{1}H NMR yields determined using 1,3-dinitrobenzene as an internal standard.

Scheme 4. Propargylic amination solvent screen using 4-phenyl-1-butyne.

With this knowledge in hand, other substrates were tested under these seemingly optimized conditions. When both 4-bromo-1-butyne (**1b)** and 1-phenyl-1-butyne (**1c**) were subjected to the reaction conditions using dioxane as a solvent, very poor reactivity was observed, giving 9% and 0% yield, respectively (Scheme 5, entries 1,4). Upon further screening, it was found that a substrate-dependent solvent effect was operational. Of the solvents tested, toluene was observed to give the highest yield of 76% of **2b** (entry 6), while DCM gave the optimal yield of 84% of **2c** (entry 8). Attempts were made to try and detail the mechanism behind this effect but were unsuccessful due to the fleeting nature of the reactive intermediates. Thus, these three solvents were tested for every substrate subjected to the reaction, and the highest yielding was reported.

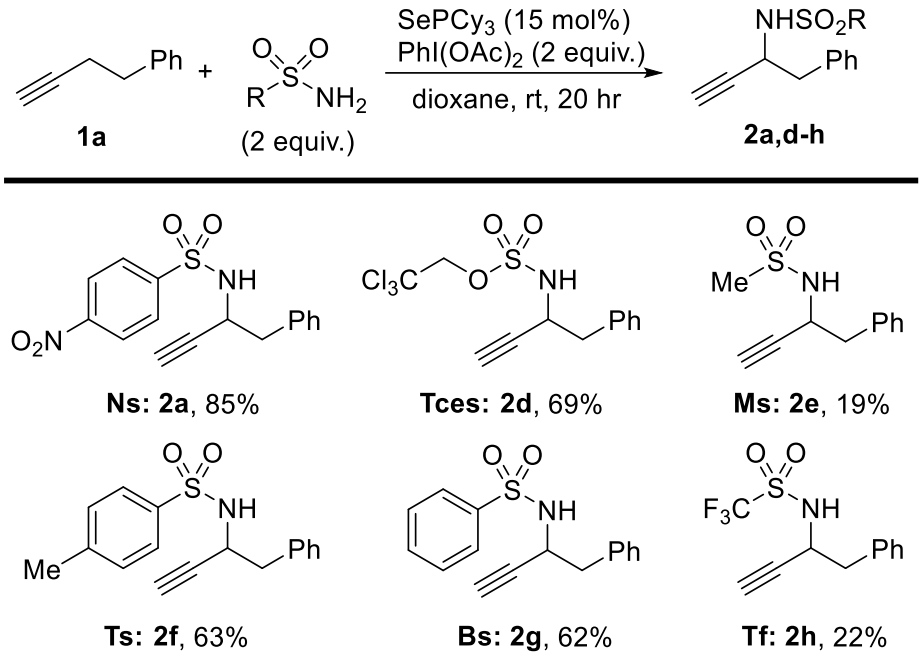


entry	solvent	alkyne	yield (%)[a]
1	dioxane	**1b**	9
2	DCM	**1b**	34
3	toluene	**1b**	76
4	dioxane	**1c**	0
5	DCM	**1c**	84
6	toluene	**1c**	61

[a] ^{1}H NMR yields determined using 1,3-dinitrobenzene as an internal standard.

Scheme 5. Solvent screen using different alkyne starting materials.

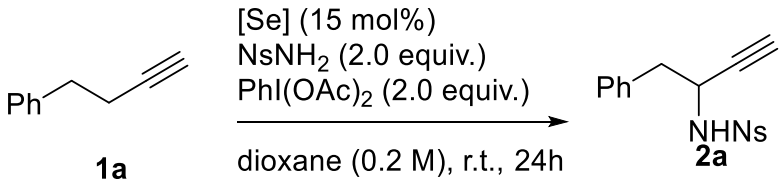
The nitrogen source was investigated next (Scheme 6). Both sulfonamides and sulfamates proved to be competent nitrogen sources, with the electron-poor $NsNH_2$ giving an 85% yield of **2a**. Aryl sulfonamides tosyl amide ($TsNH_2$) and benzenesulfonamide ($BsNH_2$) gave lower yields of 63% and 62%, respectively. The more electron-rich phenethylamine was tested as a nitrogen source but yielded no conversion to the desired product. Two equivalents of phenethylamine was added to a mixture of **1a**, $SePCy_3$, $PhI(OAc)_2$, and $NsNH_2$ in dioxane, but no amination was observed after stirring for 24 hours. This indicates that alkyl amine bases could hinder the reactivity of this method. Thus, $NsNH_2$ was chosen for further screenings.



Yields determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

Scheme 6. Propargylic amination nitrogen source screen.

The selenium catalyst was investigated next (Scheme 7). Gratifyingly, the reaction did not proceed in the absence of selenium (entry 1), or in the presence of selenium powder alone (entry 2). *N*-heterocyclic carbene (NHC) ligands afforded minimal to no desired amination product (entries 3-7). Phosphines proved to be superior ligands, with the aminophosphine, phosphite, arylphosphine, and alkylphosphine selenides all catalyzing the reaction in good to excellent yields (entries 8-14). Tert-butyl phosphine selenide (SeP*t*Bu$_3$) appeared to be the optimal catalyst (entry 14) but was not as robust as SePCy$_3$ upon further screening. Reduction of the catalyst loading to 10 mol% of SePCy$_3$ showed 43% residual starting material after 24 hours. Hence, a 15 mol% loading of SePCy$_3$, 2.0 equivalents of NsNH$_2$, and 2.0 equivalents of PhI(OAc)$_2$ in dioxane (0.2 M) were chosen as the optimal reaction conditions.



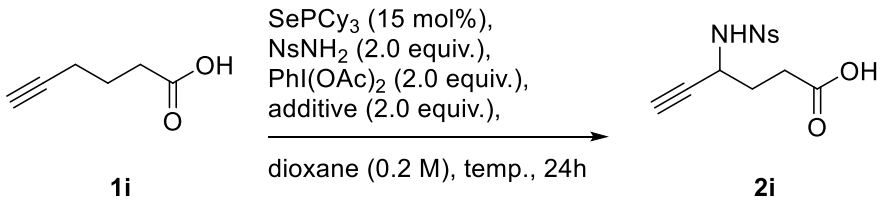
entry	[Se]	yield (%)[a]	SM (%)
1	no Se	-	94
2	Se powder	-	-
3	SeIPr	-	79
4	SeICy	-	71
5	SeIMes	2	67
6	SeIMe	8	62
7	SeI*t*Bu	14	53
8	$SeP(NEt_2)_3$	55	10
9	$SeP(OPh)_3$	73	-
10	$SePPh_3$	65	-
11	$SePNp_3$	69	49
12	SeDavePhos	36	28
13	SeJohnPhos	28	-
14	$SeP*t*Bu_3$	87	-
15	$SePCy_3$	85	-
16	$SePCy_3$ (10 mol%)	40	43

[a] ^{1}H NMR yields determined using 1,3-dinitrobenzene as an internal standard.

Scheme 7. Propargylic amination selenium catalyst screen.

Up to this point, only relatively simple alkynes had been tested, namely arylalkynes and alkylalkynes. To probe the generality of this method, substrates bearing more reactive functional groups were investigated. Substrates having pendant carboxylic acids were especially attractive given the synthetic utility of this functional group. When 5-hexynoic acid, compound **1i**, was subjected to the standard reaction conditions, a 24% yield of **2i** was observed (Scheme 8A, entry 1). It was hypothesized that transesterification with diacetoxyiodobenzene hinders productive reactivity of the substrate (Scheme 8B). The importance of the alkyl group on the oxidant can be

A. Optimzation of 5-hexynoic acid

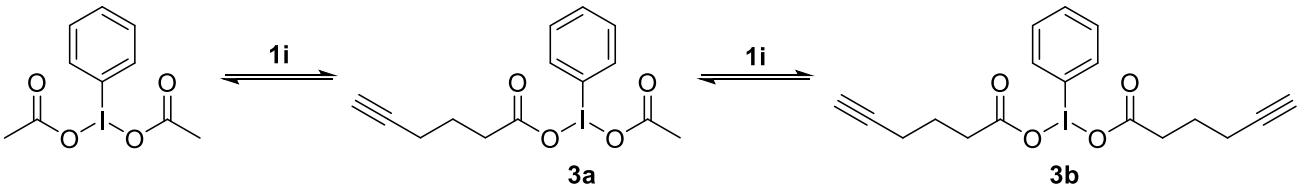


1i **2i**

entry	additive	temp.	yield (%)[a]	SM (%)
1	-	r.t.	24	45
2	PhCOOH	r.t.	49	19
3	PhCOOH	35 °C	69	-
4	4-NO_2PhCOOH	r.t.	74	-
5	4-NO_2PhCOOH	35 °C	78	-

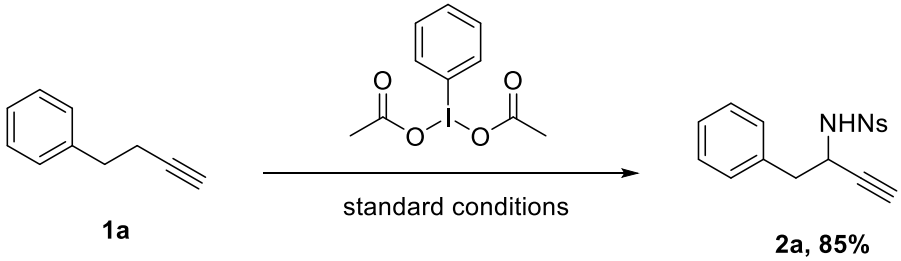
[a]^{1}H NMR yields determined using 1,3-dinitrobenzene as an internal standard.

B. Proposed equilibrium between diacetoxyiodobenzene and 5-hexynoic acid

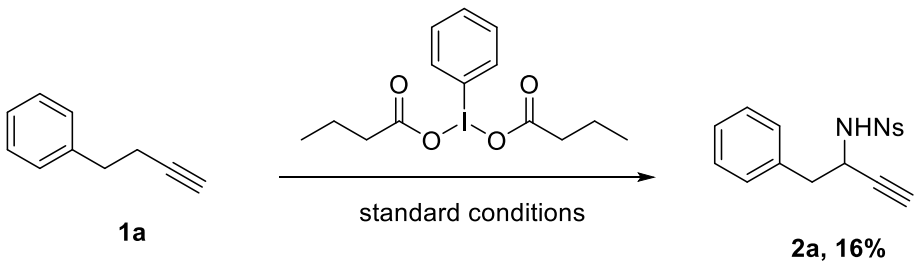


3a **3b**

C. Sensitivity towards different dialkoxyiodobenzene oxidants with 4-phenyl-1-butyne



1a **2a, 85%**



1a **2a, 16%**

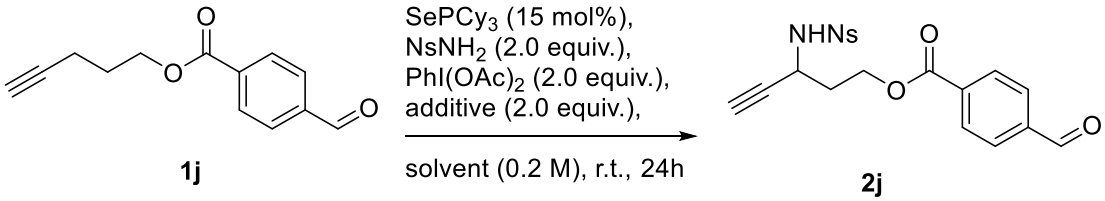
Conditions: $SePCy_3$ (15mol%), $NsNH_2$ (2.0 equiv.), $PhI(OR)_2$ (2.0 equiv.), dioxane (0.2 M), at 23 °C for 24 hours

Scheme 8. Optimization of carboxylic acid-containing substrates.

seen when diacetoxyiodobenzene is replaced by dibutyroxyiodobenzene in the reaction with 4-phenyl-1-butyne. The former gives a yield of 85%, while the simple elongation of the alkyl group by two carbons only gives 16% in the latter (Scheme 8C). Hence, exogenous carboxylic additives were added to try and perturb this equilibrium, both freeing the substrate and maintaining the integrity of the oxidant. The addition of benzoic acid doubled the yield of **2i** to 49% (entry 2), while heating this mixture at 35 ˚C further increased the yield to 69% (entry 3). Addition of the more acidic 4-nitrobenzoic acid increased the yield of **2i** to 74%, and heating was found unnecessary (entries 4-5). Thus, 4-nitrobenzoic acid was added to the reaction, and the crude mixture was treated with diazomethane after completion, affording the more easily isolable aminated methyl ester in 70% isolated yield.

