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Aldrichimica ACTA

VOL. 43, NO. 1 • 2010

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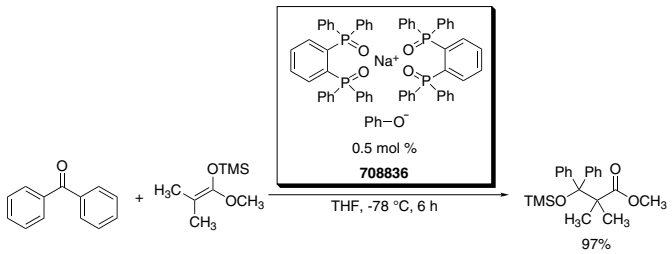
Efficient Lewis Base for Mukaiyama Aldol Reaction with Ketones

There have been few reported methods for the synthesis of tertiary aldols, due to the low reactivity of the starting ketones and the rapid retro-aldol reaction, even at low temperatures. Ishihara and coworkers recently reported the Lewis base catalyzed Mukaiyama aldol reaction using a simple, mixed sodium phenoxide–phosphine oxide catalyst. The catalyst was effective with a wide variety of TMS enolates and ketones, providing the aldol adducts in generally good-to-excellent yields. Additionally, the catalyst was also effective in Mannich-type reactions when benzyl-, Boc-, or Cbz-protected aldimines were used as substrates.



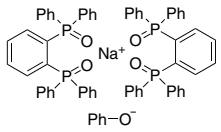
Hatano, M. et al. *Org. Lett.* **2007**, *9*, 4527.

Bis[1,2-bis(diphenylphosphine oxide)benzene] sodium phenoxide, 95%

708836 1 g

$C_{66}H_{53}NaO_5P_4$

FW: 1073.01



Indoles and Azaindoles

The indole subunit is a near-ubiquitous component of biologically active natural products, and the study of indoles has been a major focus of research for generations. Substituted indoles have frequently been referred to as privileged structures,[1] since they are capable of binding to multiple receptors with high affinity, and thus have applications across a wide range of therapeutic areas. Due to this activity, it is not surprising that the indole ring system has become an important structural motif in many pharmaceutical agents.

The azaindole moiety differs only by the presence of an additional ring nitrogen and, thus, it exhibits excellent potential as a bioisostere of the indole ring system. Although considerably more rare in nature, azaindoles still constitute essential subunits in many pharmaceutically important compounds, and have been very valuable to synthetic and medicinal chemists. 7-Azaindoles are of particular interest because of their ability to mimic purine in its role as a hydrogen-bonding partner.[2]

(1) Horton, D. A. et al. *Chem. Rev.* **2003**, *103*, 893 and references therein. (2) (a) Popowycz, F. et al. *Tetrahedron* **2007**, *63*, 1031. (b) Popowycz, F. et al. *Tetrahedron* **2007**, *63*, 8689. (c) Song, J. J. et al. *Chem. Soc. Rev.* **2007**, *36*, 1120.

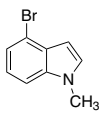
4-Bromo-1-methylindole, 95%

720860 500 mg

[*590417-55-3*]

C_9H_8BrN

FW: 210.07



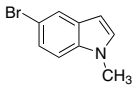
5-Bromo-1-methylindole, 97%

718300 5 g

[*10075-52-2*]

C_9H_8BrN

FW: 210.07

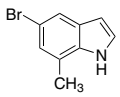


5-Bromo-7-methylindole, 97%

710822 1 g

C_9H_8BrN

FW: 210.07

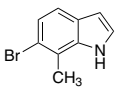


6-Bromo-7-methylindole, 97%

707155 250 mg

C_9H_8BrN

FW: 210.07



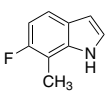
6-Fluoro-7-methylindole, 97%

707147 250 mg

[*57817-10-4*]

C_9H_8FN

FW: 149.16



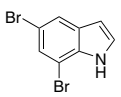
5,7-Dibromoindole, 97%

708798 1 g

[*36132-08-8*]

$C_8H_5Br_2N$

FW: 274.94

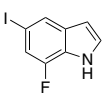


7-Fluoro-5-iodoindole, 97%

707058 500 mg

C_8H_5FIN

FW: 261.03



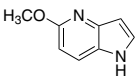
5-Methoxy-4-azaindole, 95%

707953 250 mg

[*17288-40-3*]

$C_8H_8N_2O$

FW: 148.16



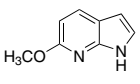
6-Methoxy-7-azaindole, 97%

702838 250 mg

[*896722-53-5*]

$C_8H_8N_2O$

FW: 148.16



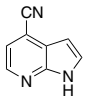
7-Azaindole-4-carbonitrile, 97%

706426 250 mg

[*344327-11-3*]

$C_8H_5N_3$

FW: 143.15



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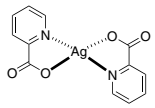
"PLEASE BOTHER US."

Joe Porwoll, President
Aldrich Chemical Co., Inc.

Professor Phil Baran of The Scripps Research Institute kindly suggested that we make silver picolinate. Baran and coworkers recently utilized silver picolinate to effect a chemoselective oxidation of the guanidine ring en route to their notable total synthesis of palau'amine.[1] This approach avoids overoxidation and laborious protecting group chemistry. Silver picolinate was also employed in the total synthesis of (±)-axinellamines A and B.[2,3]

(1) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095. (2) O'Malley, D. P.; Yamaguchi, J.; Young, I. S.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3581. (3) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854.



718157

718157 **Silver(II) picolinate, 97%** 5 g, 25 g

Naturally, we made this useful oxidation reagent. It was no bother at all, just a pleasure to be able to help.

Do you have a compound that you wish Aldrich could list, and that would help you in your research by saving you time and money? If so, please send us your suggestion; we will be delighted to give it careful consideration. You can contact us in any one of the ways shown on this page and on the back cover.

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ABOUT OUR COVER

The Grand Canal (oil on canvas, 23.0 × 33.0 cm) is one of twenty works of art by the British artist Richard Parkes Bonington (1802–1828) in the collection of the National Gallery of Art, and was painted in1826/1827. At the age of 16, Bonington moved to Paris with his parents and studied there at the French National Art School, the École des Beaux-Arts. During his brief career as an artist, he adopted the ideals of the Romantic Movement, and was influenced by the French artists Antoine-Jean Gros and Eugène Delacroix and by his fellow Englishman, John Constable.

Photograph © Board of Trustees, National Gallery of Art, Washington.

Bonington was greatly admired for his exceptional ability to capture the effects of daylight and atmosphere with unerring assurance. In this work, the lovely play of sunlight on the building facades, the delicate reflections on the water, and the sweep of the clouds across the sky entice the eye and can be appreciated independently of the subject and its imitative appeal.

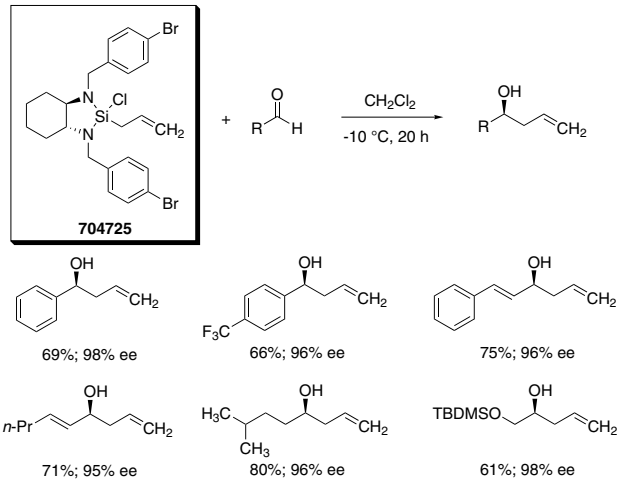
In the nineteenth century, painted scenes of Venice were very popular with the "Grand Tour" set, as post cards or photographs are today. Bonington produced many studies of this most beautiful city on the Adriatic while visiting Italy in 1826. He turned his sketches into some of his finest paintings, like the one seen here, which further enhanced his flourishing reputation as a landscape painter in London and Paris.

This painting is a gift of Roger and Victoria Sant to the National Gallery of Art, Washington, DC.

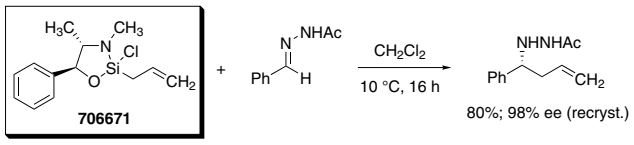
Leighton's Chiral Silane Reagents

The asymmetric allylation of carbonyl compounds remains one of the most important and fundamental addition reactions for the synthesis of optically active chiral building blocks.

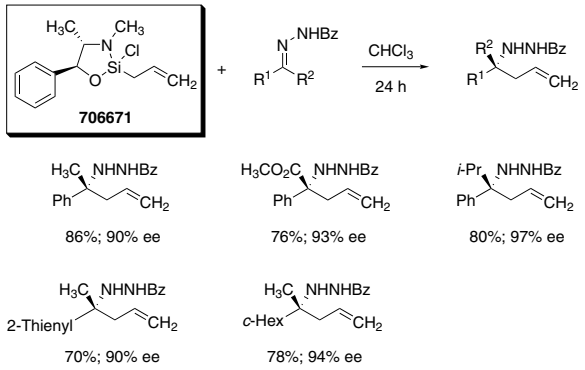
In 2002, Leighton and co-workers developed strained silacycle compounds as versatile reagents for the practical enantioselective allylation of aldehydes.[1] A newly developed chiral auxiliary based on the cyclohexane-1,2-diamine scaffold successfully allylated a broad range of aldehydes highly enantioselectively.[2]



The development of practical enantioselective syntheses of chiral amines is of great importance to synthetic organic and medicinal chemists. In 2003, Leighton and co-workers successfully used a pseudoephedrine-derived, five-membered-ring, strained silacycle reagent for the enantioselective allylation of acylhydrazones.[3]

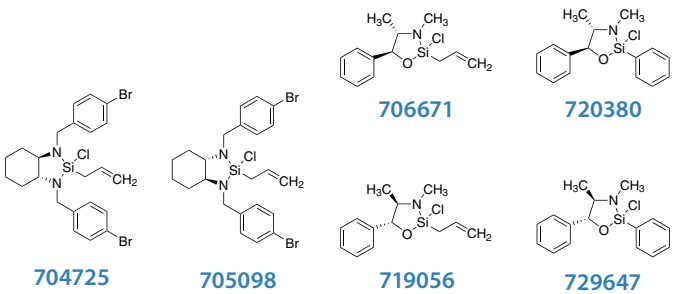


The reaction scope of these silacycles was extended to a practical method for the enantioselective synthesis of tertiary carbinamines based on the addition of this chiral allylsilane reagent to a structurally diverse array of ketone-derived benzoylhydrazones.[4] While many methods for the synthesis of quaternary α-amino acids have been published, far fewer reports have dealt with the synthesis of tertiary carbinamines. The free amines are easily accessed in good yields by treating the product hydrazides with SmI_2.



The reagents are effective with other types of imine electrophiles, and may be derivatized efficiently using cross-metathesis reactions. In addition, the corresponding phenylsilanes are effective general Lewis acids for a variety of enantioselective (nonallylation) nucleophilic addition reactions with acylhydrazones and other imine electrophiles.

References:
(1) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (2) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946. (3) Berger, R.; Rabbat, P. M. A.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 9596. (4) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686.



For more information on the applications of the Leighton silacycle reagents, please see Professor Leighton's review in this issue or visit ***sigma-aldrich.com***

Powerful and Versatile Silicon Lewis Acids for Asymmetric Chemical Synthesis

James L. Leighton
Department of Chemistry
Columbia University
3000 Broadway, MC 3117
New York, NY 10027, USA
Email: leighton@chem.columbia.edu

Professor James L. Leighton

Outline

1. Introduction

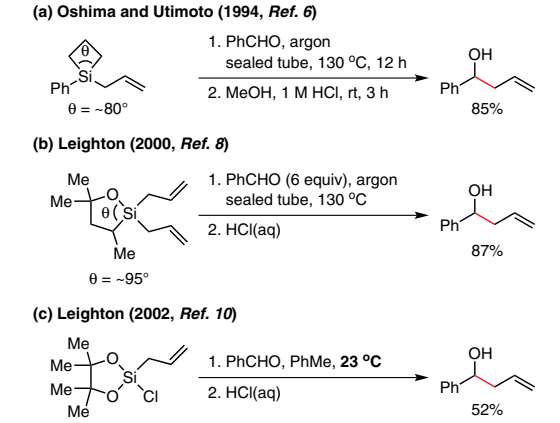
Nucleophilic addition to aldehydes, ketones, aldimines, and ketimines with activation by a chiral Lewis acid is one of the most important and fundamental reaction types in all of asymmetric chemical synthesis. If one were to ask what is the "ideal" element to serve as the Lewis acid from the standpoint of practicality, an extremely strong case could be made for silicon. It is abundant and inexpensive; it typically presents no significant issues in terms of toxicity and waste stream; and, if highly enantioselective reactions promoted by chiral silicon Lewis acids could be developed, they would possibly, if not likely, be readily adaptable for use in large-scale applications.

Such considerations, as well as the formidable and intriguing conceptual challenge, have inspired decades-long efforts to develop effective silicon Lewis acids for asymmetric synthesis. The arena of aldehyde allylation reactions has been the proving ground for many of these efforts. Three approaches have emerged for devising Type I[1] Lewis acidic allylsilanes that react with aldehydes through a closed transition state without the need for an exogenous Lewis acid: (i) the nucleophile-promoted addition of allylSiX_3 (X = F, OR) species, pioneered by Kira and Sakurai[2] and by Hosomi;[3] (ii) the related, but mechanistically distinct, Lewis base catalyzed addition of allyl$SiCl_3$, pioneered and developed into an effective asymmetric method by Denmark[4] following a report from Kobayashi;[5] and (iii) the addition of allylsilacyclobutanes disclosed by Oshima and Utimoto (**Scheme 1**, Part (a)),[6] based on a seminal report from Myers[7] who employed enoxysilacyclobutanes in Type I Mukaiyama aldol reactions.