Another functional group of interest was aldehydes due to their electrophilic nature and the presence of nucleophilic $NsNH_2$ in the reaction mixture. When 5-pentyn-(4-formyl)-benzoate, compound **1j**, was subjected to the amination conditions no conversion to **2j** was observed (Scheme 9A, entry 1). Upon passing the crude mixture through a silica plug, a white solid was collected from the top of the plug. Upon dissolution in d_6-DMSO, ^{1}H NMR analysis showed a one-to-one mixture of $NsNH_2$ and **1j**. Given that both compounds are soluble throughout the reaction and work-up procedure, it is unlikely that the isolated solid was a simple mixture of the two compounds. Instead, this one-to-one mixture is consistent with condensation of the sulfonamide and aldehyde to potentially form an insoluble hemiaminal or imine species (Scheme 9B). To try and perturb the formation of this unknown solid, 4-nitrobenzoic acid was added to the reaction, but only afforded trace amounts of **2j** (entry 2). Compound **1k** was subjected to a screen of Bronsted acids to find a suitable alternative that is compatible with the reaction conditions (Scheme

A. Optimzation of an aldehyde-containing substrate

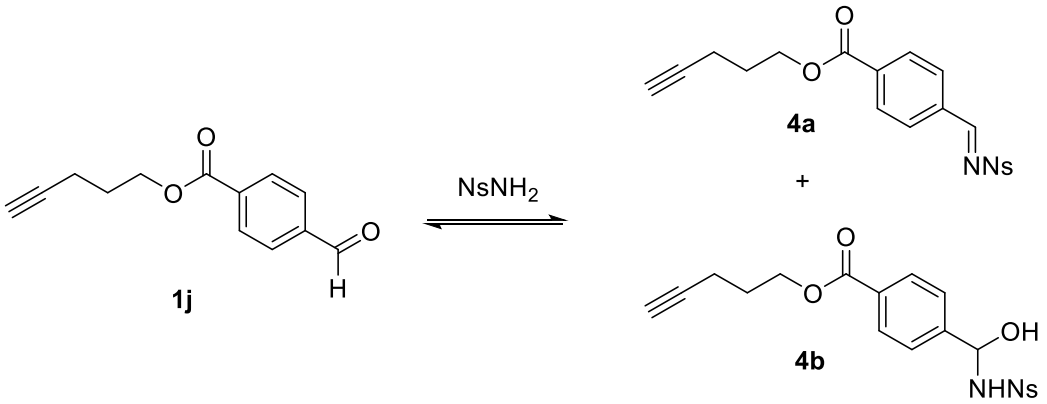


1j **2j**

entry	solvent	additive	yield (%)[a]	SM (%)
1	dioxane	-	-	88
2	dioxane	4-NO_2PhCOOH	tr	74
3	dioxane	TFA	60	-
4	toluene	-	29	-
5	DCM	-	73	7

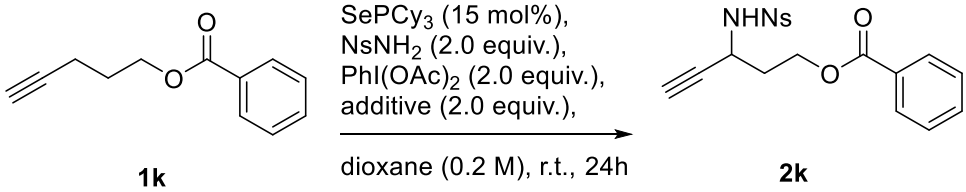
[a]^{1}H NMR yields determined using 1,3-dinitrobenzene as an internal standard.

B. Proposed equilibrium between $NsNH_2$ and 1j



1j

C. Exploration of Bronsted acids



1k **2k**

entry	additive	yield (%)[a]	SM (%)
1	-	76	-
2	HCl	-	43
3	TsOH	5	66
4	TFA	70	tr
5	4-NO_2PhCOOH	76	-

[a]^{1}H NMR yields determined using 1,3-dinitrobenzene as an internal standard.

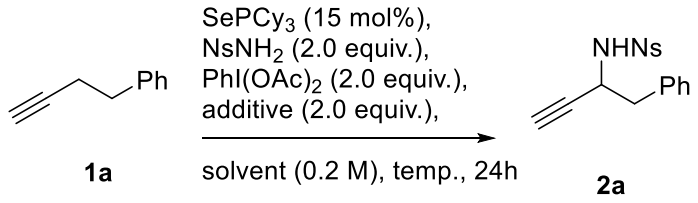
Scheme 9. Optimization of an aldehyde-containing substrate.

9C). Trifluoroacetic acid (TFA) displayed a minor decrease in yield (entry 4), while tosylic acid (TsOH) and hydrochloric acid (HCl) shut down the reaction (entries 2-3). Thus, TFA was added to the reaction mixture with compound **1j**; no solid was observed and generated a 60% yield of **2j** (Scheme 9A, entry 3). However, upon changing solvents to toluene and DCM, a 29% and 73% yield of **2j** was observed, respectively (entries 4-5). No solid was observed in these reactions either, indicating the proposed equilibrium was solvent dependent.

The effect of base additives was also investigated (Scheme 10A). Inorganic and amine bases were shown to shut down the reaction (entries 2-4). However, insoluble group 2 oxides acted as acetate scavengers and effectively slowed the reaction down (entries 5-7). Calcium oxide (CaO) gave the best mass conversion (entry 6) and was investigated further. When the reaction was run in DMSO, the mixture was homogenous, and no conversion to **2a** was observed, indicating that it is necessary for the base to be insoluble. The less polar toluene proved to be the optimal solvent; upon heating at 70 ˚C a 71% yield of **2a** was observed (entry 10). This strategy was applied to compound **1l**, which displayed poor mass conversion under the standard reaction conditions due to its highly oxidizable benzylic protons (Scheme 10B, entry 1). A 30% yield of **2l** was observed under the standard reaction conditions using toluene as the solvent (entry 3). Upon addition of CaO, the yield was improved to 52% with 26% residual starting material (entry 5). Heating the reaction mixture at 35 ˚C in toluene in the presence of 2 equivalents of CaO yielded a 73% conversion to compound **2g** (entry 6). The same conditions in dioxane only generated a 56% yield of **2g** (entry 7).

Using the knowledge of solvents and additives gained throughout this screening process, we next explored the scope of this reaction with a variety of alkynes (Scheme 11). Various terminal alkynes, aryl acetylenes, and internal alkynes were subjected to the optimized reaction conditions

A. Exploration of base additives

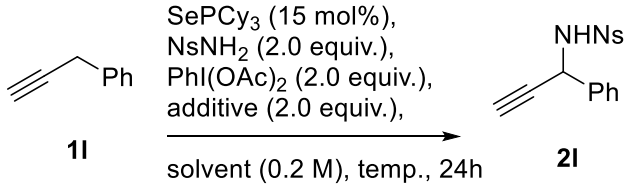


1a **2a**

entry	solvent	temp.	additive	yield (%)[a]	SM (%)
1	DCM	r.t.	-	74	-
2	DCM	r.t.	NEt_3	-	>99
3	DCM	r.t.	Al_2O_3	-	86
4	DCM	r.t.	K_2CO_3	-	>99
5	DCM	r.t.	MgO	57	24
6	DCM	r.t.	CaO	52	38
7	DCM	r.t.	BaO	26	51
8	DMSO	r.t.	CaO	-	>99
9	toluene	r.t.	CaO	42	48
10	toluene	70 °C	CaO	71	14

[a] ^{1}H NMR yields determined using 1,3-dinitrobenzene as an internal standard.

B. Optimization of 3-phenyl-1-propyne

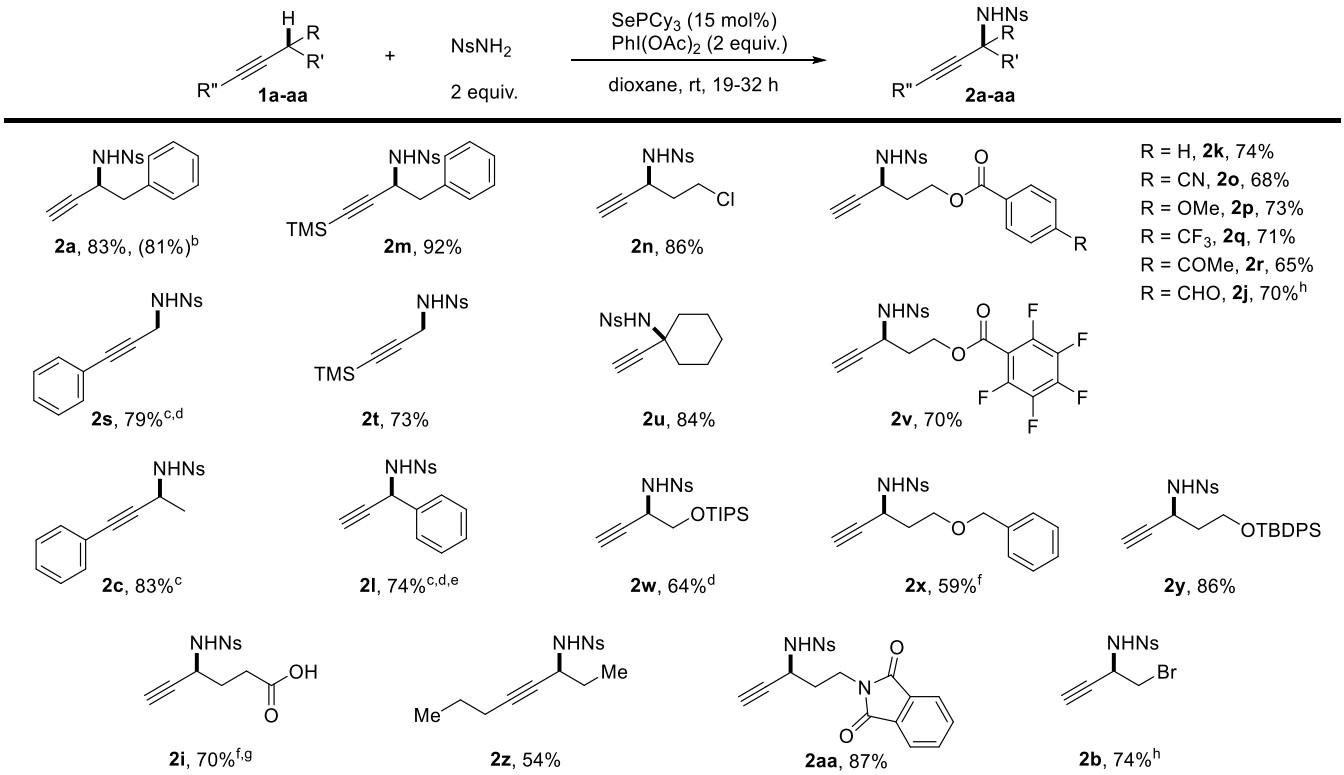


1l **2l**

entry	solvent	temp.	additive	yield (%)[a]	SM (%)
1	dioxane	r.t.	-	40	7
2	DCM	r.t.	-	22	16
3	toluene	r.t.	-	30	7
4	toluene	35 °C	-	21	5
5	toluene	r.t.	CaO	52	26
6	toluene	35 °C	CaO	73	5
7	dioxane	35 °C	CaO	56	-

[a] ^{1}H NMR yields determined using 1,3-dinitrobenzene as an internal standard.

Scheme 10. Optimization of benzylic C-H amination using base additives



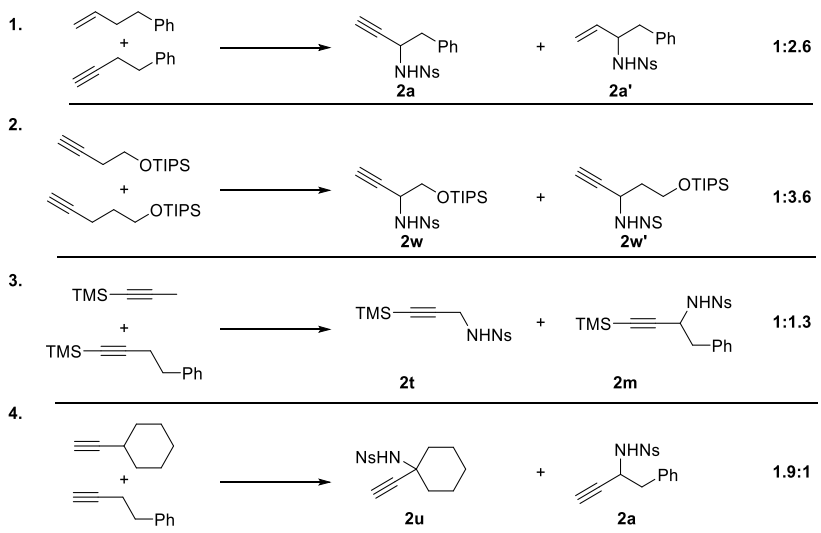
[a]Isolated yields. [b]4.0 mmol scale. [c]toluene instead of dioxane. [d]35 °C. [e]CaO (2 equiv.) [f]4-nitrobenzoic acid (2 equiv.). [g]Isolated as methyl ester after treatment of crude reaction mixture with diazomethane. [h]CH_2Cl_2 instead of dioxane.

Scheme 11. Terminal and silyl-substituted alkyne scope.

and gave the corresponding propargylic sulfonamides in moderate to excellent yields. The reaction was shown to be compatible with silyl ethers, esters, phthalimides, alkyl halides, ketones, and aldehydes. Primary, secondary, and tertiary propargylic positions were all aminated in good to excellent yields. Propargyl sulfonamide **2a** was also isolated on a 4.0 mmol scale with no significant loss in yield. Substrates containing free alcohols, free amines, cyclopropyl acetylenes, amides, and nitrogen-containing heteroaromatics displayed poor reactivity under these conditions.

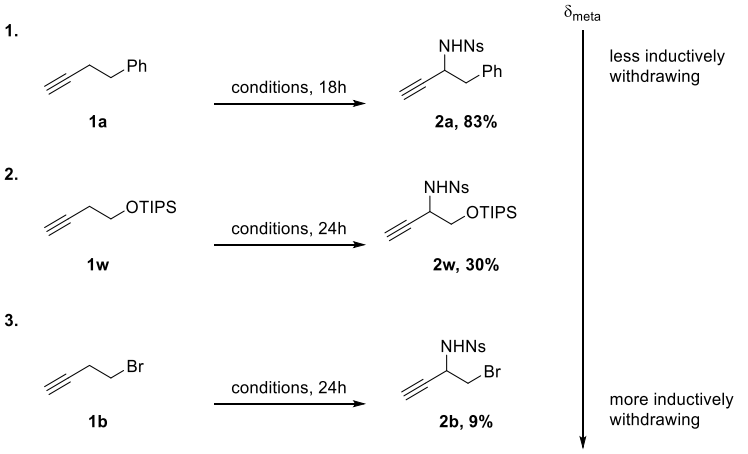
To probe the mechanism of this reaction, a series of competition experiments were undertaken (Scheme 12A). A mixture of 4-phenyl-1-butene and 4- phenyl-1-butyne were subjected to the reaction conditions with allylic amination being favored 2.6:1. Competitions between primary, secondary, and tertiary propargylic C-H bonds revealed that 1˚<2˚<3˚. This ordering can

A. Intermolecular competition experiments



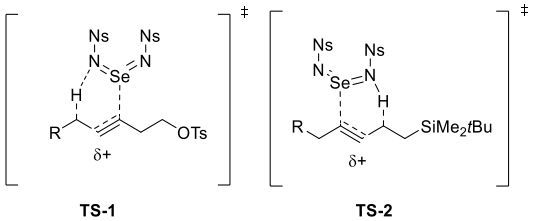
[a]Competition expirements run with 1 equivalent of each substrate under the standard reaction conditions, $SePCy_3$ (15mol%), $NsNH_2$ (2.0 equiv.), $PhI(OAc)_2$ (2.0 equiv.), dioxane (0.2 M), at 23 °C for 18 hours. The product ratio was determined by ^1H NMR of the crude reaction mixture using 1,3-dinitrobenzene as an internal standard.

B. Effect of homopropargylic group on reaction rate



Conditions: $SePCy_3$ (15mol%), $NsNH_2$ (2.0 equiv.), $PhI(OAc)_2$ (2.0 equiv.), dioxane (0.2 M), at 23 °C for 24 hours

D. Proposed asynchronous ene reaction



Scheme 12. Mechanistic studies.

be rationalized by the stability of the allene formed after the ene reaction; the more substituted the allene is, the more stable it should be. To further examine the lower yield of compound **2w** compared to other protected alcohols, a mixture of **2w** and **2w'** were subjected to the reaction conditions, favoring the protected pentynol in a 3.6:1 ratio. It was also noted during reaction optimization that as the homopropargylic substituent becomes more electron-withdrawing, the rate of reaction decreased (Scheme 12B). We hypothesized that an asynchronous ene reaction would be consistent with these observed preferences. If π-bond attack is quicker than proton abstraction, positive charge build-up will occur (Scheme 12D). Thus, it is more favorable to have the inductively withdrawing silyl ethers farther away from the propargylic position. This hypothesis was further tested Alexander Dohoda on a series of internal alkynes bearing heteroatoms at the beta- and gamma-positions. Amination occurred distal to electron-withdrawing groups like protected alcohols, halides, and phthalimides, but proximal to an electron-donating silyl group.

Section 1.3: Conclusions

In conclusion, our previously reported phosphine selenide catalyzed allylic amination protocol was successfully extended to a variety of alkynes. This method required no transition metal catalysts and displayed a predictable regioselectivity. Reaction optimization of various substrates allowed us to recognize that exogenous acids and bases could tune the reactivity of various reaction components. The effect of directing groups was also investigated, and the observed regioselectivities were rationalized by the effects of these substituents on positive charge build-up at the carbon adjacent to the C-H bond being activated.

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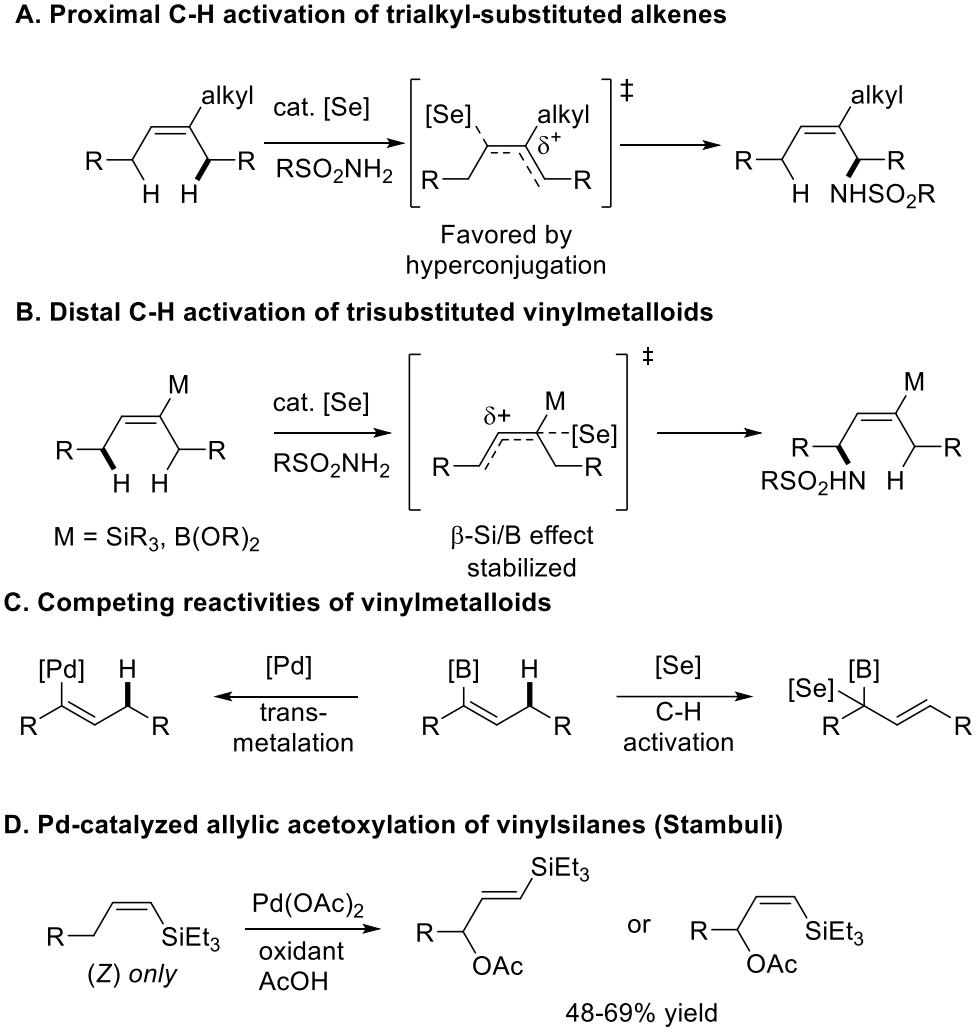
Chapter 2 – Organoselenium catalyzed C-H amination of alkynes

Section 1: Introduction

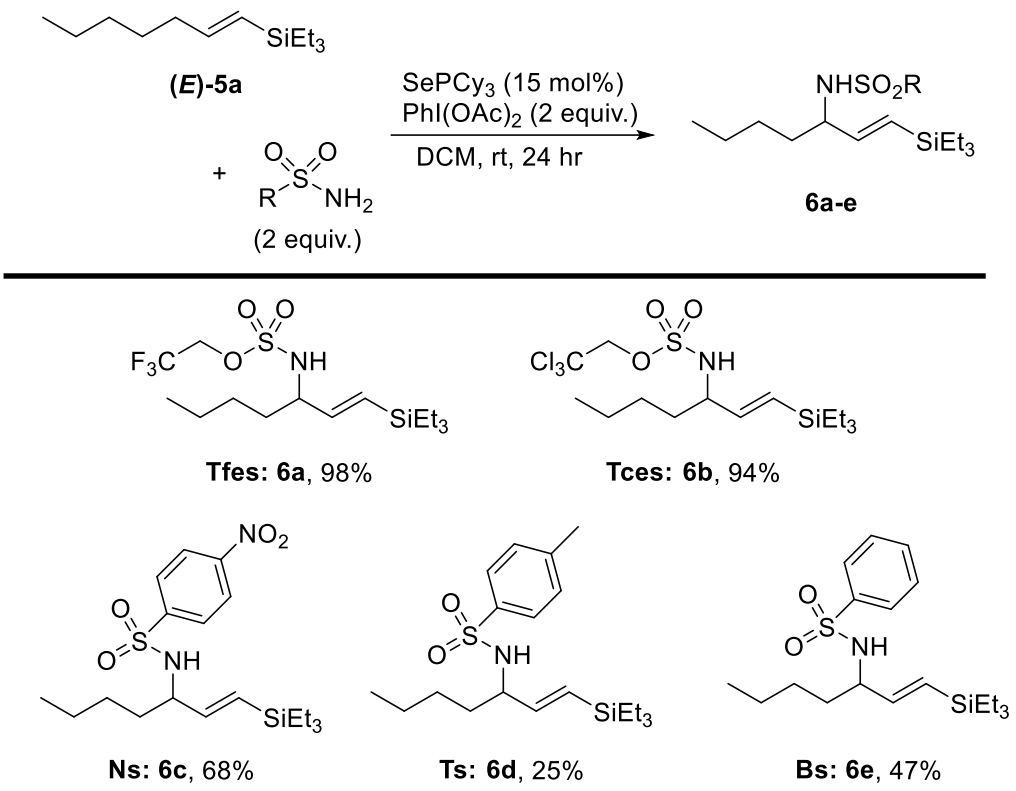
The ability to control regioselectivity by leveraging positive charge build-up in the transition state of the ene reaction of the alkyne amination reaction led us to wonder if this effect could also be exploited in the allylic amination system. Previously reported by our lab, trialkyl-substituted alkenes preferentially activated the C-H proximal to the more substituted alkene carbon.[1] This was rationalized by invoking asynchronicity in the ene reaction; we hypothesized that activation of the proximal C-H lead to positive charge build-up on the more substituted alkene carbon due to more stabilizing hyperconjugation interactions (Scheme 13A). Perhaps, by changing this third alkenyl substituent, we could instead favor distal C-H activation. Thus, we began to investigate vinylsilanes and vinylboronates as amination substrates and hypothesized that the silicon or boron atom would act as a polarity reversing group. We proposed that the development of the partial positive charge would now be stabilized by the β-silyl or β-boryl effect and invert the native regioselectivity to favor amination of the distal C-H bond (Scheme 13B). However, the ability of these substrates to undergo transmetallation reactions and their more reactive pi-system make chemoselective reactions that leave the carbon-metalloid bond intact rare, especially with transition metal-catalyzed reactions (Scheme 13C).[2] Only one C-H activation method of this substrate class has been disclosed in which Stambuli reported the Pd-catalyzed allylic acetoxylation of terminal (*Z*)-vinylsilanes (Scheme 13D).[3] Our metal-free selenium system should avoid these transition metal-promoted side reactions and leave the vinylsilane or vinylboronate intact after C-H activation for further transformations (Scheme 13C).[4]



Scheme 13. Regioselective allylic C-H amination and competing transition metal-promoted reactions.