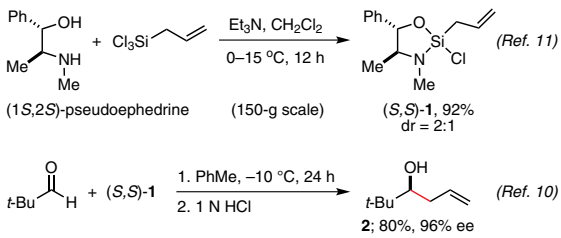
In this latter approach, the Lewis acidity of the silicon is derived from the ring strain in the silacyclobutane, which favors the rehybridization to a five-coordinate trigonal bipyramidal silane that accompanies the binding of the aldehyde. While mechanistically intriguing, this approach did not evolve into a broadly applicable asymmetric method due both to the lack of convenient synthetic access to silacyclobutanes and to the impractical conditions (130 °C in a sealed tube) of the allylation reaction. In 2000, Zacuto and Leighton provided the first unambiguous demonstration of the same phenomenon with the silicon constrained within a five-membered ring (**Scheme 1**, Part (b)).[8,9] The discovery that a similar reactivity could be realized with five-membered silacycles had profound practical implications in that one might simply constrain allylsilanes in a five-membered ring with 1,2-diols, diamines, or amino alcohols, and benefit from a boost in reactivity due to the attachment of more highly electronegative elements to the silicon. Indeed, in 2002, our group showed that the allylsilane derived from pinacol and allyltrichlorosilane smoothly allylated benzaldehyde *at ambient temperature* (**Scheme 1**, Part (c)).[10] This reaction set the stage for the development of a family of versatile and highly practical chiral silane Lewis acids for asymmetric synthesis.

2. Enantioselective Allylation of Aldehydes and Acylhydrazones—Same Allylsilane, Different Mechanisms

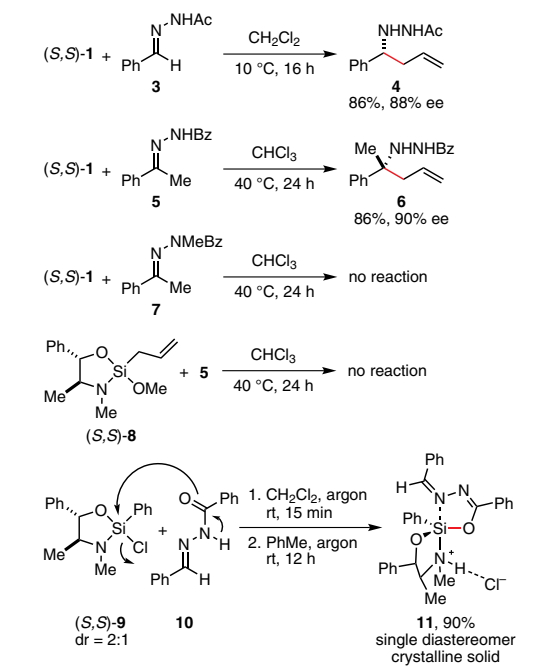
Following the discovery that allyl(chloro)dioxasilacyclopentanes react with aldehydes at ambient temperature, our group began a search for effective chiral diols, diamines, and amino alcohols. Considerations of practicality (economic and otherwise) led us to consider compounds such as pseudoephedrine: it is ready for use as is, and both enantiomers are commercially available and inexpensive. Thus, reaction of allyltrichlorosilane (also commercially available) with (1*S*,2*S*)-pseudoephedrine in the



Scheme 1. Milestones in the Development of Type I (Lewis Acidic) Allylsilanes Whose Activity Is Derived from Ring Strain.



Scheme 2. Synthesis of Chiral Allylsilane **1** and "Proof-of-Concept" Allylation of Pivalaldehyde.



Scheme 3. Discovery and Mechanistic Elucidation of the Enantioselective Allylation of Acylhydrazones. *(Ref. 11,12)*

presence of triethylamine leads to the synthesis (150-g scale) of (*S*,*S*)-**1** in 92% yield (**Scheme 2**).[11] It is important to note that the silicon atom is a stereogenic center and that **1** is isolated as a ~2:1 mixture of (unassigned) diastereomers. Despite this potentially complicating feature, **1** was found to react with pivalaldehyde to give alcohol **2** in 96% ee.[10] With less hindered aliphatic aldehydes and with aromatic and α,β-unsaturated aldehydes, however, **1** was found to be less effective, providing enantioselectivities in the 78–88% range. Nevertheless, this study served as a convincing proof of concept of the remarkably simple and yet previously unrecognized fact that one could simply react allyltrichlorosilane with a chiral amino alcohol, and thereby prepare an effective chiral allylsilane that reacts in a Type I sense. As described in Section 2.1, a highly enantioselective and more general second-generation, diamine-derived silacycle was developed for aldehyde allylation and crotylation.

The performance of allylsilane **1** in imine allylation reactions was also examined, but it quickly became clear that **1** is *not* competent to allylate a variety of imine derivatives (PhCH=N-R; where R = Bn, Ph, $SiMe_3$, OH, OMe, SO_2Ar).[11] Acylhydrazones, however, were found to react smoothly with **1**, and upon optimization, reaction of (*S*,*S*)-**1** with acetylhydrazone **3** gave hydrazide **4** in 86% yield and 88% ee.[11] Similarly, reaction of (*S*,*S*)-**1** with ketone-derived benzoylhydrazone **5** gave hydrazide **6** in 86% yield and 90% ee (**Scheme 3**).[12,13] It was subsequently determined that *N*-methylbenzoylhydrazone **7** was completely inert to the action of (*S*,*S*)-**1**, and that methoxysilane (*S*,*S*)-**8** was unreactive with hydrazone **5**. These data strongly implied that the unique reactivity of acylhydrazones among the imine derivatives examined was due to the amide-like portion of the acylhydrazone acting as an oxygen nucleophile and displacing the chloride from the silane, and the liberated HCl protonating the amino group of the bound pseudoephedrine. *It is this protonation that is the key to the reactivity of the system*, as it would be expected to dramatically increase the Lewis acidity of the silicon center.[14] To secure evidence for this proposal, phenylsilane (*S*,*S*)-**9** was prepared (and was isolated as a ~2:1 mixture of diastereomers, as was the case with allylsilane **1**) and treated with hydrazone **10**. When this reaction was carried out in toluene, a precipitate formed and was isolated in 90% yield. The ^{1}H NMR spectrum of this material is that of a single species, and is consistent with structure **11**—most notably, the NMe signal is a doublet. Recrystallization of the precipitate from CH_2Cl_2–hexanes provided X-ray quality crystals and the resulting X-ray data confirmed the structure of **11**.[12] That a single species, **11**, is formed in 90% yield is significant, because it provides compelling evidence that, in the reaction of **1** with acylhydrazones, the two diastereomers of the starting silane converge on a common complex prior to transfer of the allyl group.

The same allylsilane, **1**, thus reacts with aldehydes and acylhydrazones by distinct mechanisms. While the ring strain alone is sufficient for reactivity with aldehydes, it is insufficient for reactivity with ketones, aldimines, and ketimines. For these substrates, a suitably disposed directing and activating group (a protic nucleophile that can displace the chloride from the silane and generate an equivalent of HCl in situ) is required. As described below, a significant variety of effective directing/activating groups have been found, and significant advantages in terms of reactivity and selectivity accrue from employing this strategy. Finally, it is important to emphasize again that the fact that the pseudoephedrine-derived silane Lewis acids discussed herein are produced as mixtures of diastereomers is irrelevant for all of the chemistry described below. In the chloride displacement–HCl

activation manifold (all reactions other than aldehyde allylation), the two diastereomers converge on a common intermediate prior to the nucleophilic addition event.

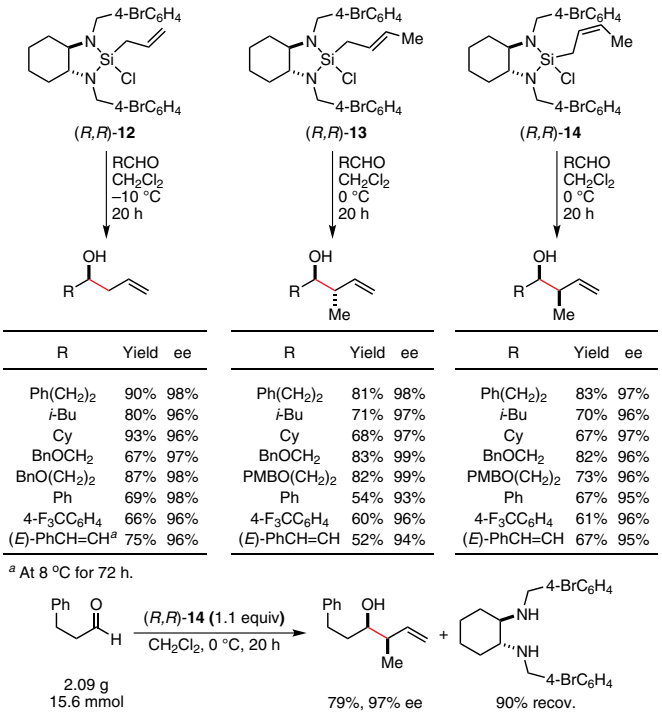
2.1. Allylation and Crotylation of Aldehydes

Because allylsilane **1** provided only moderate levels of enantioselectivity with many different classes of aldehydes, and because there was evidence that the two diastereomers of **1** were reacting independently and with different enantioselectivities, a second-generation reagent based on a C_2-symmetric chiral controller was developed. We quickly found that *N*,*N*'-dialkylcyclohexanediamine-derived allylchlorosilanes provided superior levels of enantioselectivity in aldehyde allylation reactions, and eventually settled on *p*-bromobenzyl groups because they—uniquely among the *N*-alkyl groups examined—rendered the allylsilane reagent, (*R*,*R*)-**12**, crystalline (**Scheme 4**).[15–17] As shown, **12** reacts with a variety of aldehydes to provide the homoallylic alcohol products in 96–98% ee.[15] The *trans*-crotylsilane (*R*,*R*)-**13** and the *cis*-crotylsilane (*R*,*R*)-**14** were also prepared, and were also crystalline solids.[17] These silanes crotylate a variety of aldehydes with uniformly excellent enantioselectivities (93–99% ee). From a practical standpoint, it is noteworthy that these reactions are carried out under highly convenient and scalable conditions: the crotylsilane is simply added to a cooled (0 °C) solution of the aldehyde in CH_2Cl_2.[17] As shown, a larger-scale crotylation reaction (2.09 g, 15.6 mmol of aldehyde) was demonstrated, wherein the chiral diamine was recovered in 90% yield.

2.2. Allylation and Crotylation of Ketones

In principle, the enantioselective allylation of ketones provides convenient access to chiral tertiary carbinols, but in practice this has proven a significantly more difficult problem than the corresponding allylation of aldehydes. Recently, there have been several enantioselective ketone allylation methods reported that employ allylboranes or allylboronates,[18] and one report that employs allylsilanes.[19] Despite these successes, the substrate scope remains limited for the most part to ketones wherein one side must be a methyl or linear alkyl group.

While allylsilanes **1** and **12** do not possess sufficient reactivity to allylate acetophenone, the mechanism of the acylhydrazone allylation reaction discussed above suggested an opportunity to install a directing/activating group on the ketone substrate. While this would limit the reaction scope in a different way, we wondered whether it might also allow the enantioselective allylation of aryl *branched*-alkyl ketones, as well as aryl aryl ketones—two important classes of ketone for which there had not been an effective solution. We found that allylsilane **12** smoothly allylates 2'-hydroxyacetophenone and, upon optimization, the product could be obtained in 75% yield and 83% ee (**eq 1**).[20] When the substrate scope was examined, it was found that not only could 2'-hydroxy-isobutyrophenone be smoothly allylated (88% ee), but also, remarkably, could the corresponding *tert*-butyl ketone (93% ee). A series of 2'-hydroxybenzophenones and related diaryl ketones could be allylated as well, including those with ortho substitution. The last two examples also demonstrate the highly diastereoselective and enantioselective crotylation of 2'-hydroxybenzophenone. Complex/transition state **15** represents a reasonable model for how these reactions proceed, with the key point being the highly significant boost in the reactivity of the silane that derives from the protonation of one of the amino groups attached to silicon, a protonation that attends the reaction of the hydroxyl group with the chlorosilane.



R	Yield	ee
$Ph(CH_2)_2$	90%	98%
i-Bu	80%	96%
Cy	93%	96%
$BnOCH_2$	67%	97%
$BnO(CH_2)_2$	87%	98%
Ph	69%	98%
4-$F_3CC_6H_4$	66%	96%
(*E*)-PhCH=CH[a]	75%	96%

R	Yield	ee
$Ph(CH_2)_2$	81%	98%
i-Bu	71%	97%
Cy	68%	97%
$BnOCH_2$	83%	99%
$PMBO(CH_2)_2$	82%	99%
Ph	54%	93%
4-$F_3CC_6H_4$	60%	96%
(*E*)-PhCH=CH	52%	94%

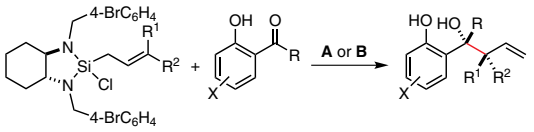
R	Yield	ee
$Ph(CH_2)_2$	83%	97%
i-Bu	70%	96%
Cy	67%	97%
$BnOCH_2$	82%	96%
$PMBO(CH_2)_2$	73%	96%
Ph	67%	95%
4-$F_3CC_6H_4$	61%	96%
(*E*)-PhCH=CH	67%	95%

[a] At 8 °C for 72 h.