Section 2: Results and discussion

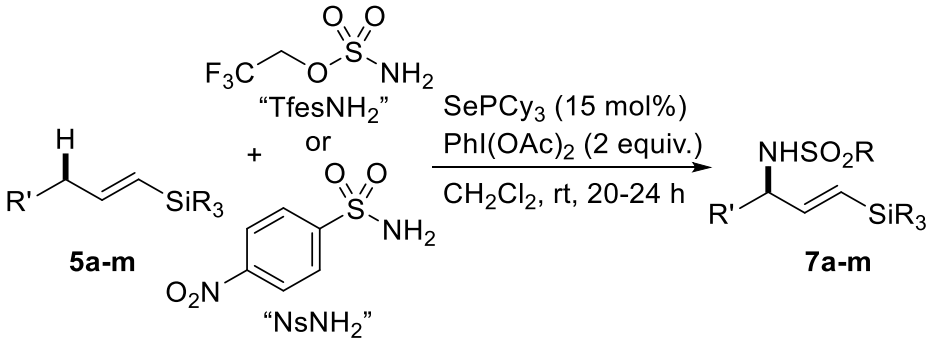
We began optimization on terminal vinyl silane (*E*)-**5a** using our previously reported allylic amination conditions (Scheme 14).[1] Sulfamates were higher yielding for terminal vinylsilanes than sulfonamides, with $TfesNH_2$ being more robust than $TcesNH_2$ towards a larger scope of vinylmetalloids. A solvent, catalyst, and oxidant screen confirmed that the $SeP(Cy)_3$, $PhI(OAc)_2$, DCM system was optimal.

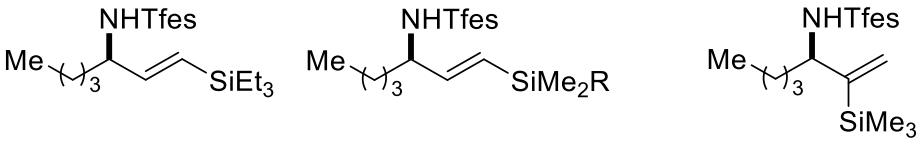


Yields determined by ^{1}H NMR spectroscopy using 1,3-dinitrobenzene as internal standard.

Scheme 14. Vinylsilane allylic amination nitrogen source screen.

With these conditions in hand, we began to explore the scope of this reaction (Scheme 15). Amination of either (*E*) or (*Z*)-**5a** afforded exclusively the (*E*)-**7a**. Both the vicinal disubstituted vinylsilane **5e** and compound **5d** only bearing an allylic C-H proximal to the silyl group were successfully aminated, indicating that amination will occur proximal to the silyl group if given no other choice. The amination of tertiary and benzylic C-H bonds was also high yielding. Trisubstituted vinylsilanes **5h-n** were tested by Janna Berman and confirmed our hypothesis that amination would occur distal the silyl group when multiple allylic C-H sites were present. Selectivity for the (*E*)-isomer of the product was also observed. However, when using $TfesNH_2$, some proximal

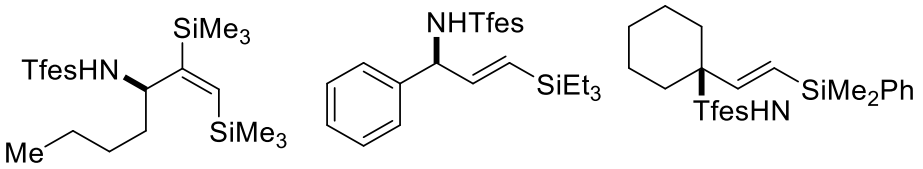




7a, 97% (from (*E*)-**5a**)
97% (from (*Z*)-**5a**)
(*E*:*Z* >95:5)

R = Ph, **7b**, 52%
R = Bn, **7c**, 72%
(*E*:*Z* >95:5)

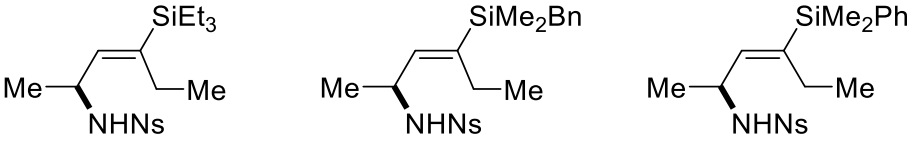
7d, 90%



7e, 63%
(*E*:*Z* >95:5)

7f, 85%
(*E*:*Z* >95:5)

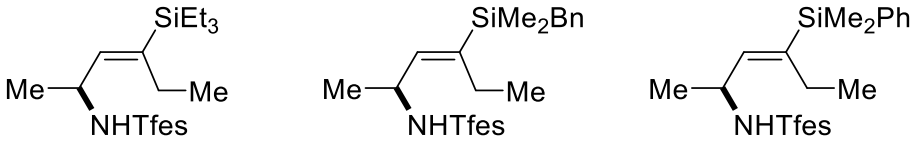
7g, 80%
(*E*:*Z* >95:5)



7h, 80%
(*E*:*Z* = 6:1)

7i, 81%
(*E*:*Z* = 3:1)

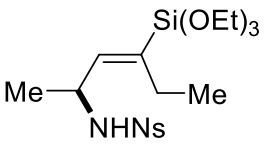
7j, 80%
(*E*:*Z* = 6:1)



7k, 83%
(*E*:*Z* = 5:1)

7l, 84%
(*E*:*Z* = 2.5:1)

7m, 76%
(*E*:*Z* = 3:1)

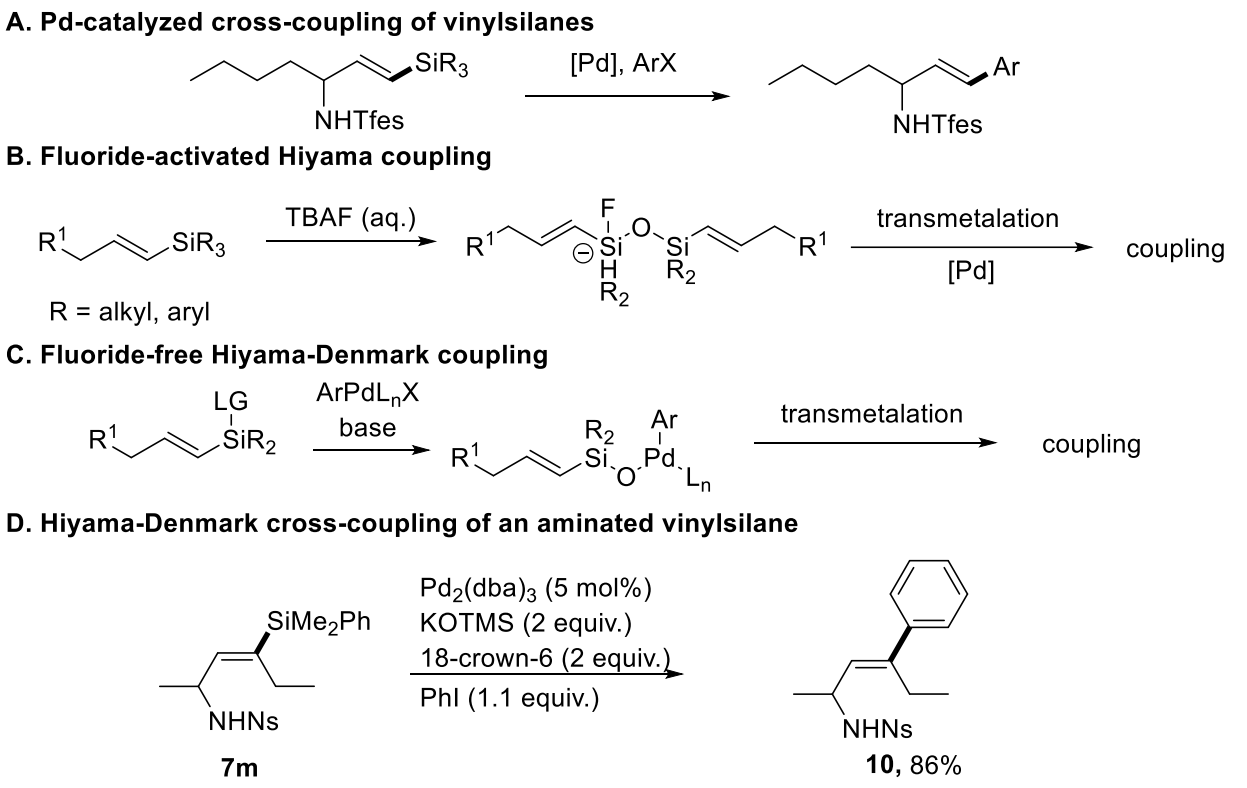


7n, 27%
(*E*:*Z* >95:5)

Scheme 15. Vinylsilane substrate scope.

amination was observed. $NsNH_2$ was found to be an alternative nitrogen source for the internal vinylsilanes, giving exclusively distal amination.

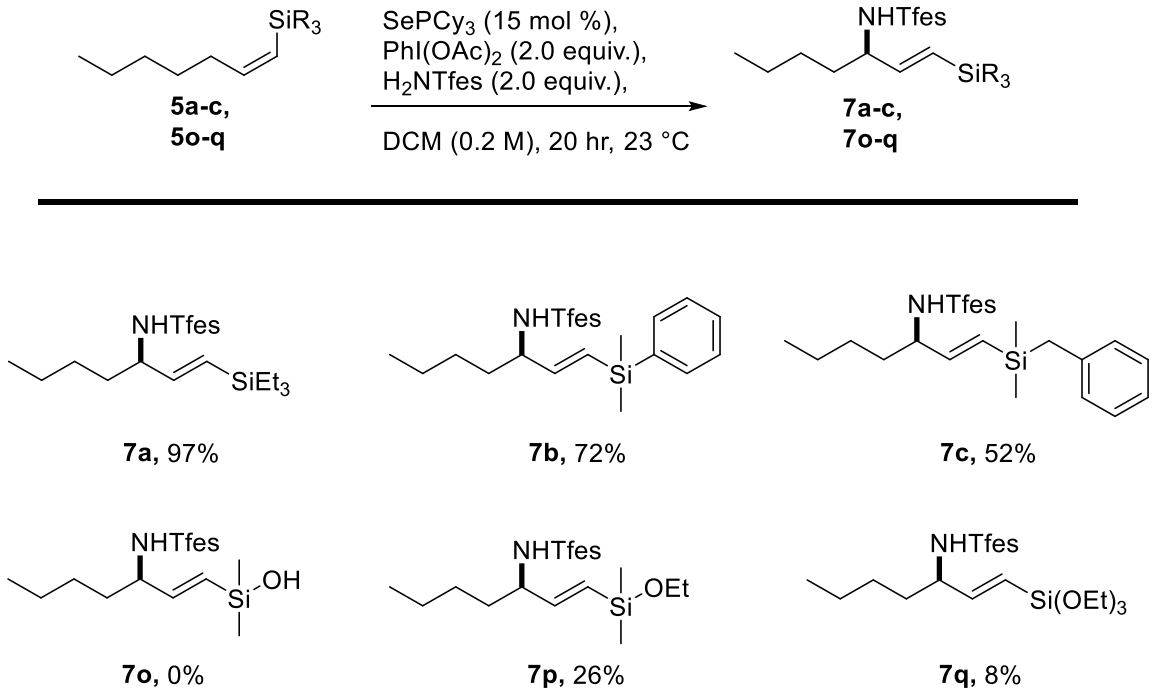
One focus of this scope was to explore the amination of synthetically useful substrates. Arguably, the most useful reaction of vinylsilanes is transition-metal catalyzed cross-coupling reactions (Scheme 16A).[5] The conditions of these cross-coupling reactions depend on the substituents of the starting vinylsilane. Hiyama reported that simple alkyl or aryl substituted vinylsilanes can undergo Pd-catalyzed coupling reactions with aryl halides in the presence of a fluoride source (Scheme 16B).[5b] However, Denmark developed fluoride-free conditions that instead rely on some hydrolyzable leaving group on the starting vinylsilane to access the active



Scheme 16. Cross-coupling reactions of vinylsilanes.

transmetalation species (Scheme 16C).[5a]

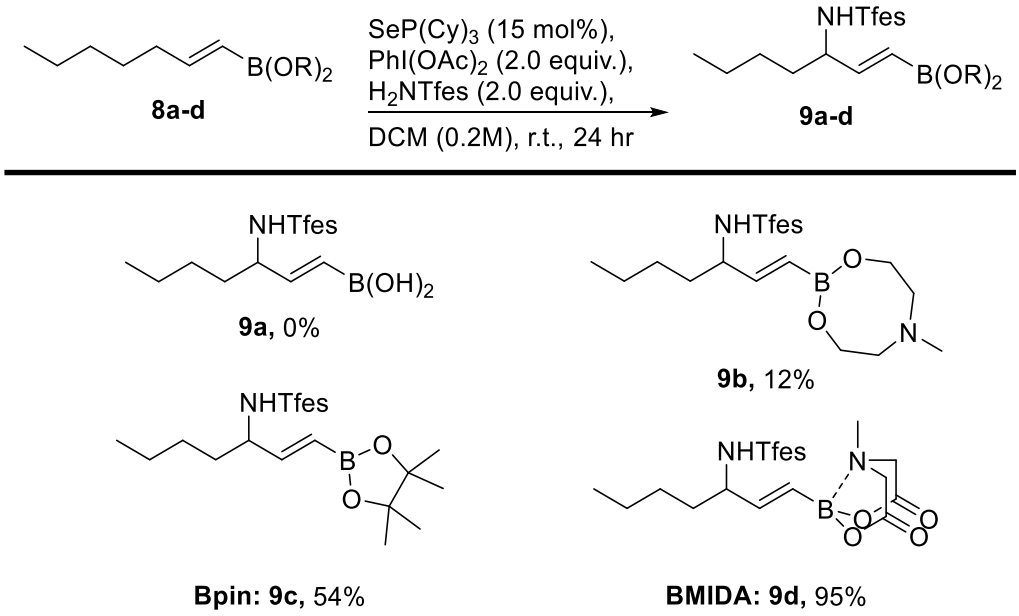
Hence, we tested the reactivity of some hydrolyzable vinylsilanes under our amination protocol (Scheme 17). Vinylsilanes **5b** and **5c** bearing a dimethylphenyl or a dimethylbenzyl group were aminated in 52% and 72% yield, respectively. However, vinylsilanes **5p** and **5q** bearing siloxy groups gave poor yields under these reaction conditions due to the observed release of ethanol, which reacted with the hypervalent iodine oxidant. Additionally, vinylsilanol **5o** did not display productive reactivity under these conditions. We also demonstrated that the aminated vinylsilane **7p** bearing a dimethylphenyl substituent was a competent coupling partner with iodobenzene in an established Hiyama-Denmark coupling protocol (Scheme 16D).[6]



Scheme 17. Vinylsilane substituent scope.

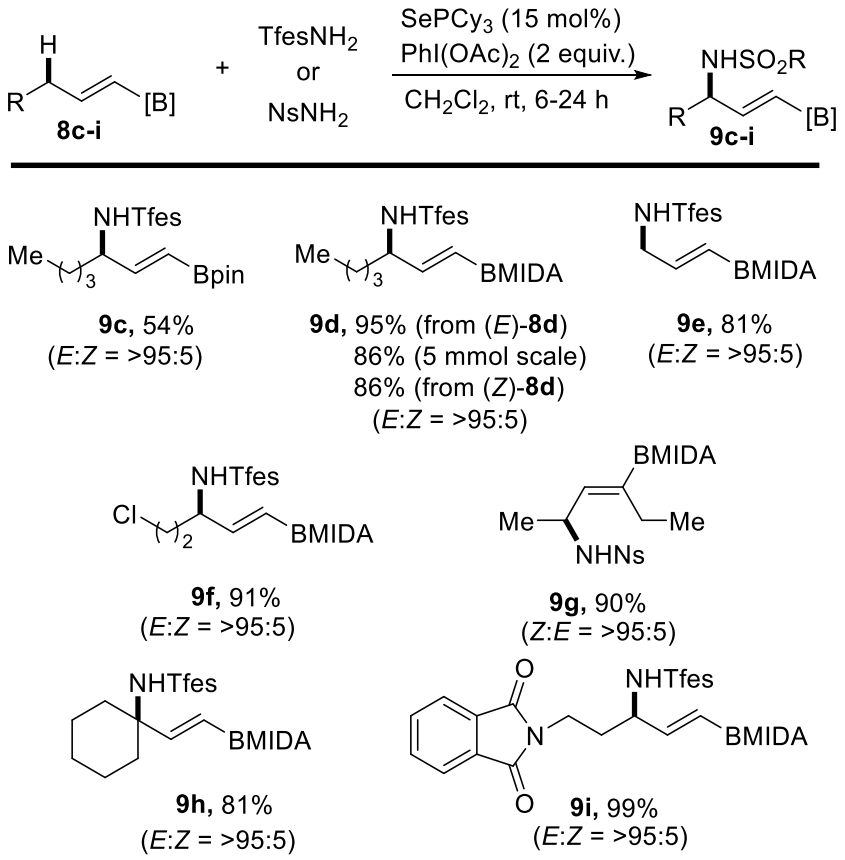
Having successfully aminated terminal and internal vinylsilanes, we moved our attention to vinylboronates. Exploration of the substituents on boron revealed that the vinylboronic acid **8a** gave complete degradation of the starting material under the reaction conditions (Scheme 18). The

pinacol vinylboronate ester **8c** gave a 54% yield of aminated product **9c**, while the *N*-methyliminodiacetic acid (MIDA) vinylboronate ester **8d** gave 95% yield of **9d**. The nitrogen of the BMIDA group irreversibly (>120 ˚C) coordinates to the empty p-orbital on boron, making it less likely to release free boronic acid under these reaction conditions.[7] The poor yield of compound **9b**, which bears a less rigidly coordinated nitrogen lone pair, is consistent with the importance of this rehybridization of the boron center.



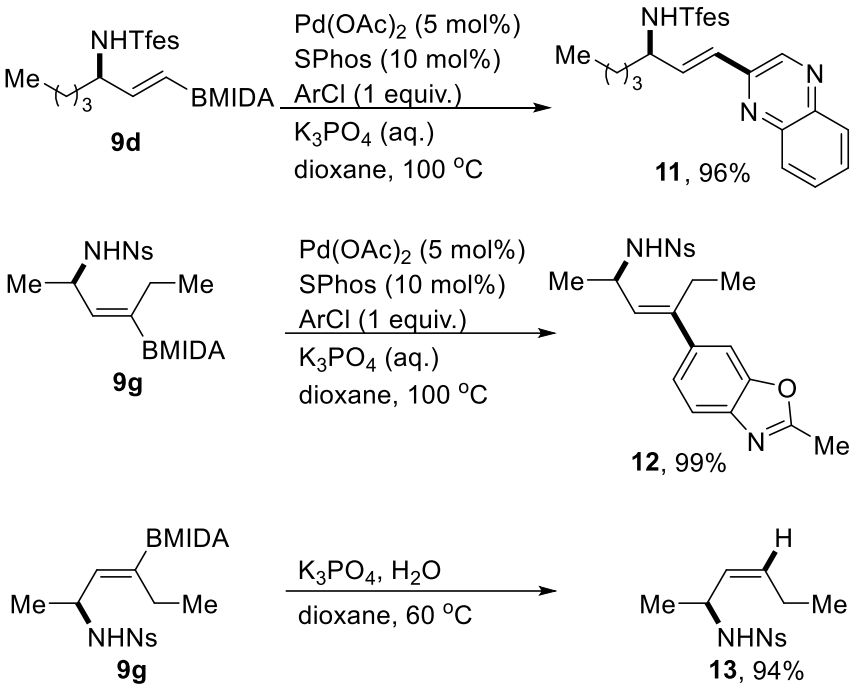
Scheme 18. Vinylboronate substituent screen.

Next, a series of vinylboronate substrates were tested under these conditions and generally gave excellent yields (Scheme 19). Both (*E*)-**8d** and (*Z*)-**8d** converged to the (*E*)-aminated isomer **9d** in 95% and 86% yields, respectively. The reaction could also be run at a 5.0 mmol scale with a moderately lower yield. Amination was observed exclusively at the distal position for compound **8g** containing multiple allylic C-H sites. Surprisingly, sulfamates were unreactive towards compound **8g**.

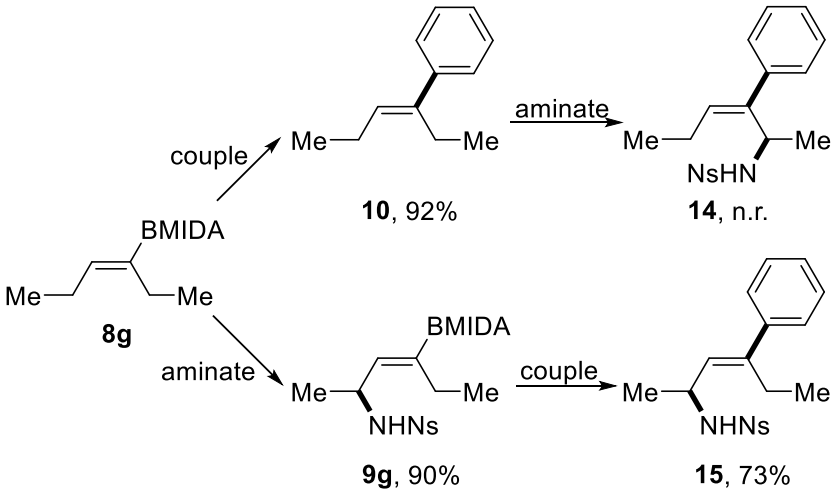


Scheme 19. Vinylboronate scope.

Further derivatizations were then undertaken to show the synthetic utility of these aminated vinylboronate substrates (Scheme 20). A Suzuki cross-coupling of **9d** and **9g** gave the styrenyl *N*-heterocycles in excellent yields.[8] Compound **9g** was protodeborylated stereospecifically to give the allylically aminated (*Z*)-1,2-disubstituted alkene **13**.[9] This substrate is inaccessible via the direct amination of the simple (*Z*)-alkene because it would isomerize to yield the (*E*)-product during the amination reaction. We also demonstrated that trisubstituted alkenes previously inaccessible by undirected allylic amination could be synthesized by a specific series of transformations (Scheme 21). Starting from compound **8g**, the sequence of coupling followed by amination would yield compound **14**. However, no reaction was observed under the standard



Scheme 20. Derivatization of aminated vinylboronate products.

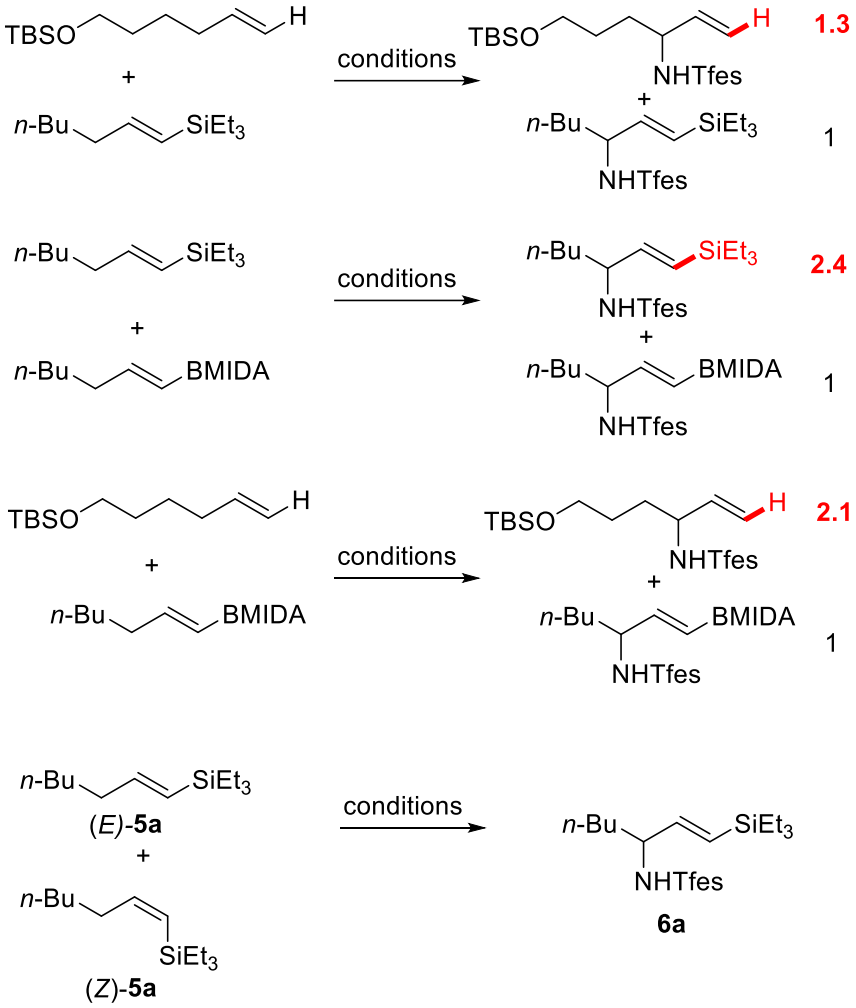


Scheme 21. Regio-divergent amination by changing reaction sequence.

amination conditions and no attempts were made to optimize these conditions. Alternatively, using boron to direct the amination first, and then coupling accesses allylic sulfonamide **15**.