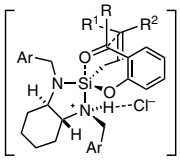
Scheme 4. Chiral Allyl- and Crotylsilanes for Highly Enantioselective Aldehyde Allylation and Crotylation Reactions. *(Ref. 15,17)*

2.3. Allylation of Aldehyde- and Ketone-Derived Acylhydrazones

As described above, allylsilane **1** is effective for the enantioselective allylation of aldehyde- *and* ketone-derived acylhydrazones. A full account of the substrate scope for both reactions is provided in **Scheme 5**.[11,12] For aldehyde-derived substrates, *acetyl*hydrazones proved most effective in terms of enantioselectivity,[11] while *benzoyl*hydrazones provided superior results for ketone-derived substrates.[12] Other than the pivalaldehyde-derived hydrazone, hydrazones of aliphatic aldehydes provided poor results. In contrast, in the ketone-derived hydrazone series, substrates derived from aryl alkyl and alkyl alkyl ketones gave useful levels of enantioselectivity. While in some cases the enantioselectivities observed were only moderately good (e.g., 83% or 85% ee) this need not be of concern from a practical point of view: we have demonstrated several of the reactions on a 5-g scale, wherein the products were isolated (without chromatography) by recrystallization, leading to a significant enhancement in their enantiomeric purity.[11] In one of these cases, the reductive cleavage of the N–N bond with SmI_2 was demonstrated, as was the recovery of pseudoephedrine (by extraction and without chromatography) in near-quantitative yield (98%).[12]



(*R,R*)-**12**; $R^1 = R^2 = H$
(*R,R*)-**13**; $R^1 = H$, $R^2 = Me$
(*R,R*)-**14**; $R^1 = Me$, $R^2 = H$



15

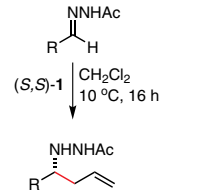
Silane	R	X	Method[a]	Yield	ee
12	Me	H	**A**	75%	83%
12	Me	4-Cl	**A**	65%	81%
12	*i*-Pr	H	**A**[b]	67%	88%
12	*t*-Bu	H	**A**[b]	63%	93%
12	Ph	H	**B**	62%	93%
12	2-MeC_6H_4	H	**B**	75%	94%
12	furan-2-yl	H	**B**	76%	88%
12	MeN-indol-2-yl	H	**B**	69%	95%
12	4-NC-2-$MOMOCH_2C_6H_3$	5-F	**B**[c]	90%	90%
13	Ph	H	**B**[d]	58%	92%
14	Ph	H	**B**[d]	63%	95%

[a] Method **A**: PhMe, 40 °C, 24 h; Method **B**: CH_2Cl_2, 23 °C, 48 h. [b] Reaction time = 48 h. [c] (*S,S*)-**12** was used at 0 °C, giving the opposite configuration at the benzylic carbon. [d] dr >20:1; ee is of the major diastereomer.

eq 1 *(Ref. 20)*

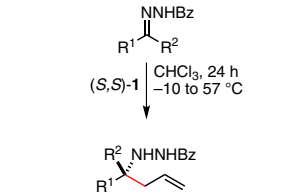
2.4. Allylation and Crotylation of Aldimines and Ketimines

While, as mentioned above, *N*-phenylimines were unreactive towards allylsilane **1**, the mechanism of the acylhydrazone allylation suggested that placement of a hydroxyl group at the ortho position of the *N*-phenyl ring of the imine might lead to successful reactions, wherein the phenol functionality would direct the chloride displacement–protonation steps.[21] Indeed, this strategy proved successful, leading to highly enantioselective reactions that are carried out at ambient temperature (**Scheme 6**).[22] This approach provided a solution to the problem of aliphatic aldimines, and allowed highly diastereoselective and enantioselective crotylation reactions with crotylsilanes **16** and **17** as well. Alternatively, the phenol functionality can be a

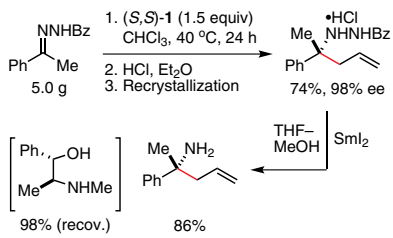


R	Yield	ee
Ph[a]	86%	88%
2-MeC_6H_4	75%	85%
4-BrC_6H_4	88%	85%
4-$MeOC_6H_4$	82%	86%
1,3-benzodioxol-5-yl	93%	83%
2-Np	85%	87%
furan-2-yl	89%	88%
furan-3-yl	78%	86%
thien-2-yl	76%	89%
BocN-indol-3-yl	96%	83%
BocN-pyrrol-2-yl[b]	49%	92%
t-Bu	88%	97%

[a] When this reaction was run on a 5-g scale, the recrystallized product was isolated in 80% yield and 98% ee. [b] 40% of unreacted starting material was also isolated.



R^1	R^2	Yield	ee
Ph	Me	86%	90%
Ph	Et	91%	89%
Ph	Bn	95%	84%
Ph	CO_2Me	76%	93%
Ph	*i*-Pr	80%	97%
4-BrC_6H_4	Me	92%	89%
4-$MeOC_6H_4$	Me	70%	85%
3-$O_2NC_6H_4$	Me	79%	88%
2-Np	Me	80%	89%
furan-2-yl	Me	46%	88%
thien-2-yl	Me	70%	90%
BocN-indol-3-yl	Me	64%	86%
$Ph(CH_2)_2$	Me	86%	87%
Cy	Me	78%	94%



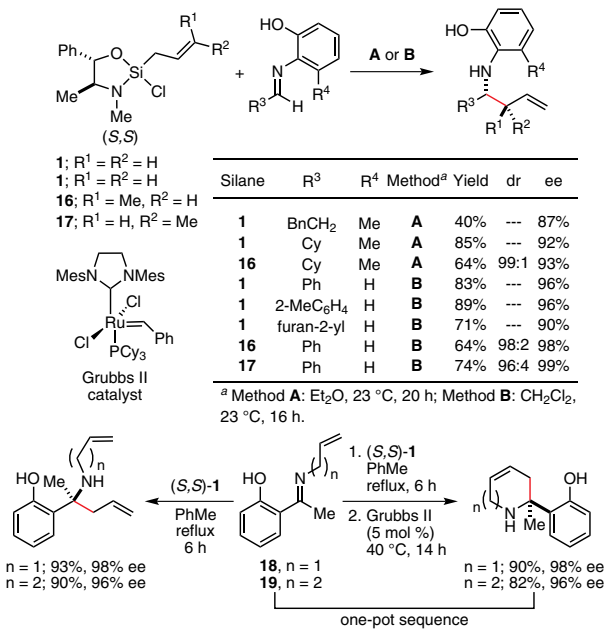
Scheme 5. Scope of the Enantioselective Allylation of Aldehyde- and Ketone-Derived Acylhydrazones. *(Ref. 11,12)*

part of the substrate, as in ketimines **18** and **19**, leading to the successful reaction of these. Despite the fact that these are more sluggish reactions (they are carried out in refluxing toluene), the enantioselectivities are remarkably high. Because the directing/activating group is already part of the ketone or aldehyde structure in these cases, there is flexibility in the choice of the imine N-substituent, which may then be thought of as part of a desired target structure and not as a protecting group to be removed later. As one example of this strategy, allylation of **18** and **19** may be followed by in situ ring-closing metathesis (RCM) to give the illustrated piperidine and azepine derivatives in a single-pot operation.[22]

The success with the phenol moiety as the directing/activating group inspired further inquiries into what other groups—especially those that might have relevance to medicinal chemistry—could successfully direct and activate reactions with allylsilane **1**. Among the groups considered was imidazole, and, indeed, it was found that the *N*-allylimine derived from 2-formylimidazole reacted smoothly with **1**. Unfortunately, the enantioselectivity of this reaction was very low (< 20% ee), and we began a search for more effective chiral controllers. Eventually the aminoindanol-derived allylsilane (1*S*,2*R*)-**20** was found to give good results (**Scheme 7**).[23] As shown, **20** is effective for the enantioselective allylation of a variety of 2-imidazolyl aldimines *and* ketimines, and crotylsilanes **21** and **22** may be employed for the diastereoselective and enantioselective crotylation of 2-imidazolylaldimines. The convenience of these reaction conditions, the fact that unprotected imidazoles may be employed (indeed, it is necessary that they be unprotected), and the flexibility in the choice of the imine N-substituent all combine to render this a reaction of significant potential utility in medicinal chemistry. As in Scheme 6, in situ ring-closing metathesis may be employed, following allylation of 2-acetylbenzimidazole-derived ketimines **23** and **24**, to provide access to stereochemically and functionally complex heterocycles in a simple one-pot procedure. From a strategy or reaction design perspective, it is noteworthy that the metathesis is unsuccessful when attempted on the isolated allylation products, presumably due to binding of the imidazole to the Grubbs II catalyst. Thus, the allylation reaction requires the use of unprotected imidazoles, and produces unprotected imidazoles, but the in situ silylation of the imidazole in the course of the allylation may be leveraged to allow the RCM to occur.

2.5. Tandem Cross-Metathesis–Diastereodivergent Cinnamylation of Aldimines

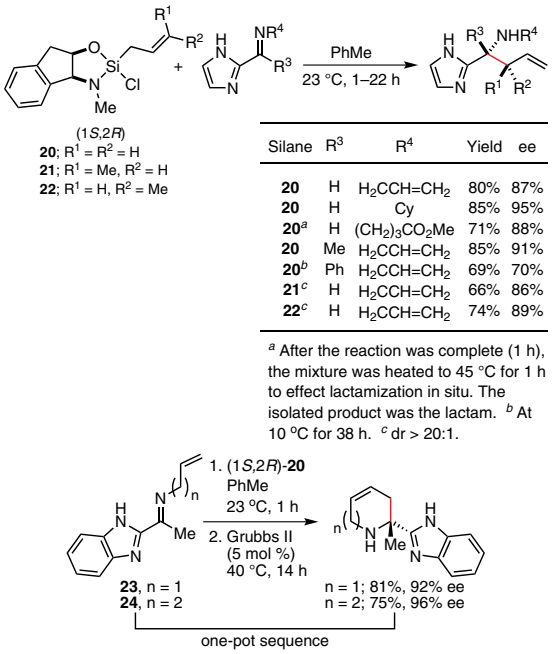
Because of the success observed with the crotylation reactions described in Schemes 6 and 7, we wondered whether substitution of the allylsilane with groups other than methyl might be tolerated as well. Indeed, in the arena of imine allylation (as opposed to aldehyde allylation) there is no particular reason for an emphasis on crotylation. The incorporation of aryl groups into the allylic position of the products by way of cinnamylation reactions might be expected to be far more important, especially from a medicinal chemistry perspective. Gratifyingly, cinnamylsilane **25** smoothly cinnamylated the benzaldimine derived from 2-aminophenol to give the syn product as the major diastereomer (**Scheme 8**).[24] Remarkably, the product was produced in 99% ee despite the fact that, to achieve a reasonable reaction rate, the cinnamylation had to be carried out in refluxing 1,2-dichloroethane (DCE). Furthermore, when the same reaction was carried out with the related benzaldimine derived from 2-(aminomethyl)phenol, the corresponding anti diastereomer was obtained exclusively in 97% ee. Both diastereomers of the product amines are thus accessible *from the same trans cinnamylsilane* based only on the absence or presence of a methylene group between the imine nitrogen and the phenol ring. Such a "diastereochemical switch" based on a seemingly trivial change to the structure of the imine is unprecedented and has significant practical implications, not least of all that it obviates the traditional necessity of synthesizing both the trans



Silane	R^3	R^4	Method[a]	Yield	dr	ee
1	$BnCH_2$	Me	**A**	40%	---	87%
1	Cy	Me	**A**	85%	---	92%
16	Cy	Me	**A**	64%	99:1	93%
1	Ph	H	**B**	83%	---	96%
1	2-MeC_6H_4	H	**B**	89%	---	96%
1	furan-2-yl	H	**B**	71%	---	90%
16	Ph	H	**B**	64%	98:2	98%
17	Ph	H	**B**	74%	96:4	99%

[a] Method **A**: Et_2O, 23 °C, 20 h; Method **B**: CH_2Cl_2, 23 °C, 16 h.

Scheme 6. Phenol-Directed/Activated Enantioselective Allylation and Crotylation of Aldimines and Ketimines. *(Ref. 22)*



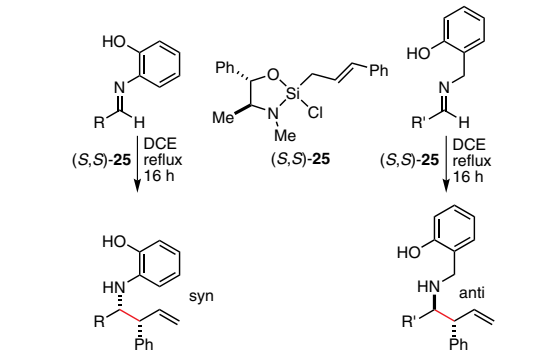
Silane	R^3	R^4	Yield	ee
20	H	$H_2CCH{=}CH_2$	80%	87%
20	H	Cy	85%	95%
20[a]	H	$(CH_2)_3CO_2Me$	71%	88%
20	Me	$H_2CCH{=}CH_2$	85%	91%
20[b]	Ph	$H_2CCH{=}CH_2$	69%	70%
21[c]	H	$H_2CCH{=}CH_2$	66%	86%
22[c]	H	$H_2CCH{=}CH_2$	74%	89%

[a] After the reaction was complete (1 h), the mixture was heated to 45 °C for 1 h to effect lactamization in situ. The isolated product was the lactam. [b] At 10 °C for 38 h. [c] dr > 20:1.