Finally, a set of competition experiments was performed between vinylsilane, vinylborane, and a terminal alkene (Scheme 22). This revealed that the silyl group has a small effect on the rate

of reaction, while the boryl group slows the reaction. Additionally, a one-to-one mixture of (*E*)-**5a** and (*Z*)-**5a** was subjected to the reaction conditions yielding only (*E*)-**6a**, showing the starting alkene does not need to be diastereomerically pure due to this stereoconvergence.



Scheme 22. Competition experiments and stereoconvergence.

Section 2.3: Conclusions

In conclusion, we have extended our allylic amination protocol to vinylsilanes and vinylboronates. This selenium-catalyzed reaction avoids competing transmetalation of the C-Si and C-B bond common in transition metal-catalyzed methods, leaving them intact for future

manipulation. Positive charge build-up in the transition state of the ene reaction allowed us to selectively activate the distal allylic C-H via stabilization of this charge by the β-silyl or β-boryl effect. This directing effect allowed us to invert the native selectivity of simple trisubstituted alkenes and access previously inaccessible allylically aminated products.

Section 2.4: References

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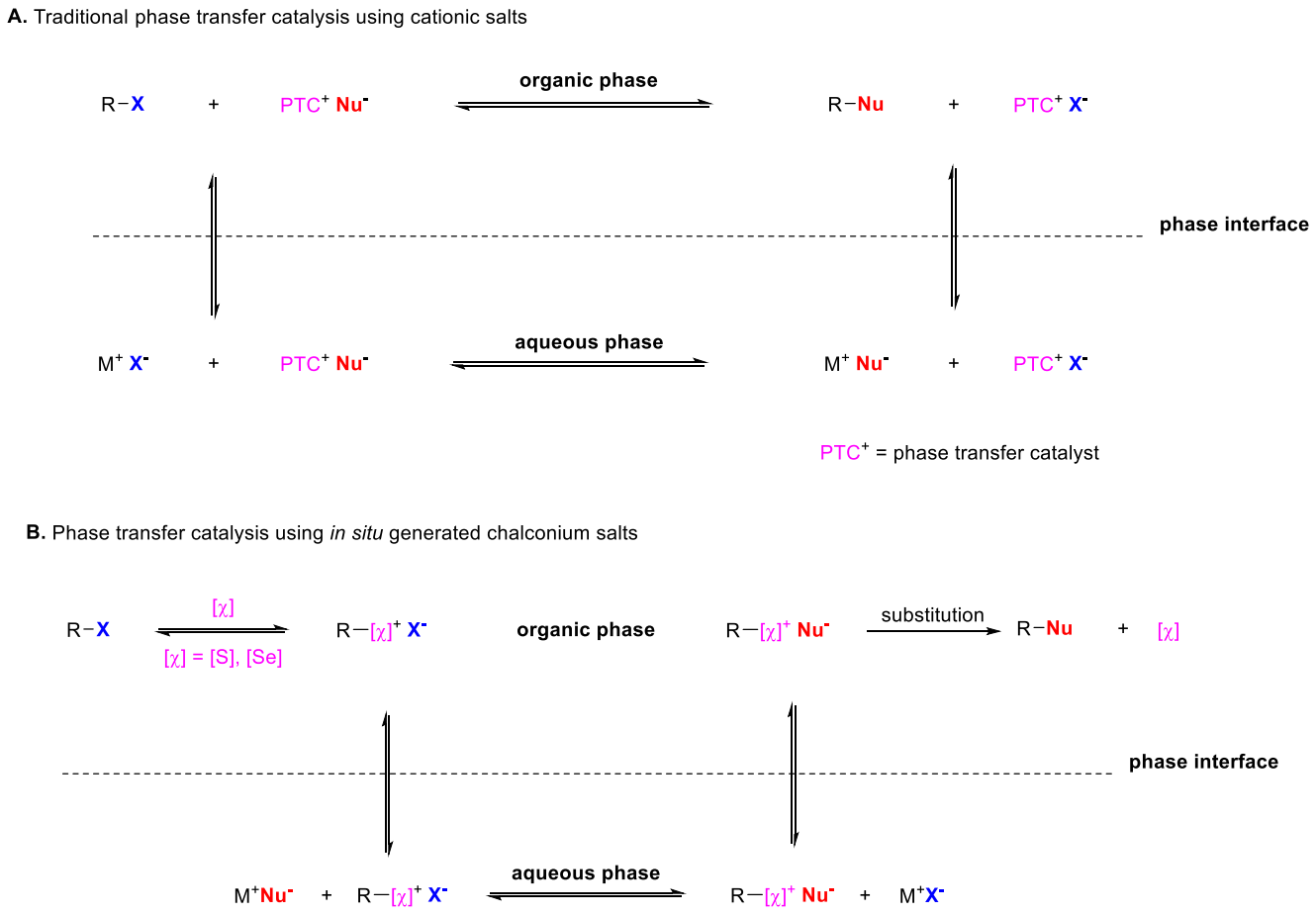
Chapter 3 - Organochalcogen-catalyzed phase-transfer reactions via *in situ* generated chalconium salts

Section 1: Introduction

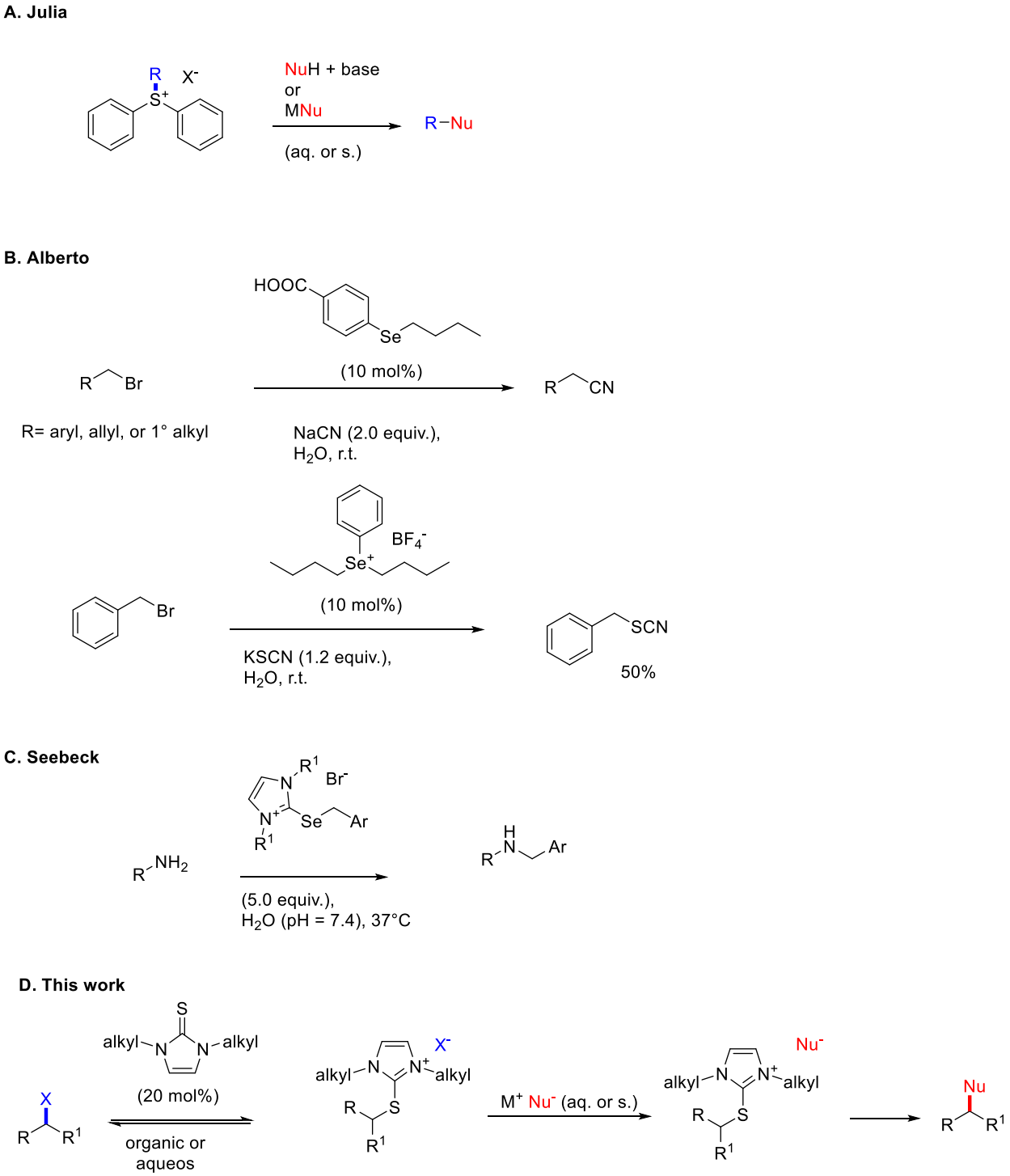


Scheme 23. Phase transfer catalysis mechanism.

Since Starks' initial report that addition of quaternary ammonium or phosphonium salts to biphasic mixtures of aqueous nucleophiles and alkyl leavings groups successfully catalyzed nucleophilic displacements,[1] the field of phase transfer catalysis has undergone a tremendous amount of research in the past 50 years. Regardless of the nature of the nucleophile or the phase-transfer agent, a vast majority of this research has focused on adding an exogenous agent that can alter a species solubility via intermolecular interactions. A common reaction manifold uses a

premade salt, usually an alkyl-sulfonium, -phosphonium, or -ammonium cation, which is both soluble in organic and aqueous media.[2] This species can undergo a metathesis with an organic insoluble anionic nucleophile, and, due to the lipophilic nature of the -onium salt, it solubilizes this nucleophile in the organic phase (Scheme 23A). Now that the nucleophile and electrophile are in the same phase, nucleophilic displacement can occur. Although this approach has proven to be extremely effective, it is fundamentally limited by using this premade salt. Given the salt's ionic character and solubility properties, recovery of the catalyst by methods such as chromatography or extraction can be troublesome. The generality of electrophiles that can be used for a single transformation can also be limited.[3] These -onium salts also may need specialty counterions to increase their solubility in non-polar media. The decomposition of quaternary -onium salts under basic solid-liquid and liquid-liquid conditions has also been reported.[4] These limitations can increase the cost of the process. Instead, we envisioned forming the ionic phase transfer catalyst *in situ* from a neutral precatalyst via nucleophilic displacement of an alkyl leaving group (Scheme 23B). This increases the ease of recovery of the precatalyst and could allow a broader range of electrophiles to be used under the same conditions. Also, by choosing a precatalyst whose structure can be easily tuned, we can have simpler control over properties like solubility.