Scheme 7. Imidazole-Directed/Activated Allylation of Aldimines and Ketimines. *(Ref. 23)*

and cis cinnamylsilanes in order to access both diastereomers of the cinnamylated product.

As synthetically powerful as this methodology may be, its broad use in medicinal chemistry still faced a significant obstacle in that each different aryl group to be incorporated in this fashion would require a de novo synthesis of the corresponding cinnamylsilane. We therefore sought a method by which a collection of simple and readily available arene building blocks might be employed in this chemistry in easy-to-perform one-pot operations. Cross metathesis (CM) between allylsilane **1** (which can easily and inexpensively be prepared in multikilogram quantities) and vinylarenes seemed a direct and potentially straightforward solution, and indeed the second-generation Grubbs catalyst (Grubbs II) smoothly catalyzed a highly trans-selective CM between allylsilane **1** and vinylarenes.[25,26] The imine of choice may be added to the reaction pot upon completion of the CM reaction, and several examples of this simple one-pot procedure are summarized (**Scheme 9**). Stereochemically and functionally complex homoallylamines may thus be assembled in a single step from (*S*,*S*)-**1**, an imine, and a vinylarene. The example with 2-chloro-3-vinylpyridine makes clear the excellent functional group tolerance of the process, and the one-pot hydroformylation–reductive amination of the CM–cinnamylation product into the corresponding piperidine derivative illustrates the power of this method to deliver complex heterocyclic structures in just two operationally simple steps.



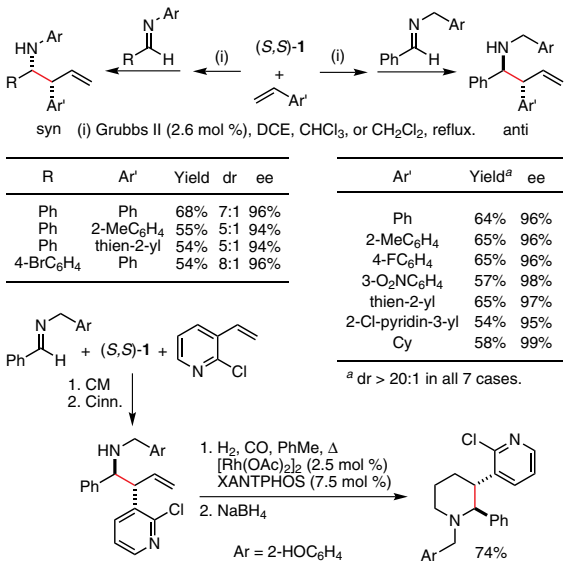
R	Yield	dr	ee
Ph	87%	7:1	99%
4-BrC$_6$H$_4$	79%[a]	13:1	97%
4-NCC$_6$H$_4$	66%	18:1	90%
4-MeOC$_6$H$_4$	53%	5:1	96%
thien-2-yl	69%	11:1	96%
Cy	60%[b,c]	>20:1	95%
BnCH$_2$	53%[b,d]	>20:1	98%

[a] At 60 °C. [b] The N-substituent was 2-HO-6-MeC$_6$H$_3$ instead of 2-HOC$_6$H$_4$. [c] In $CHCl_3$ at 50 °C. [d] In CH_2Cl_2 at reflux.

R'	Yield[a]	ee
Ph	91%	97%
4-O$_2$NC$_6$H$_4$	70%	95%
4-NCC$_6$H$_4$	73%	96%
4-MeOC$_6$H$_4$	89%	94%
thien-2-yl	77%	93%
2-MeOC$_6$H$_4$	77%	99%
BocN-indol-3-yl	51%[b]	98%

[a] In all cases, dr > 20:1. [b] At 60 °C.

Scheme 8. Diastereodivergent Cinnamylation of Aldimines. *(Ref. 24)*



R	Ar'	Yield	dr	ee
Ph	Ph	68%	7:1	96%
Ph	2-MeC$_6$H$_4$	55%	5:1	94%
Ph	thien-2-yl	54%	5:1	94%
4-BrC$_6$H$_4$	Ph	54%	8:1	96%

Ar'	Yield[a]	ee
Ph	64%	96%
2-MeC$_6$H$_4$	65%	96%
4-FC$_6$H$_4$	65%	96%
3-O$_2$NC$_6$H$_4$	57%	98%
thien-2-yl	65%	97%
2-Cl-pyridin-3-yl	54%	95%
Cy	58%	99%

[a] dr > 20:1 in all 7 cases.

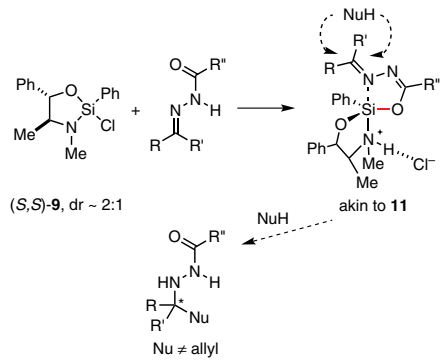
Scheme 9. Tandem Cross-Metathesis–Cinnamylation of Aldimines. *(Ref. 25)*

3. Nucleophilic Additions to Acylhydrazones Activated with Silane Lewis Acids

Encouraged by the remarkable synthetic power and generality of allylsilane **1**, and informed by the X-ray crystal structure of **11** (see Scheme 3), it was natural to wonder whether the related phenylsilane **9** might serve as a general Lewis acid for the activation of acylhydrazones towards non-allyl nucleophiles (**Scheme 10**).[27] We were particularly intrigued by the notion of devising a "universal" Lewis acid—one that can activate any member of a given class of electrophile (acylhydrazones, in this case) towards a variety of different nucleophilic addition reactions—and we were further hopeful that this approach might facilitate otherwise difficult transformations. As will be described below, silane **9** is not only generally effective for the activation of acylhydrazones towards a variety of different nucleophilic addition reactions, but is also effective for the activation of other imine derivatives as well.

3.1. Friedel–Crafts Alkylations with Acylhydrazones

The addition of electron-rich arenes to glyoxylate-derived imines, in an overall Friedel–Crafts-like alkylation reaction, provides access to valuable arylglycine derivatives.[28] We have found that silane **9** smoothly promotes the addition of anilines to the benzoylhydrazone of isopropyl glyoxylate (**Scheme 11**).[27] Ortho substitution on the arene nucleophile is well tolerated, as is the use of heteroaromatic nucleophiles, and the products are obtained with good-to-excellent levels of enantioselectivity. The reaction is easily scaled as the illustrated example (5-g scale) documents, and pseudoephedrine is recovered in essentially quantitative yield. Conversion of the hydrazide functionality into the more generally useful Boc-protected amine was straightforward and proceeded without racemization.



Scheme 10. Proposed Enantioselective Nucleophilic Additions to Silane–Acylhydrazone Complexes. *(Ref. 27)*

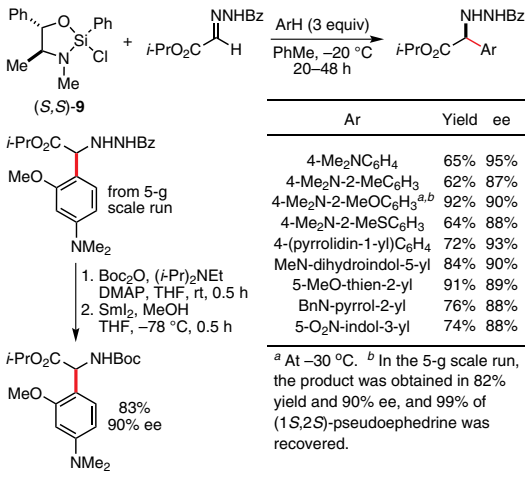
3.2. Acylhydrazone–Alkene [3 + 2] Cycloaddition Reactions

Silane **9** is also competent to activate acylhydrazones towards nucleophilic attack by electron-rich olefins, such as enol ethers. In contrast to the Friedel–Crafts chemistry, the oxocarbenium ion intermediate that results from attack of an enol ether on the silane-acylhydrazone complex persists long enough to be trapped by the acylated nitrogen atom, and a (stepwise) [3 + 2] cycloaddition reaction is the result. A variety of aliphatic and aromatic aldehyde-derived benzoylhydrazones may be reacted with *tert*-butyl vinyl ether to give pyrazolidines with excellent levels of enantioselectivity (**eq 2**).[29,30] Larger-scale (5 g of hydrazone) reactions of two substrates were carried out in order to demonstrate the true practicality and scalability of the method. These are "dump-and-stir" reactions that are carried out in toluene at ambient temperature, and the products may be isolated by recrystallization as single diastereomers in high yield and 99% ee. In both cases, pseudoephedrine was recovered in essentially quantitative yield as well.

3.3. Tandem Aza-Darzens–Ring-Opening Reactions

Silane **9** is effective in the promotion of aza-Darzens reactions[31,32] of acylhydrazones with the stabilized sulfonium ylide derived from the rhodium-catalyzed reaction of ethyl diazoacetate and diphenyl sulfide.[33] Rather than the aziridine products, however, it is the ring-opened β-chloro-α-hydrazido esters that are isolated as single diastereomers with good-to-excellent levels of enantioselectivity, albeit with varying levels of regioselectivity (**eq 3**).[34] The chloride ion is liberated in the silane–acylhydrazone complexation event and is competent to open the initially formed aziridine products. Thus, it is important to note that the silane Lewis acid not only activates the hydrazone toward attack by the ylide, but also activates the aziridine toward nucleophilic ring opening by the chloride ion.

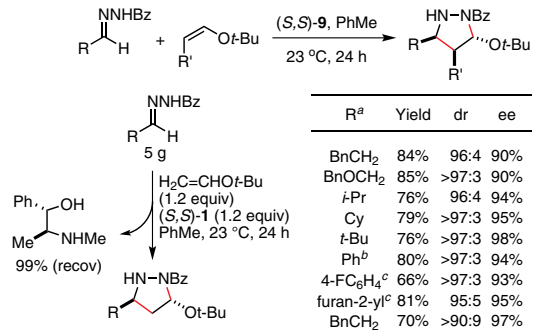
If the same reaction is carried out and a nucleophilic arene and $ZnCl_2$ are added prior to workup, the products formed are diarylalanine derivatives (**Scheme 12**).[34] The products are produced and isolated as single diastereomers and single regioisomers in 91–94% ee. The two-step conversion of one of the products into a trifluoroacetamide-protected α-amino ester was demonstrated as well. The role of $ZnCl_2$ appears to be to accelerate the reversion of the initially produced β-chloro-α-hydrazido esters back to the aziridines, which, activated by the silane Lewis acid, undergo nucleophilic attack by the arene. Stereochemically and functionally complex diarylalanine derivatives may thus be assembled from an acylhydrazone, ethyl diazoacetate, and an arene in a one-pot operation, in which silane Lewis acid **9** performs two distinct functions.



Ar	Yield	ee
4-$Me_2NC_6H_4$	65%	95%
4-Me_2N-2-MeC_6H_3	62%	87%
4-Me_2N-2-$MeOC_6H_3$[a,b]	92%	90%
4-Me_2N-2-$MeSC_6H_3$	64%	88%
4-(pyrrolidin-1-yl)C_6H_4	72%	93%
MeN-dihydroindol-5-yl	84%	90%
5-MeO-thien-2-yl	91%	89%
BnN-pyrrol-2-yl	76%	88%
5-O_2N-indol-3-yl	74%	88%

[a] At –30 °C. [b] In the 5-g scale run, the product was obtained in 82% yield and 90% ee, and 99% of (1*S*,2*S*)-pseudoephedrine was recovered.

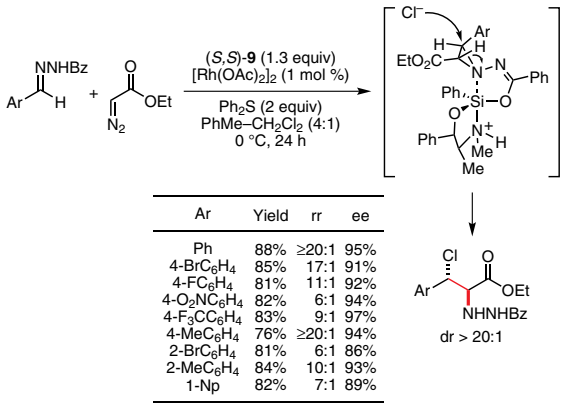
Scheme 11. Enantioselective Friedel–Crafts Alkylations with Acylhydrazones. *(Ref. 27)*



R^a	Yield	dr	ee
$BnCH_2$	84%	96:4	90%
$BnOCH_2$	85%	>97:3	90%
i-Pr	76%	96:4	94%
Cy	79%	>97:3	95%
t-Bu	76%	>97:3	98%
Ph[b]	80%	>97:3	94%
4-FC_6H_4[c]	66%	>97:3	93%
furan-2-yl[c]	81%	95:5	95%
$BnCH_2$	70%	>90:9	97%

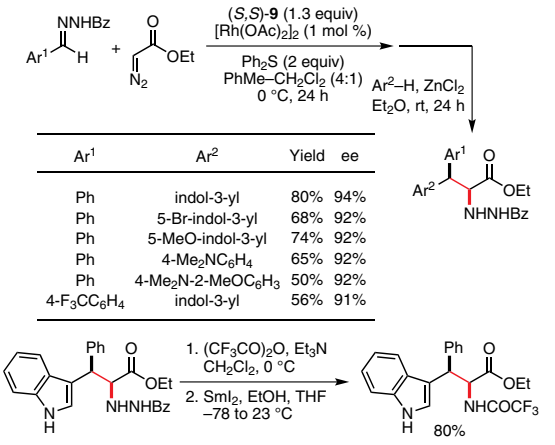
[a] R' = H, except for the last entry where R' = Me. [b] At 40 °C for 50 h. [c] At 40 °C.

eq 2 *(Ref. 29)*



Ar	Yield	rr	ee
Ph	88%	≥20:1	95%
4-BrC_6H_4	85%	17:1	91%
4-FC_6H_4	81%	11:1	92%
4-$O_2NC_6H_4$	82%	6:1	94%
4-$F_3CC_6H_4$	83%	9:1	97%
4-MeC_6H_4	76%	≥20:1	94%
2-BrC_6H_4	81%	6:1	86%
2-MeC_6H_4	84%	10:1	93%
1-Np	82%	7:1	89%

eq 3 *(Ref. 34)*



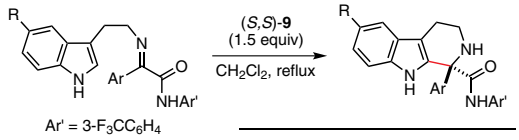
Ar^1	Ar^2	Yield	ee
Ph	indol-3-yl	80%	94%
Ph	5-Br-indol-3-yl	68%	92%
Ph	5-MeO-indol-3-yl	74%	92%
Ph	4-$Me_2NC_6H_4$	65%	92%
Ph	4-Me_2N-2-$MeOC_6H_3$	50%	92%
4-$F_3CC_6H_4$	indol-3-yl	56%	91%

Scheme 12. Enantioselective Tandem Aza-Darzens–Ring-Opening Reactions. *(Ref. 34)*

4. Pictet–Spengler Reactions with α-Ketoamide-Derived Ketimines

We have recently sought to explore the possibility that silane **9** might effectively activate imine types other than acylhydrazones. This effort was inspired by consideration of the Pictet–Spengler reaction, since the imine N-substituent must, by definition, be a two-carbon chain and cannot therefore perform the requisite directing/activating function. From a synthetic perspective, we hoped to provide a solution to the challenging problem of enantioselective *ketimine* Pictet–Spengler reactions, as there have only been a few examples of this reported to date.[35,36] It was found that ketimines prepared from α-ketoamides and tryptamines were indeed subject to smooth promotion of Pictet–Spengler reactions by silane **9**, wherein it is the amide functionality that, in analogy to the acylhydrazones, displaces the chloride from the silane Lewis acid and generates the activating equivalent of HCl.[37] Upon optimization, a very straightforward procedure was developed, a range of aryl ketone derived substrates were employed, and the corresponding tetrahydro-β-carboline products isolated with good-to-excellent levels of enantioselectivity (**eq 4**).[37] A larger-scale (5 mmol of substrate) example was also performed, wherein the product was isolated without chromatography in 79% yield and 99% ee (after recrystallization), and with quantitative recovery of pseudoephedrine.

It was further found that α-ketoamide-derived imines with aliphatic substituents also perform well in the asymmetric Pictet–Spengler reaction promoted by silane **9**. A reoptimization of the amide-directing group was necessary, as was a reoptimization of the reaction conditions. Eventually, a convenient one-pot procedure was developed, wherein the tryptamine and ketone are heated at reflux in toluene with a Dean–Stark trap, and then silane **9** is simply added (**eq 5**).[37] Using this procedure, 1-alkyl-1-carboxamide-substituted tetrahydro-β-carbolines were prepared with good-to-excellent levels of enantioselectivity.

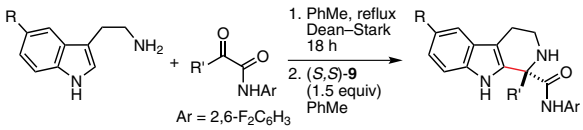


Ar' = 3-$F_3CC_6H_4$

R	Ar	Time	Yield	ee
H	Ph	48 h	93%	93%
H[a]	Ph	48 h	79%	99%
Br[b]	Ph	70 h	68%	89%
MeO	Ph	27 h	93%	82%
H	4-BrC_6H_4	48 h	85%	90%
H	4-$F_3CC_6H_4$	48 h	89%	90%
H[b]	4-$MeOC_6H_4$	20 h	94%	87%
H	2-Np	46 h	82%	91%
H	pyridin-3-yl	42 h	77%	87%
H[c]	1-Np	60 h	50%	87%
H[c]	2,4-$Cl_2C_6H_3$	60 h	86%	90%

[a] 5-mmol scale run: product was isolated by recrystallization and pure (1*S*,2*S*)-pseudoephedrine was recovered in quantitative yield. [b] $CHCl_3$ employed instead of CH_2Cl_2. [c] 2 equiv of (*S*,*S*)-**9** utilized, and DCE used instead of CH_2Cl_2.

eq 4 *(Ref. 37)*



R	R'	Temp	Time	Yield	ee
H	Me	50 °C	36 h	78%	89%
Br	Me	80 °C	48 h	67%	86%
MeO	Me	50 °C	48 h	86%	81%
H	*i*-Bu	50 °C	26 h	81%	90%
H	*i*-Pr	55 °C	25 h	83%	94%

eq 5 *(Ref. 37)*

5. Conclusions and Outlook

The chemistry described herein represents a significant advance in the effective use of silicon as a Lewis acid. The deceptively simple notion that launched this program was that synthetically useful levels of Lewis acidity may be induced in silanes merely by constraining them within 5-membered rings with 1,2-diols, amino alcohols, or diamines. It also led to the discovery of the chloride displacement–HCl activation mechanism, which provided the boost in reactivity that was essential for the development of almost all of the chemistry discussed in this review. Among the noteworthy features of the silane Lewis acid motif that we have developed is the remarkable generality of pseudoephedrine as the chiral controller. Whether the directing/activating group is an acylhydrazone, an aminophenol, an aminomethylphenol, or an *N*-arylamide; and whether the directing/activating functionality is the imine N-substituent or is contained within the substrate; silanes **1** and **9** provide consistently high levels of enantioselectivity for a wide range of substrates in both allylation and non-allylation nucleophilic addition reactions. While they are a long way from being truly "universal" Lewis acids, they can lay a strong claim to a high degree of versatility.

The use of silanes **1** and **9** in stoichiometric amounts (a consequence of the mechanism by which they act) may cause consternation to the extent that it cuts against current dogma in asymmetric reaction design, but the fact remains that, by any criteria that can be measured, the use of pseudoephedrine in stoichiometric amounts is, in practical and economic terms, competitive with most chiral ligands employed in sub-stoichiometric quantities. The considerable practical advantages that accrue to the use of silicon as the Lewis acidic element; the ease of recovery of pseudoephedrine by extraction, as demonstrated in several gram-scale reactions; and, most importantly, the fact that this strategy has led to the development of practical and scalable solutions to several otherwise difficult asymmetric transformations (e.g., ketimine allylations and Pictet–Spengler reactions) all strongly support claims of practicality and justify the development of this methodology. We anticipate that there will be many other effective directing/activating groups discovered, and many other important and otherwise challenging transformations that may be effectively addressed by silanes **1** and **9**. We are confident that these extraordinarily simple, yet highly effective, Lewis acids will find widespread utility, particularly in the arena of pharmaceutical chemistry.

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Keywords: silicon Lewis acid; strained silacycles; allylsilane; asymmetric synthesis; chiral carbinamines.

About the Author

James L. Leighton was born in 1964 in New Haven, Connecticut. He received a B.S. degree in chemistry in 1987 from Yale University, where he worked in the laboratory of Professor Samuel Danishefsky. After a year and a half as a research chemist with the

West Point, PA, medicinal chemistry group of Merck Research Laboratories, he headed off in 1989 to Harvard University, where he initiated Ph.D. studies in the laboratory of Professor David A. Evans. He received his Ph.D. degree in 1994 and, in that same year, began postdoctoral work in the laboratory of Professor Eric N. Jacobsen as a National Science Foundation Postdoctoral Fellow. He was appointed to the position of Assistant Professor at Columbia University in 1996, and he was promoted to Associate Professor in 1999 and to Professor in 2004. Professor Leighton's research program is focused on the development of highly efficient and stereoselective C–C-bond-forming reactions, with a particular emphasis on tandem reactions for the step-economical assemblage of complex structures from simple and readily available starting materials. Highlights include: (i) synthesis of the tetracyclic phomoidride ring system by a tandem carbonylation–spirocyclization–Cope rearrangement sequence, (ii) the first examples of alkene silylformylation and the subsequent development of the tandem silylformylation–allylsilylation–Tamao oxidation sequence for the rapid assemblage of polyketide macrolide fragments, (iii) the first total syntheses of leucascandrolide A and dolabelide D, (iv) the development of the first highly enantioselective silicon Lewis acid catalyst, and (v) the development of a family of chiral silane Lewis acids for the highly practical and scalable synthesis of a variety of complex chiral carbinamine structures of potential relevance to medicinal chemistry. Awards to Professor Leighton include the Mark van Doren Award (2009) and the Distinguished Columbia Faculty Award (2005) both from Columbia University, the Arthur C. Cope Scholar Award (2003), the Alfred P. Sloan Foundation Fellowship (2000), the Camille Dreyfus Teacher-Scholar Award (2000), the Cottrell Scholar Award (1999), the Bristol-Myers Squibb Unrestricted Award in Synthetic Organic Chemistry (1999), the AstraZeneca Excellence in Chemistry Award (1999), the Glaxo Wellcome Chemistry Scholar Award (1999), and the Lilly Grantee Award (1999).

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		100	8	Z569305-5EA
		200	7	Z569313-5EA
		200	8	Z569321-5EA
		400	7	Z569348-5EA
		400	8	Z569356-5EA
		500	7	Z569364-5EA
		500	8	Z569372-5EA
		600	7	Z569380-5EA
		600	8	Z569399-5EA
		800	7	Z569402-5EA
		800	8	Z569410-5EA
Thrift	Yellow	200	7	Z569216-5EA
		200	8	Z569224-5EA
		300	7	Z569232-5EA
		300	8	Z569240-5EA
		400	7	Z569259-5EA
		400	8	Z569267-5EA
		500	7	Z569275-5EA
		500	8	Z569283-5EA
Disposable	Blue	200	7	Z569194-50EA
		200	8	Z569208-50EA

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Copper-Free Click Chemistry: Bioorthogonal Reagents for Tagging Azides

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Outline

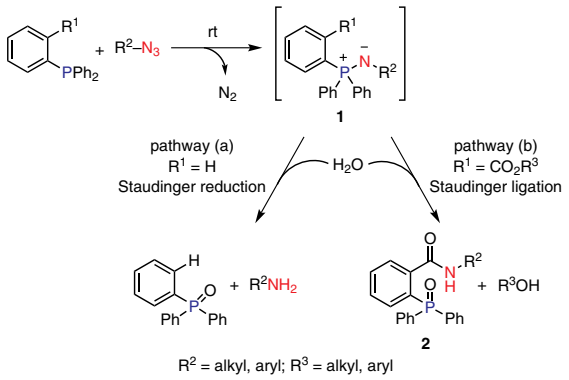
1. Introduction

In the 20th century, the azide functional group was widely used in the synthesis of nitrogen-containing natural products and medicinal agents. For example, the azide is one of the most popular amine precursors, and its ability to undergo 1,3-dipolar cycloadditions and diazo-transfer reactions has been capitalized on in many transformations. In biological settings, however, the azide played a relatively minor role during the same period of time. Sodium azide is a familiar metabolic poison and preservative, and aryl azides are well-known photoactivated cross-linkers; but, otherwise, azides were of little consequence to chemical biologists.[1,2] In the last decade, however, the azide has emerged as a rising star in bioconjugation chemistry, as numerous research groups have capitalized on its dual nature as a soft electrophile and a 1,3-dipole to develop highly selective, water-compatible reactions that employ the azide as a coupling partner. These "azido ligation" reactions have opened the door to applications beyond organic synthesis in fields as diverse as molecular imaging and biomaterials synthesis. These reactions are now at the leading edge of the emerging field of bioorthogonal chemistry (vide infra).

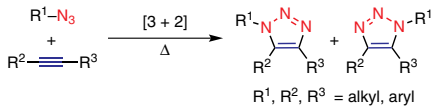
The first reported ligation strategy involving azides was a modification of the classical Staudinger reduction with phosphines. In the traditional Staudinger reduction,[3] attack of the nucleophilic phosphine on the γ position of the azide generates aza-ylide intermediate **1**, which undergoes hydrolysis to produce an amine and a phosphine oxide (**Scheme 1**, pathway (a)). We realized that under the right circumstances, the nucleophilic character of the aza-ylide intermediate could be harnessed for selective acylation of the α-nitrogen atom.[3] This feat was accomplished by installing an ester at a position on triphenylphosphine that would facilitate rapid intramolecular reaction with the aza-ylide. After hydrolysis, an amide bond was formed, and the phosphine oxide was part of the final ligation product, **2**. The overall transformation was named the Staudinger ligation (**Scheme 1**, pathway (b)).[3]

This reaction displays exquisite chemoselectivity. Not only does it proceed with no observable aza-ylide hydrolysis in aqueous solution, but the reaction can occur in the presence of numerous nucleophiles and electrophiles that are present within complex biological systems.[3] Importantly, the triarylphosphine reagents are not toxic to cultured mammalian cells or laboratory mice, setting the stage for numerous biological applications.[4] As a second-order chemical reaction, however, the Staudinger ligation possesses modest kinetic parameters ($k = 2.4 \times 10^{-3}$ $M^{-1}s^{-1}$ for reaction with benzyl azide ($PhCH_2N_3$) in 9:1 CD_3CN–H_2O).[5] Attempts to increase the intrinsic rate constant, which would enable more efficient ligation under circumstances where reaction time or reagent concentration are limiting, have thus far proven futile, in part due to the unfortunate side reaction of phosphine oxidation.[5]

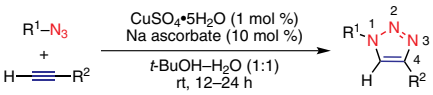
Thus, some chemists have turned to another of the azide's modes of reactivity, its 1,3-dipolar character. Again, the classic organic chemistry literature provided a starting point: in this case, studies of [3 + 2] cycloadditions between azides and alkynes to form 1,2,3-triazoles, first observed in 1893 by Michael and examined thoroughly by Huisgen seventy years later (**eq 1**).[6,7] The reaction intrigued physical organic chemists, but its high activation barrier, which could only be overcome by elevated temperatures or pressures, deterred synthetic organic chemists from using the reaction. In 2002, Sharpless and Meldal independently discovered that copper catalysis dramatically accelerates the rate of formal cycloaddition between azides and terminal alkynes.[8,9] This variant of the Huisgen cycloaddition, termed CuAAC for Cu-catalyzed azide–alkyne cycloaddition, proceeds rapidly at ambient temperatures and pressures to form 1,4-disubstituted 1,2,3-triazoles exclusively (**eq 2**).[8] CuAAC is an exceptional example of "click chemistry", a term coined by Sharpless and co-workers to describe a set of chemical reactions that efficiently link two components in high yield and with minimal byproducts.[10]



Scheme 1. The Staudinger Reduction and Staudinger Ligation. (For more details, see the entry for reference 3 in Section 6.)