The crux of this different approach to phase-transfer relies on identifying a species that is both nucleophilic enough to displace alkyl leaving groups under mild conditions, and electrophilic enough to be potentially displaced by a nucleophile. We were inspired by various reports of chalconium salts acting as alkyl-transfer reagents under phase-transfer type conditions.[5] Julia reported on phase-transfer alkylation using sulfonium salts (Scheme 24A).[6] He found that under both liquid-liquid and solid-liquid conditions, a stoichiometric quantity of these sulfonium salts



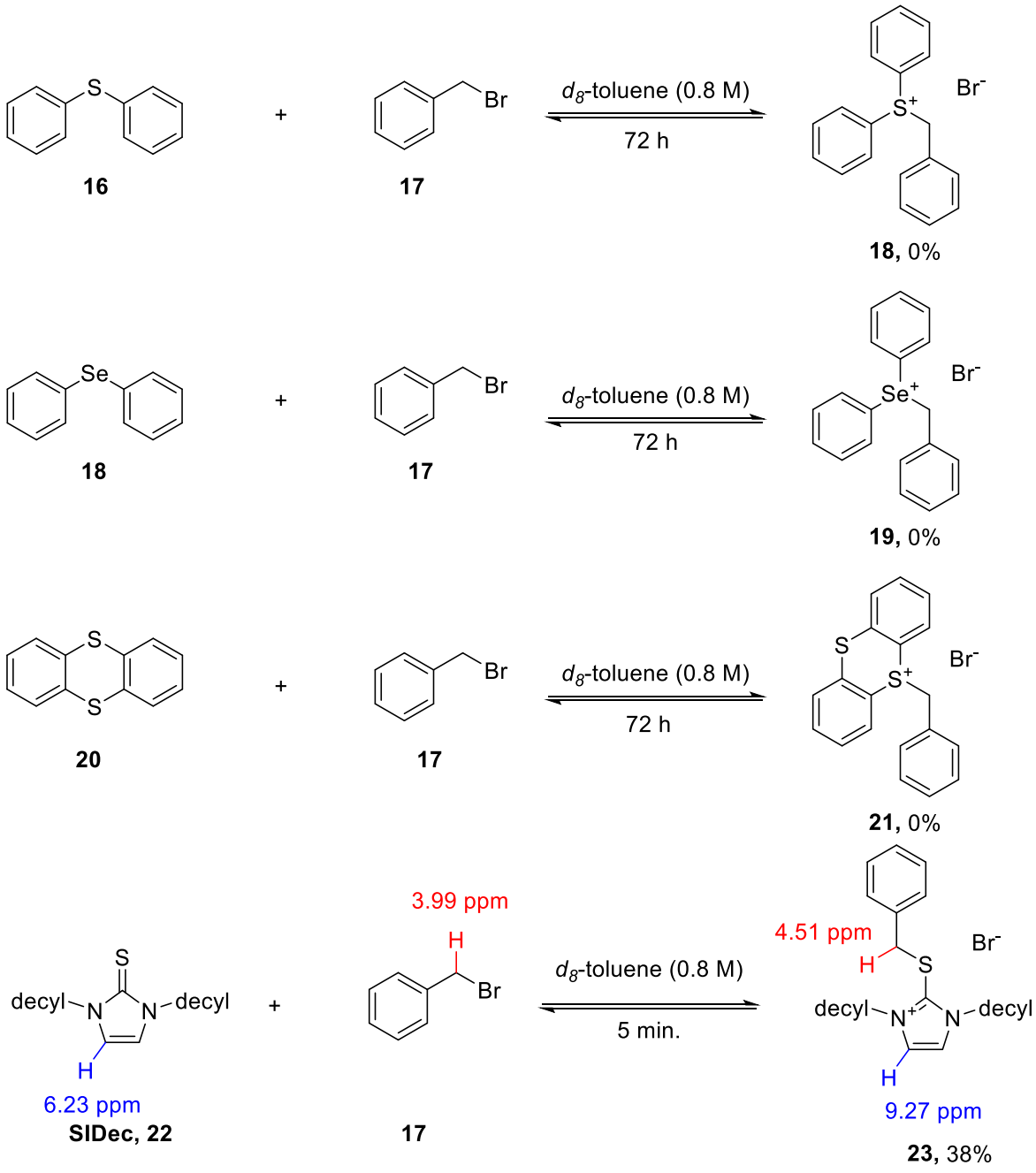
Scheme 24. Chalconium salts as alkyl-transfer reagents and phase transfer catalysts.

were able to alkylate a variety of oxygen, carbon, and nitrogen nucleophiles. More recently, Alberto disclosed that a catalytic amount of a selenide bearing a pendant carboxylic acid

successfully catalyzed the displacement of activated and unhindered bromides by aqueous sodium cyanide (Scheme 24B).[7] He claims that the active catalytic species is a selenonium salt formed by attack on the alkyl bromide. However, the sulfide analogue is inactive under these conditions. In another report, Alberto also demonstrates that a premade selenonium salt is effective at catalyzing the displacement of benzyl bromide by aqueous potassium thiocyanate.[8] Seebeck noted that selenoimidazolium salts were competent *N*-benzylating agents of lysozymes under aqueous conditions (Scheme 24C).[9] Consistent with other reports, during our labs work with sulfur- and selenium-imidazole compounds, we observed a reversible displacement with alkyl leaving groups. This reversibility hints that these compounds would be capable nucleophiles and electrophiles bearing easily tuned *N*-alkyl or *N*-aryl groups and backbone positions. Thus, we began exploring these neutral sulfur and selenium species as precatalysts to access chalconium salts in solution and their subsequent phase-transfer capabilities.

Section 2: Results and discussion

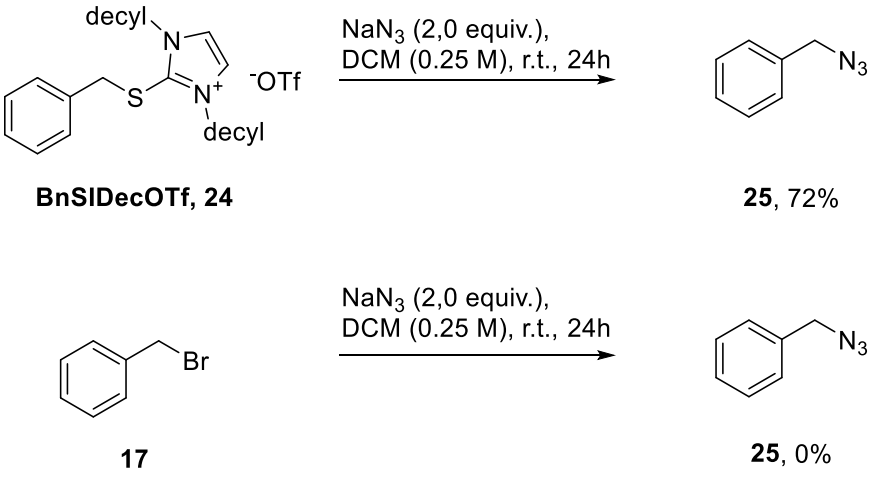
We began our investigation by probing the nucleophilic displacement capabilities of neutral chalcogen species in non-polar solvents. We were not able to observe any chalconium salt formation (compounds **18**, **19** and **21**) by ^{1}H NMR analysis when diphenyl sulfide, diphenyl selenide, and thianthrene were mixed in a one-to-one ratio with benzyl bromide in d_8-toluene (Scheme 25). After reviewing the literature, these types of chalconium salts are usually prepared either by forcing this equilibrium through precipitation of the nucleophilic counterion using silver salts, or pre-oxidation of the chalcogen center followed with attack by an organometallic nucleophile.[10] Under the conditions we tested, these chalcogen species do not seem to be nucleophilic enough to form the desired salt, or the equilibrium is highly unfavorable. However, upon addition of benzyl bromide to sulfur imidazole **22**, immediate formation of the desired sulfur



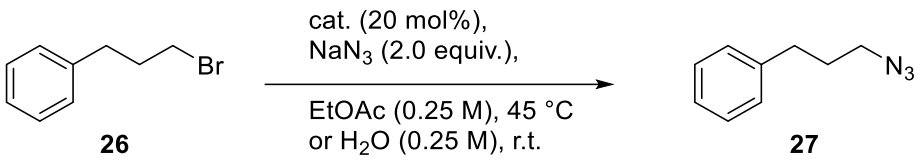
Scheme 25. Stoichiometric displacement studies using neutral chalcogen species.

imidazolium salt **23** was observed by ^{1}H NMR spectroscopy. This can be attributed to resonance donation of the lone-pair on nitrogen to the sulfur center, which should increase the nucleophilicity of this species relative to the simple diaryl chalcogenides.

Having demonstrated the successful *in situ* formation of the sulfur imidazolium salt, we next turned our attention to probing this salt's ability to participate in phase-transfer type reactions. We first synthesized the benzyl sulfur imidazolium triflate **24** and subjected this salt to a slurry of solid sodium azide in DCM (Scheme 26). We observed 72% yield of benzyl azide **25**, while no product was observed when simply using benzyl bromide **17**. This is consistent with the sulfonium salt **24** acting as both a phase-transfer and alkylating agent, since the neutral bromide was unreactive. Next, an initial screen was undertaken using 3-bromopropylbenzene (**26)** and sodium azide in either water or ethyl acetate as the solvent to probe the catalytic activity of various chalcogen species and phase-transfer agents (Scheme 27). No background reactivity was observed in the absence of catalyst (entry 1). All three diaryl chalcogen species tested also displayed no catalytic activity, consistent with our inability to detect any salt formation in previous experiments (entries 3-5). Two common phase-transfer catalysts were also tested, with only tetrabutylammonium bromide showing little activity (entries 6-7). Gratifyingly, catalytic amounts of SIDec **22** gave excellent yields of the alkyl azide product **27** under both solid-liquid and liquid-liquid conditions (entry 2).



Scheme 26. Stoichiometric phase-transfer using an alkyl sulfur imidazolium salt.

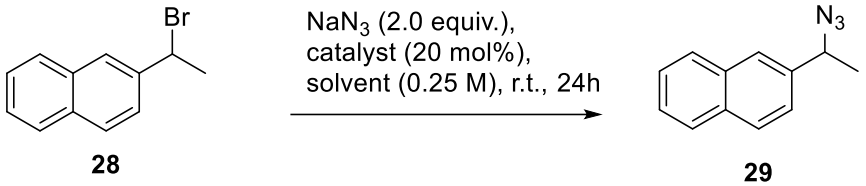


26 **27**

entry	catalyst	yield (%, in EtOAc)	yield (%, in H_2O)
1	none	0	0
2	SIDec	88	84
3	PhSPh	0	0
4	PhSePh	0	0
5	thianthrene	0	0
6	Schreiner's thiourea	0	0
7	NBu_4Br	3	8

Scheme 27. Phase-transfer catalyst comparison screen.

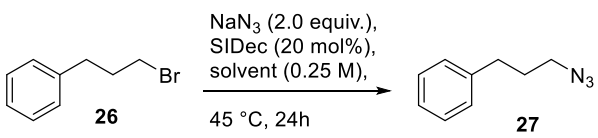
Further exploration using 2-(bromoethyl)naphthalene (**28)** showed little difference between SIDec and SeIDec in this system (Scheme 28, columns b,d). However, the size of the *N*-alkyl substituent proved to be pivotal in achieving reasonable reaction rates. For example, a 37% yield of alkyl azide **29** was observed when using SIMe in EtOAc (entry 4c), while SIDec, under the same conditions, gave a 94% yield of **29** (entry 4d). This can be attributed to the enhanced lipophilicity of the decyl chains, which better helps solubilize the azide anion in EtOAc. A more extensive screen using SIDec as the catalyst revealed the extensive tolerance of this system to both polar and non-polar solvents (Scheme 29). The primary, unactivated 3-bromopropylbenzene was heated at 45 ºC for 24 hours and gave excellent yields of the alkyl azide product from 80-96% (Scheme 29A). The secondary, benzylic bromide 2-(bromoethyl)naphthalene was stirred at room temperature for 48 hours and also gave excellent yields of the alkyl azide product from 76-99% (Scheme 29B).



	column	a	b	c	d
entry	**solvent**	**SeIMe**	**SeIDec**	**SIMe**	**SIDec**
1	DCM	99	98	94	99
2	toluene	6	52	12	58
3	dioxane	18	63	35	75
4	EtOAc	36	98	37	94
5	acetone	98	98	95	98
6	pentane	10	61	13	75

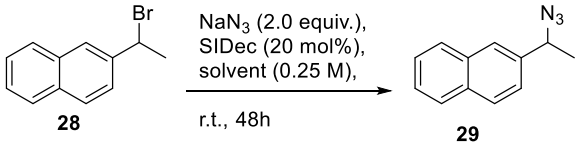
Scheme 28. Comparison of sulfur and selenium imidazoles in different solvents.