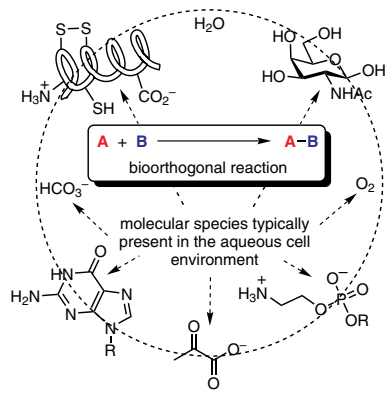


eq 1 *(Ref. 6,7)*



R^1	R^2	Yield
$BnOC(O)CH_2$	Ph	92%
$[(HO)CH_2]_2C(CH_2)_2$	Ph	93%
2-HO-cyclohexyl	Ph	82%
1-Ad	Ph	84%
$3\text{-}H_2NO_2SC_6H_4$	$H_2NC(=NH)NHCH_2$	91%
3-(tetrazol-5-yl)$C_6H_3CH_2$	$H_2NC(=NH)NHCH_2$	88%
$BnOCH_2$	CO_2H	88%
Bn	(*E*)-$HOCH_2CH{=}C(Me)$	84%
Bn	phthalimide-*N*-CH_2	88%
Bn	Et_2NCH_2	90%
(*S*)-$HOCH_2CH(OH)CH_2$	estradiol-17-yl	94%

eq 2 *(Ref. 8)*



eq 3 *(Ref. 14,15)*

The applications of CuAAC have grown tremendously since the reaction was first reported in 2002. In fact, its popularity as the archetypal "click" reaction has led many to simply refer to it as click chemistry. Some applications of CuAAC include the synthesis of small-molecule libraries for drug discovery,[11] the creation of novel supramolecular assemblies such as polymers and dendrimers,[12] and the selective labeling of biological molecules.[13] Though the technological breakthrough of Cu catalysis has enabled these and countless other applications, CuAAC is not without its limitations. Most problematic is the toxic nature of the requisite metal catalyst, which precludes many applications of CuAAC in living biological systems (e.g., imaging proteins and other biomolecules within live cells and animals).

Inspired by the ability of a simple copper catalyst to dramatically improve the kinetics of the Huisgen 1,3-dipolar azide–alkyne cycloaddition, we sought to identify an alternate means of alkyne activation that avoided the use of a toxic catalyst. Such a copper-free, [3 + 2] cycloaddition would, in theory, combine the desirable characteristics of CuAAC and the Staudinger ligation: rapid kinetics and biocompatibility.

This review describes our and others' efforts in developing "copper-free click chemistry", as well as selected applications in chemical biology and materials science. Central to the development of new reagents for this type of chemistry is the concept of bioorthogonality (**eq 3**).[14,15] For a chemical reaction to be useful for labeling applications within a biological system, the reagents must (i) not cross-react with any of the functional groups present in cells, (ii) selectively form covalent bonds in aqueous media at ambient temperatures and pressures, and (iii) be nontoxic to the biological system. In short, the reagents must be bioorthogonal, i.e., noninteracting with biology.

2. Development of Copper-Free Click Chemistry

2.1. Strain-Promoted [3 + 2] Cycloaddition of Cyclooctynes with Azides

The introduction of strain into organic molecules can raise their ground state energies and hence lower reaction barriers in cycloaddition reactions. Classic examples include the use of strained alkenes such as norbornene in Diels–Alder [4 + 2] cycloadditions. We reasoned that an alkyne constrained in a medium-size ring might display enhanced reactivity toward azides in a 1,3-dipolar cycloaddition. In fact, Wittig and Krebs observed in 1961 that cyclooctyne, the smallest stable cycloalkyne, reacted "like an explosion" when mixed with phenyl azide to produce a single triazole product.[16] The enhanced reactivity in the [3 + 2] cycloaddition of cyclooctyne, as compared to a linear, unstrained alkyne, likely derives from the roughly 18 kcal/mol of ring-strain energy present in cyclooctyne, a portion of which is released during the reaction.[17]

Motivated by these studies, we set out to synthesize a derivative of cyclooctyne containing a readily functionalizable side chain, in this case a carboxylic acid.[18] The installation of such a side chain enabled the facile conjugation of the cyclooctyne nucleus to molecular probes (e.g., fluorophores or affinity agents) or supramolecular scaffolds (e.g., polymers, cross-linking agents, resins, etc.). We termed this first-generation reagent OCT, for cyclooctyne, and synthesized it using a modification of the route of Reese and Shaw,[19] via a *trans*-1-bromocyclooctene intermediate. We first determined the stability, selectivity, and reaction kinetics of the new reagent. Fortunately, OCT was stable in water and to model nucleophiles (e.g., 2-mercaptoethanol). Kinetic studies of model [3 + 2] cycloadditions performed with a variety of organic azides (e.g., benzyl azide, 2-azidoethanol,

and *N*-butyl-α-azidoacetamide) revealed efficient formation of two regioisomeric 1,2,3-triazoles (**eq 4**) with second-order rate constants of 1.1–2.4 × 10^{-3} $M^{-1}s^{-1}$, comparable to those measured for model Staudinger ligations.[18]

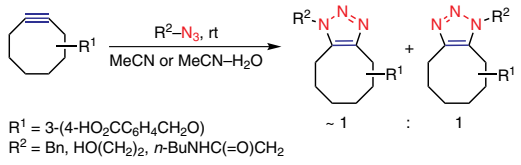
To evaluate the ability of this "strain-promoted" cyclooctyne–azide [3 + 2] cycloaddition to occur selectively within a biological system, we metabolically installed azides into cell-surface glycans using a synthetic azidosugar precursor and then reacted the cells with a biotinylated OCT derivative (OCT-biotin). In this case, we first treated Jurkat T cells with peracetylated *N*-azidoacetylmannosamine (Ac_4ManNAz), which is biosynthetically converted into an azido sialic acid residue (SiaNAz) within cell-surface glycans.[20] We then treated the cells with OCT-biotin and detected the extent of [3 + 2] cycloaddition at the cell surface by staining the cells with a fluorescent avidin conjugate and analyzing them by flow cytometry. Through these studies, we demonstrated that OCT-biotin has no cellular toxicity and displays similar reaction kinetics to the Staudinger ligation in the context of cell-surface labeling.[18]

At this point, we were keen to improve the sensitivity of the cyclooctyne reagents for detecting azides, with an eye toward biological imaging applications (i.e., using cyclooctyne-fluorophore conjugates). To accomplish this, we needed to enhance the kinetics of the [3 + 2] cycloaddition, which would require either an increase in (i) reagent concentration, (ii) reaction temperature, or (iii) reaction time; or else (iv) an improvement in the intrinsic second-order rate constant. Among the items on that list, the first two risk generating toxicity problems, as well as potential background fluorescence arising from the inability to rinse away unreacted cyclooctyne-fluorophore conjugate in the case of (i). While increased reaction time can afford higher yields and therefore greater sensitivity, biological systems are inherently dynamic and, therefore, to image rapid biological processes that occur on the second and minute timescales, increasing the reaction time is not an ideal solution. Thus, we set out to improve the intrinsic kinetics of the strain-promoted cycloaddition by synthesizing cyclooctynes that would be more reactive toward azides.

2.2. Improving [3 + 2] Cycloaddition Kinetics by Using Fluorinated Cyclooctynes

Our initial efforts to improve the kinetics of the [3 + 2] cycloaddition centered on the installation of electron-withdrawing groups (EWGs) adjacent to the triple bond in the cyclooctyne ring. This approach—appending EWGs to the 2π component in a [4π + 2π] cycloaddition—has been highly successful both in Diels–Alder and 1,3-dipolar cycloadditions.[7] Among the various options, we elected to attach fluorine atoms, which are strongly electron-withdrawing through σ bonds, to the cyclooctyne ring. Importantly, this choice avoided the use of a π-based electron-withdrawing group such as a carbonyl, which could have created a Michael acceptor capable of alkylating biological nucleophiles.

In the design of a monofluorinated cyclooctyne, termed MOFO (**Figure 1**),[18,21–23] we eliminated the propargylic ether linkage present in OCT, which exhibited slow decomposition, even at –20 °C.[21] These changes necessitated an entirely different synthetic route, starting with cyclooctanone and principally employing enolate chemistry. Kinetic studies of model [3 + 2] cycloadditions with benzyl azide revealed that MOFO (k = 4.3 × 10^{-3} $M^{-1}s^{-1}$) reacted more rapidly than OCT (k = 2.4 × 10^{-3} $M^{-1}s^{-1}$), suggesting that substitution of the cyclooctyne moiety with a fluorine atom did increase the rate of the strain-promoted cycloaddition (**eq 5**).[21] To quantify the precise effect of fluorine,



eq 4 *(Ref. 18)*

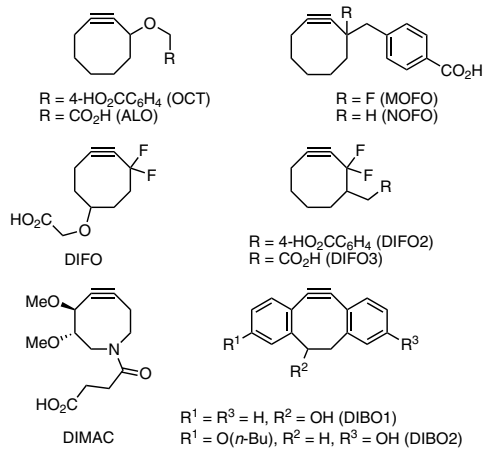
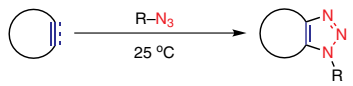


Figure 1. Cyclooctyne Reagents for Copper-Free Click Chemistry. *(Ref. 18,21–23,30–32)*



Alkyne	R[a]	Solvent	k (x 10^{-3} $M^{-1}s^{-1}$)	*Ref.*
OCT	Bn	CD_3CN	2.4	*18*
OCT	*n*-BuNHC(=O)CH_2	CD_3CN	1.9	*18*
OCT	$HO(CH_2)_2$	CD_3CN	1.1	*18*
OCT	$HO(CH_2)_2$	CD_3CN:D_2O[b]	2.0	*18*
MOFO	Bn	CD_3CN	4.3	*21*
NOFO	Bn	CD_3CN	1.2	*21*
DIFO	Bn	CD_3CN	76	*22*
DIFO2	Bn	CD_3CN	42	*23*
DIFO3	Bn	CD_3CN	52	*23*
ALO	Bn	CD_3CN	1.3	*21*
DIMAC	Bn	CD_3CN	3.0	*32*
DIBO1	Bn	CH_3OH	57	*31*
DIBO2[c]	Bn	CH_3OH	76	*31*
DIBO2[c]	*n*-Bu	CH_3OH	59	*31*
DIBO2[c]	Bn(Me)CH	CH_3OH	34	*31*
DIBO2[c]	Ph	CH_3OH	16	*31*
DIBO2[c]	*d*	CH_3OH	44	*31*
Oxanorbornadiene[e]	Bn	CD_3OD	0.85	*34*
Oxanorbornadiene[e]	$H_2N(CH_2)_3$	D_2O	0.70	*34*
Oxanorbornadiene[e]	HO_2CCH_2	D_2O	1.1[f]	*34*

[a] The product triazoles were obtained as ~1:1 mixtures of regioisomers. [b] CD_3CN–D_2O (55:45). [c] In this case, the DIBO2 employed had R^1 = R^3 = O(*n*-Bu) and R^2 = H. [d] *N*-Azidoacetylmannosamine used. [e] 2-Trifluoromethyl-oxanorbornadiene-3-carboxylic acid. [f] Only one regioisomer was observed.

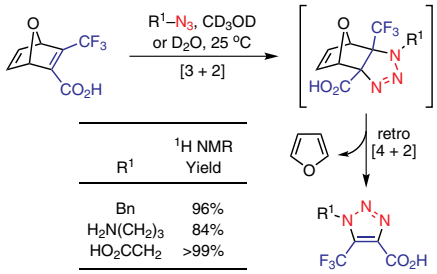
eq 5

we synthesized a nonfluorinated analogue of MOFO termed NOFO (see Figure 1); the rate constant for its reaction with benzyl azide is 1.2×10^{-3} $M^{-1}s^{-1}$, leading us to conclude that a single fluorine atom at the propargylic position increases the reaction rate by almost four-fold (see eq 5).[21]

We then immediately set out to further increase the rate constant by synthesizing difluorinated cyclooctyne reagents, selecting the 3,3-difluorocyclooctyne skeleton, rather than the 3,8-difluorocyclooctyne one, because of the ease of synthesis of the former. The first such difluorinated cyclooctyne reagent, termed DIFO (see Figure 1), was synthesized in nine linear steps and 1% overall yield.[22] Subsequent second-generation reagents, DIFO2 and DIFO3 (see Figure 1), retained the 3,3-difluorocyclooctyne core but contained different linkers and were generated by using vastly simplified synthetic routes.[23] Again, model [3 + 2] cycloaddition reactions with benzyl azide were employed to determine the kinetic parameters, with second-order rate constants in the range of $4.2–7.6 \times 10^{-2}$ $M^{-1}s^{-1}$ (see eq 5).[22,23]

Based on the results of the kinetic studies of the [3 + 2] cycloadditions of NOFO and MOFO with BnN_3, we had anticipated that DIFO would be roughly four-fold faster than MOFO. However, these estimates had assumed a linear relationship between the number of fluorine atoms and reaction kinetics. It is possible that the two fluorine atoms in the CF_2 group act synergistically in terms of their electron-withdrawing power. Indeed, an examination of mean C–F bond lengths in monofluorinated and difluorinated alkanes supports this claim. The mean C–F bond length in all reported small-molecule structures as determined by X-ray and neutron diffraction in monofluoromethine groups (R_3Csp^3–F, where R is an alkyl group) is 1.428 ± 0.009 Å, while that for difluoromethylene groups (R_2Csp^3–F_2) is 1.349 ± 0.012 Å, a difference of 0.08 Å.[24] Based on the simple inverse relationship between force and distance, therefore, the shorter bond lengths in difluoromethylene groups imply that the fluorine-bound carbon is more electropositive than would be predicted from simply doubling the effect of two isolated C–F bonds.

This line of reasoning offers a qualitative explanation for why the DIFO reagents are more than four times faster in model reactions with benzyl azide than MOFO is. In a series of computational studies of 1,3-dipolar cycloadditions between azides and cyclooctynes, Houk and others have proposed that the origin of the observed rate enhancements lies in an evaluation of two energy terms: (a) the distortion energy required to achieve the transition state, and (b) the interaction energies within the transition state.[25–27] More specifically, the rate enhancement using



R^1	^1H NMR Yield
Bn	96%
$H_2N(CH_2)_3$	84%
HO_2CCH_2	>99%

Scheme 2. Rutjes's Tandem [3 + 2] Cycloaddition–Retro-Diels–Alder Reaction of Azides with Electron-Deficient Oxanorbornadiene Derivatives. *(Ref. 34)*

cyclooctyne relative to an unstrained, linear alkyne is attributable to a decrease in distortion energy, while the rapid kinetics utilizing difluorinated relative to nonfluorinated cyclooctynes is explained by an increase in interaction energies.

Studies using live cells whose cell-surface glycans had been metabolically labeled using Ac_4ManNAz revealed that the efficiency of cell-surface labeling amongst the family of cyclooctyne and phosphine reagents mirrored the rate constants determined in model [3 + 2] cycloadditions and Staudinger ligations.[21–23] Applications of these reagents will be discussed in Section 3.

2.3. Other Strained Alkynes and Alkenes for Copper-Free Click Chemistry

Numerous other approaches for improving cyclooctyne kinetics have been taken in the quest for an optimal bioorthogonal reagent for detecting azides. An obvious choice would be to further increase ring strain. While cycloheptynes and cyclooctenynes are isolable but unstable at room temperature, dibenzocyclooctyne, containing two fused benzene rings formally in conjugation with the alkyne, has long been known to be an unexpectedly stable molecule.[28,29] Boons and co-workers recently synthesized dibenzocyclooctynol (DIBO) reagents (DIBO1 and DIBO2; see Figure 1) that can be easily functionalized, and they demonstrated that these compounds underwent rapid copper-free [3 + 2] cycloaddition with azides.[30] Kinetic measurements by Boons, Popik, and co-workers of model reactions of the two DIBO probes with various azides yielded second-order rate constants of $1.6–7.6 \times 10^{-2}$ $M^{-1}s^{-1}$, similar to those of reactions involving DIFO reagents (see eq 5).[31] In comparative biological labeling studies—in which Jurkat cells displaying SiaNAz residues in their cell-surface glycans were incubated with biotin derivatives of either DIBO1, DIFO, DIFO2, or DIFO3—we have determined that the labeling efficiency of DIBO1 is slightly better than that of DIFO2 or DIFO3 but slightly worse than that of DIFO, consistent with the rates measured in model reactions (see eq 5).[22,31] Further electronic and steric modifications to the dibenzocyclooctyne scaffold represent a fruitful area for reagent optimization. Additionally, Boons, Popik, and co-workers demonstrated that the dibenzocyclooctyne functionality could be masked as a cyclopropenone, enabling the light-triggered unveiling of the alkyne with spatial and temporal control.[31]

Beyond improved reaction kinetics, we had recognized early on that the hydrophobicity of the cyclooctyne probes could present problems in terms of limited water solubility and nonspecific adhesion to membranes and other hydrophobic surfaces in biological systems. To address these concerns, we designed two compounds with increased hydrophilicity, an arylless cyclooctyne analogue of OCT termed ALO and a heterocyclic dimethoxyazacyclooctyne termed DIMAC (see Figure 1).[21,32] Though these compounds lack the difluoromethylene moiety, which we later determined dramatically increases the rate of the 1,3-dipolar cycloaddition with azides, our motivation for the design of these compounds was to minimize lipophilic interactions in complex in vivo settings (e.g., adhesion to membranes or serum proteins in mammals). Indeed, both ALO and DIMAC outperform OCT in their ability to detect azidoglycans on cell surfaces within living mice.[33]

Lastly, Rutjes and co-workers have reported a tandem [3 + 2] cycloaddition–retro-Diels–Alder reaction between azides and electron-poor oxanorbornadienes to yield stable triazoles (**Scheme 2**).[34] The tandem reaction ensures that the unstable triazolene, the initial [3 + 2] cycloadduct between the azide and

the alkene, is converted into the stable, aromatic triazole product. While this reaction has been employed for protein bioconjugation in vitro, its sluggish kinetics ($k \approx 10^{-4}$ to 10^{-3} $M^{-1}s^{-1}$) has limited the use of oxanorbornadiene reagents for in vivo applications, in which extended reaction times are not ideal and toxicity concerns limit the concentration of reagent that can be utilized (see eq 5).[34]

3. Applications of Copper-Free Click Chemistry

In a broad sense, copper-free click chemistry has been applied in two fields of study: chemical biology and materials science. Biological applications range from imaging experiments in live cells and whole organisms to proteomic strategies to identify metabolically labeled biomolecules by mass spectrometry. In materials science, copper-free click chemistry has contributed to the growing area of biocompatible hydrogel development.

3.1. Chemical Biology Applications

Many different approaches have been employed in chemical biology to install the azide functional group as a bioorthogonal handle onto a variety of biological molecules. Within the area of glycobiology, we and others have utilized numerous azidosugars as metabolic labels of cell-surface and intracellular glycans, and we have used copper-free click chemistry to image glycan dynamics in biological systems.[20,22] In particular, fluorophore conjugates of DIFO have proven valuable in this regard, as we have successfully employed these probes to track glycans in cultured cells and in live zebrafish embryos, a useful model for studying vertebrate development (**Figure 2**).[22,35] We have also shown that copper-free click chemistry proceeds in mice, setting the stage for future imaging studies in this valuable model organism for human disease.[22,33]

In addition to glycans, other biomolecules have been imaged within live cells using copper-free click chemistry. Ting and co-workers utilized cyclooctyne probes as part of a method for site-specific protein labeling in mammalian cells. In their approach, the bacterial enzyme lipoic acid ligase (LplA) directs the attachment of an azido lipoic acid analogue to recombinant proteins bearing a consensus sequence termed the lipoate acceptor peptide (**Figure 3**).[36] In a second step, azide-labeled proteins were reacted with MOFO-fluorophore conjugates, enabling the imaging of the trafficking patterns of various cell-surface proteins, including the low-density lipoprotein and epidermal growth factor receptors.[36,37] Cyclooctyne-containing phospholipids have been used to visualize plasma membranes in live cells using copper-free click chemistry.[38] In this case, because the cyclooctyne was first incorporated into the biomolecule, a "fluorogenic" azide—one which only becomes fluorescent upon [3 + 2] cycloaddition—could be used, resulting in very low background due to unreacted fluorescent probe.[39]

Beyond molecular imaging, copper-free click chemistry has seen other applications within chemical biology. Tirrell and co-workers have utilized OCT-biotin to label a library of unnatural proteins displayed on *E. coli* cell surfaces in order to help select for mutant tRNA-synthetase activities.[40] Along a similar vein, Zou and Yin employed a DIFO-biotin derivative to select for adenylase activities in nonribosomal peptide synthase (NRPS) enzymes using a phage display approach.[41] Burkart and co-workers also used copper-free click chemistry to probe the biochemistry of an NRPS system.[42] In

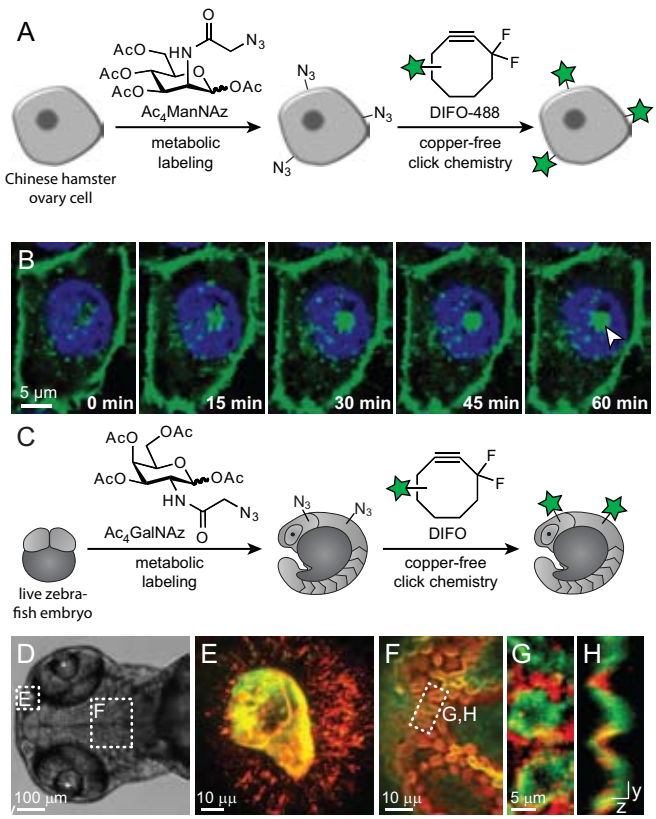


Figure 2. In Vivo Imaging of Glycans in Cultured Cells and Developing Zebrafish Using Copper-Free Click Chemistry. (Parts A and B are reproduced with permission from reference 22. Copyright (2007) National Academy of Sciences U.S.A. Parts C–H are reproduced from reference 35. Copyright (2008) American Association for the Advancement of Science. For more details, see the entries for references 22 and 35 in Section 6.)

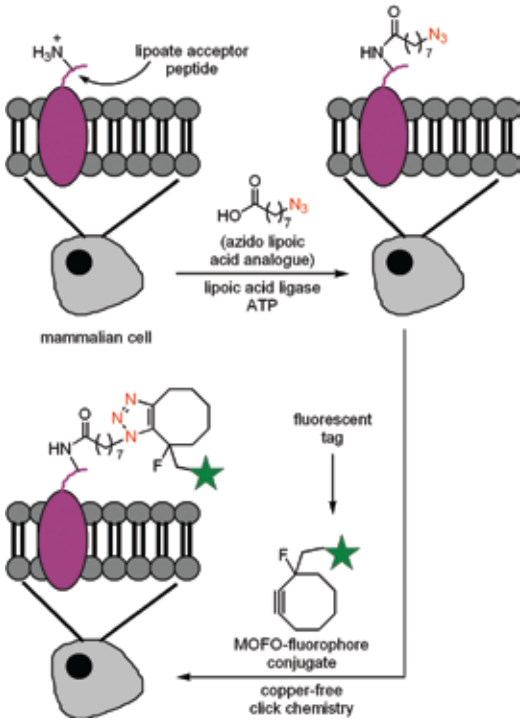


Figure 3. Site-Specific Labeling of Membrane-Resident Proteins Using Lipoic Acid Ligase and Copper-Free Click Chemistry. (For more details, see the entry for reference 36 in Section 6.)

their work, azido and DIFO derivatives of the cofactor pantetheine, which occurs as a posttranslational modification of certain NRPS domains, were utilized to study the assembly of NRPS enzymes. A successful protein–protein interaction between two cognate communication-mediating (COM) domains put the azide and DIFO moieties in close proximity, leading to triazole formation and, hence, NRPS subunit cross-linking, which was easily visualized by polyacrylamide gel electrophoresis (**Figure 4**). In this manner, copper-free click chemistry enabled a simple readout of otherwise difficult-to-observe noncovalent macromolecular interactions.