A. Primary, unactivated bromide



solvent	**yield (%)**
EtOAc	96
MEK	89
CPME	82
MTBE	81
iPrOAc	86
2-MeTHF	97
toluene	92
xylenes	95
isooctane	80
cyclohexane	82
heptane	88
acetone	90
H_2O (r.t.)	85

B. Secondary, activated bromide

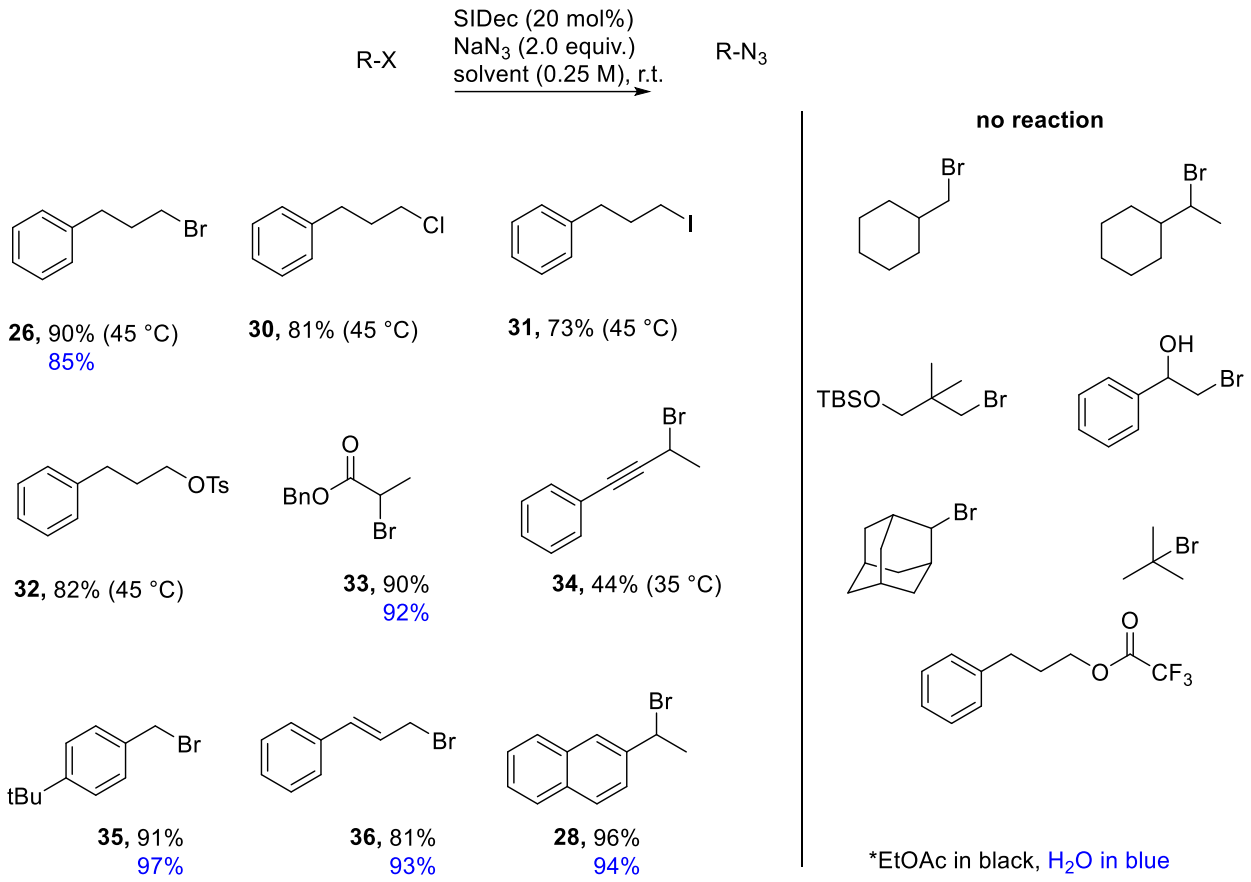


solvent	**yield (%)**
EtOAc	96
MEK	95
CPME	91
MTBE	98
iPrOAc	95
2-MeTHF	99
toluene	97
xylenes	87
isooctane	76
cyclohexane	91
heptane	82
H_2O (r.t., 24h)	94

Scheme 29. Phase-transfer solvent screen.

Having identified the ideal catalyst for this phase-transfer azidation and exploring the scope of solvents tolerated, we next investigated the reactivity of activated and unactivated leaving groups using ethyl acetate or water as the solvent (Scheme 30). Various alkyl leaving groups including bromide, chloride, iodide, and tosylate gave good to excellent yields (compounds **26**-**32**). Compounds bearing activated bromides in the α-ester, benzylic, allylic, and

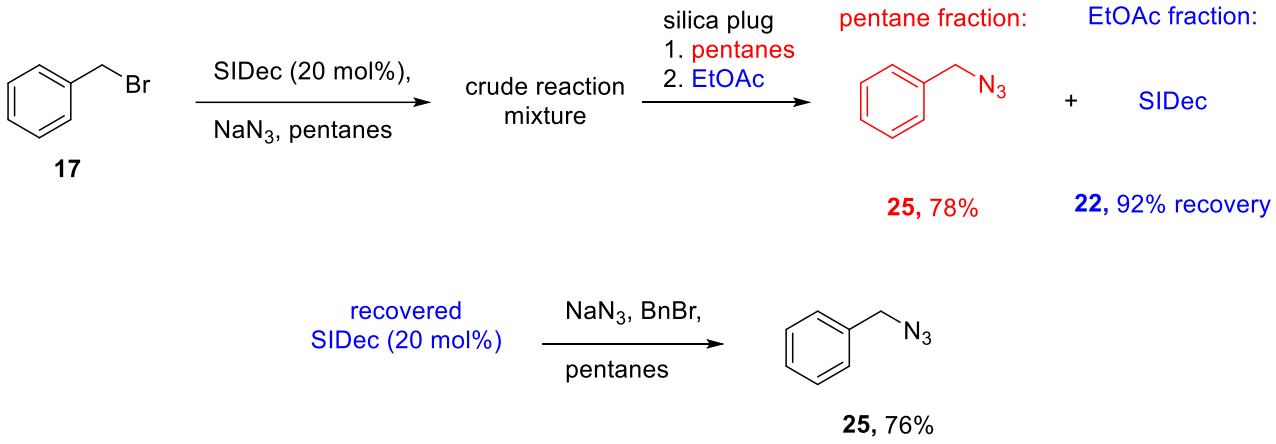
propargylic positions were also azidated successfully (compounds **33-37**). However, given that this reaction is fundamentally limited by its S_N2 nature, bulkier alkyl bromides with α-alkyl substitution were unreactive under these conditions. Similarly, tert-butylbromide was unreactive using ethyl acetate as a solvent.



Scheme 30. Substrate scope for phase-transfer azidation.

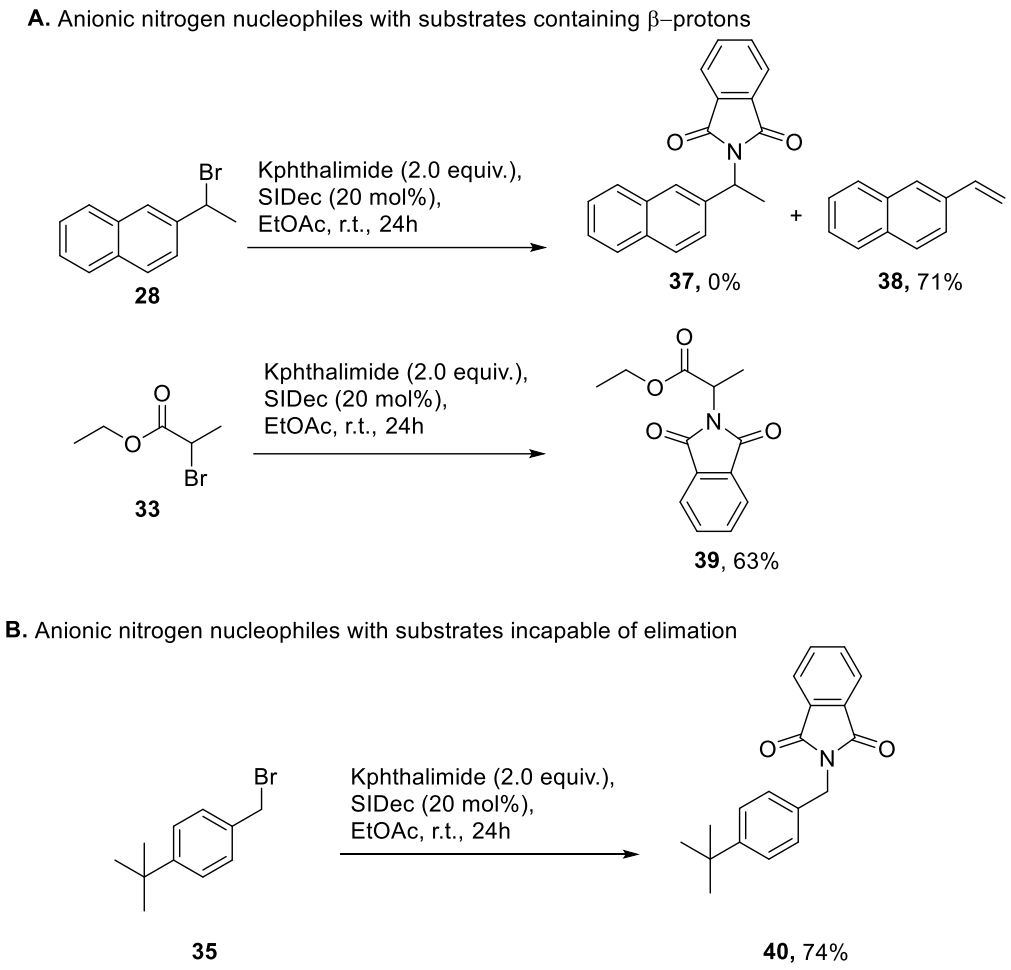
To show the utility of using a neutral precatalyst, we demonstrated that the sulfur imidazole precatalyst **22** can be recovered and reused without loss of catalytic activity (Scheme 31). Benzyl bromide **17** was subjected to the azidation conditions using pentanes as a solvent and **22** as a catalyst. After stirring for 24 hours, the crude reaction mixture was diluted with pentanes, pushed through a silica plug, and the pentanes fraction was collected. Next, ethyl acetate was used as the eluent, and this fraction was collected. After evaporation, the pentanes fraction

contained pure benzyl azide **25** in 78% yield, while the ethyl acetate fraction contained pure **22** with a 92% recovery. The recovered **22** was added to a new reaction mixture of **17**, sodium azide, and pentanes, which, after stirring for 24 hours, gave **25** in a 76% yield. This simple recycling protocol would be extremely problematic if the catalyst was a premade salt like tetrabutylammonium bromide.

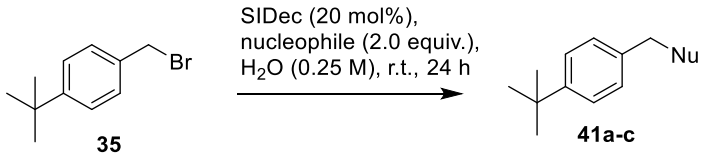


Scheme 31. Recycling the phase-transfer catalyst.

We next attempted to explore nucleophiles other than sodium azide to varying degrees of success. The anionic nitrogen nucleophile potassium phthalimide was mixed with **28** in the presence of **22**, however only the elimination product was observed (Scheme 32A). When 4-(tert-butyl)benzylbromide **35** or alpha-bromo ester **33** were subjected to these conditions, 74% and 63% yield of the substituted product was observed, respectively (Scheme 32A,B). The oxygen nucleophiles potassium acetate and potassium phenoxide were investigated next (Scheme 33). Potassium acetate successfully reacted with benzylic bromide **35**, although the reaction was sluggish at room temperature and yielded 40% of the ester product **41b** (entry 2). Potassium phenoxide gave 72% yield of the ether product **41a** (entry 1) while sodium thiocyanate gave a 83% yield of compound **41c** (entry 3).



Scheme 32. Other anionic nitrogen nucleophiles.



entry	nucleophile	yield (%)	SM (%)
1	KOPh	72	12
2	KOAc	40	57
3	NaSCN	83	-

Scheme 33. Chalcogen nucleophile screen.

Section 3.3: Conclusions

We have successfully demonstrated that chalconium salts can be generated *in situ* from alkyl leaving groups and chalcogen imidazole precatalysts in a wide variety of non-polar and polar solvents. The subsequent ability of these salts to catalyze both solid-liquid and solid-solid phase-transfer reactions was investigated and a plethora of leaving groups were effectively substituted. The catalyst was easily recovered and recycled in opposition to premade salts used for phase-transfer reactions.

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