De Koster and co-workers have recently applied copper-free click chemistry to the area of proteomics.[43] In this work, an azide-reactive cyclooctyne resin containing disulfide-linked NOFO molecules was synthesized and used to capture azidopeptides from whole-cell lysates in which newly synthesized proteins had been metabolically labeled using an azido amino acid. Release of the captured peptides was accomplished by treatment with an alkyl phosphine reagent to reduce the disulfide; subsequent mass spectrometric analysis of the purified peptides enabled the identification of the de novo biosynthesized proteome. Lastly, Wolfbeis and co-workers demonstrated that copper-free click chemistry and CuAAC could be employed sequentially for dual labeling of proteins and nanoparticles, confirming the orthogonality of these two reactions.[44] Furthermore, the same research group monitored matrix metalloproteinase activity in vitro by utilizing a FRET-based silica nanoparticle probe (FRET = Fluorescence Resonance Energy Transfer) that was assembled by using sequential click reactions.[45]

3.2. Materials Science Applications

Copper-free click chemistry has become a valuable tool for materials science applications as well. In some instances, the requirement for a copper-free approach arises from a desire to

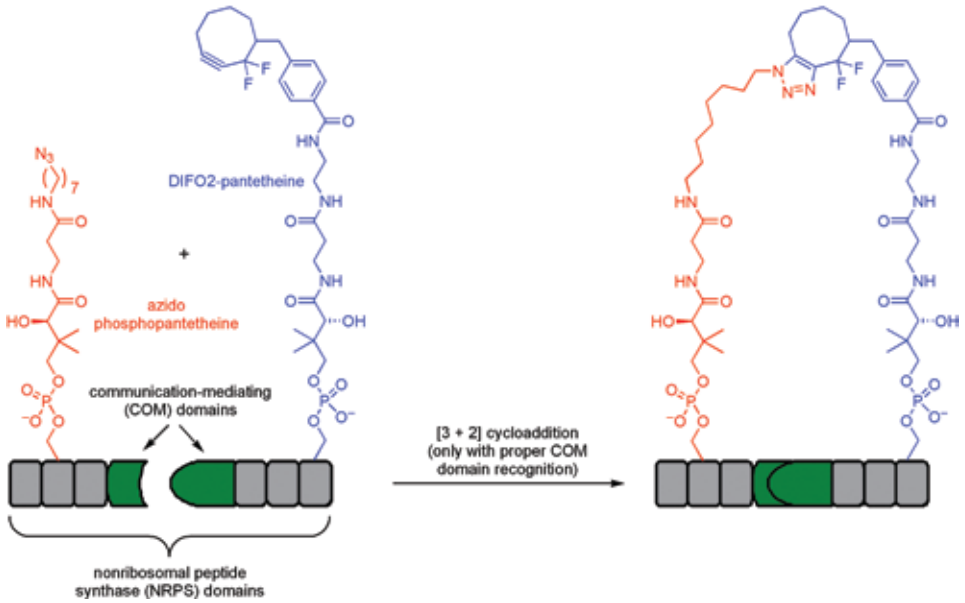


Figure 4. Probing Protein–Protein Interactions Among Nonribosomal Peptide Synthase (NRPS) Family Members Using Unnatural Pantetheine Analogues and Copper-Free Click Chemistry. (For more details, see the entry for reference 42 in Section 6.)

create materials that can interface with biological systems in a nontoxic manner (e.g., synthesis of hydrogels for encapsulation of live cells in 3D). Beyond these biological applications, though, other scenarios exist where utilizing copper is detrimental, necessitating the use of copper-free click chemistry. For example, Fernandez-Megia, Riguera, and co-workers reported that the use of CuAAC to functionalize chitosan–polyethylene glycol (PEG) nanostructures with fluorophores and other probes led to depolymerization of the polysaccharide-based chitosan polymers, presumably through the action of hydroxyl radicals generated by Fenton chemistry in the presence of Cu(I).[46] The same research group discovered that the use of cyclooctyne-functionalized fluorophores, monosaccharides, and even antibodies enabled efficient decoration of the chitosan–PEG nanostructures without any depolymerization.[46]

In addition to the functionalization of traditional nanomaterials, copper-free click chemistry has been utilized to create novel materials (**Figure 5**). Turro and co-workers created photodegradable gels by using a biscyclooctyne compound to cross-link tetraazido "star" polymers containing *ortho*-nitrobenzyl groups, which decompose under UV light.[47] The use of either MOFO or DIFO in the cross-linker enabled the tuning of the gelation kinetics. While these studies employed organic-soluble gels, they set an important precedent that the nontoxic copper-free click chemistry could be utilized to initiate a gelation process. Anseth and co-workers recently reported the generation of biologically compatible hydrogels by using copper-free click chemistry with DIFO3-based peptides to cross-link macromolecular precursors.[48] They encapsulated live cells within the hydrogel with no observed cellular toxicity. Additionally, they incorporated alkene groups into the precursors, allowing further functionalization of the intact hydrogel, with spatial control, by using a photochemically induced thiol–ene coupling reaction.

4. Summary and Outlook

In the six years since the original report that a cyclooctyne reagent could selectively tag azides in a nontoxic reaction,[18] copper-free click chemistry has emerged as a popular bioorthogonal ligation strategy. This reaction has been employed to solve many problems in chemical biology and materials science, and it will undoubtedly have additional applications in these and other areas in the future.[49] Moreover, the methodology itself is ripe for future development. Beyond the strain energy inherent in the cyclooctyne reagent, the second-generation reagents described in this review demonstrate that improved reaction kinetics can be achieved through the fluorination and fusion of benzene rings to the cyclooctyne. Other factors, such as hydrophilicity and synthetic tractability, have also driven methodology development. In the future, entirely novel azide-reactive scaffolds, exemplified by the oxanorbornadiene system, may yield useful reagents. Lastly, chemists have begun to develop new bioorthogonal reactions that do not employ the azide. These include inverse-electron-demand [4 + 2] Diels–Alder cycloadditions of tetrazines with alkenes[50–53] and 1,3-dipolar cycloadditions of nitrile oxides with strained alkenes.[54] Moreover, light-catalyzed processes are gaining in popularity, including thiol–ene reactions[55] and "photoclick" chemistry between in situ generated nitrile imines and alkenes.[56–58] The combination of methodology development and an expanding set of applications underscores the reach of copper-free click chemistry into many areas of science.

5. Acknowledgments

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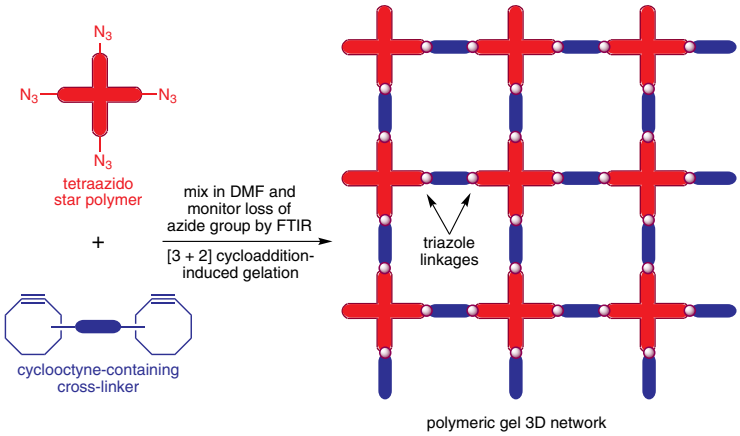

Figure 5. Generation of Novel Gels Using Copper-Free Click Chemistry. (For more details, see the entry for reference 47 in Section 6.)

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of soluble tetraazido star polymers (red) and biscyclooctyne-containing cross-linkers (blue) causes the formation of a 3D gel network (triazole linkages are shown in purple). The use of different star polymers and cross-linkers enables the modulation of gel properties (e.g., solubility, ability to be degraded by UV light, ability to be further functionalized post-gelation with imaging agents, drugs, or other probes). Incorporation of different cyclooctynes into the cross-linker (e.g., MOFO vs DIFO) allows for the tuning of gelation kinetics. See also reference 48.

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Keywords: click chemistry; [3 + 2] cycloaddition; bioorthogonal reagent; cyclooctynes; azides.

About the Authors

Jeremy M. Baskin was born in Montreal, Canada. He received his B.S. degree in chemistry in 2004 from the Massachusetts Institute of Technology (M.I.T.), with minors in biology and music. While at M.I.T., he performed research in the laboratories of Professor Stephen L. Buchwald and Professor Alice Y. Ting. In 2004, Jeremy began graduate studies in the laboratory of Professor Carolyn R. Bertozzi at the University of California, Berkeley. As a graduate student, Jeremy's research focused on the development of fluorinated cyclooctyne reagents for copper-free click chemistry and their application to imaging glycans in vivo. He earned his Ph.D. degree in 2009 and is currently conducting postdoctoral research under the guidance of Professor Pietro De Camilli at the Yale School of Medicine.

Carolyn R. Bertozzi is the T. Z. and Irmgard Chu Distinguished Professor of Chemistry and Professor of Molecular and Cell Biology at UC Berkeley; an Investigator of the Howard Hughes Medical Institute; and Director of the Molecular Foundry, a DOE Nanoscale Science and Research Center at the Lawrence Berkeley National Laboratory. She received her undergraduate degree in chemistry from Harvard University in 1988 and her Ph.D. degree in chemistry from UC Berkeley in 1993. After postdoctoral work at UC San Francisco in the field of cellular immunology, she joined the UC Berkeley faculty in 1996.

Professor Bertozzi's research interests span the disciplines of chemistry and biology with an emphasis on studies of cell surface glycosylation pertinent to disease states. Her lab focuses on profiling changes in cell surface glycosylation associated with cancer, inflammation, and bacterial infection, and on exploiting this information for the development of diagnostic and therapeutic approaches. In addition, her group develops nanoscience-based technologies for probing cell function and for medical diagnostics.

Professor Bertozzi has been recognized with many honors and awards for both her research and teaching accomplishments. She is an elected member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the German Academy of Sciences Leopoldina. She has been awarded the Whistler Award, the Ernst Schering Prize, a MacArthur Foundation Fellowship, the ACS Award in Pure Chemistry, a Presidential Early Career Award in Science and Engineering, and the Irving Sigal Young Investigator Award of the Protein Society, among many others. Her efforts in undergraduate education have earned her a UC Berkeley Distinguished Teaching Award and the Donald Sterling Noyce Prize for Excellence in Undergraduate Teaching. Professor Bertozzi participates in high-school outreach programs such as the Catalyst Program sponsored by the Camille and Henry Dreyfus Foundation, as well as programs that promote the participation of women in science. She was recently presented with the Li Ka Shing Award for Women in Science in recognition of these efforts.

New Catalysis Products from Aldrich R&D

Palladium(II) Acetate, Recrystallized

It has been shown that in some applications recrystallized palladium(II) acetate, $Pd(OAc)_2$, performs better than typical grades. White and Overman have both independently demonstrated that in some applications a particular grade of $Pd(OAc)_2$ is necessary. In particular, the preparation of the White catalyst as well as the preparation of the COP catalysts-$[COP\text{-}OAc]_2$ and $[COP\text{-}Cl]_2$ by Overman successfully employ and require recrystallized $Pd(OAc)_2$.

720070

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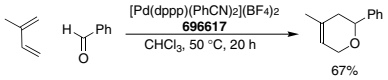
Cationic Palladium Complexes, $[Pd(dppp)(PhCN)_2](BF_4)_2$

Cationic palladium(II) complexes are utilized in a variety of reactions. $[Pd(dppp)(PhCN)_2](BF_4)_2$ catalyzes the hetero-Diels–Alder reaction of dienes with aldehydes. The reaction yields substituted 5,6-dihydro-2*H*-pyrans without the use of Lewis acids and is believed to proceed through a stepwise mechanism.



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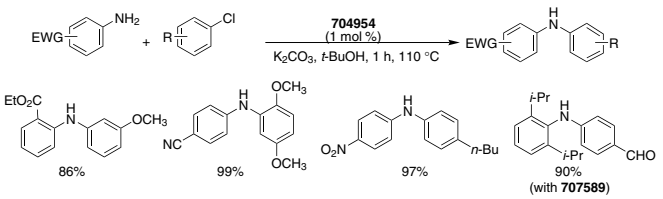
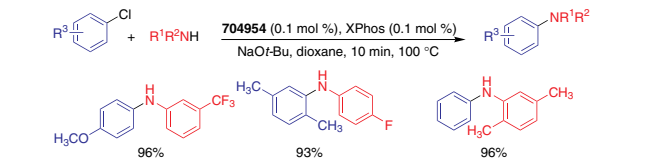
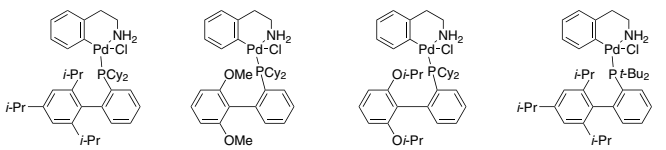
Air-Stable Precatalysts for Amination

C–N-bond-forming cross-coupling reactions typically require a palladium source along with associated ligands. Most Pd(0) sources are not air-stable, while the commonly employed air-stable Pd(0) source, $Pd_2(dba)_3$, contains associated ligands which could impede the reaction in some cases. Stable Pd(II) precursors require reduction under the reaction conditions. In either case, a ligand must be added to the reaction in order to lead to the active Pd species. Buchwald and coworkers recently reported the use of highly active air- and moisture-stable precatalysts, which, under the standard reaction conditions, form the active monoligated Pd species. These precatalysts are exceptionally efficient even under challenging conditions, such as coupling electron-poor anilines with deactivated aryl chlorides. The catalyst precursors also offer other advantages including low catalyst loadings and short reaction times.







704954 (from XPhos) **704946** (from SPhos) **707589** (from RuPhos) **708739** (from *t*-BuXphos)

Reference: Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.

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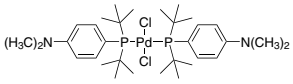
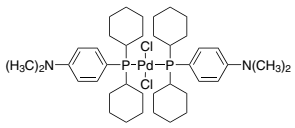
Nonproprietary Catalysts for Cross-Coupling Reactions

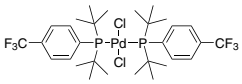
The cross-coupling reaction of heteroaryl halides is of particular interest to the pharmaceutical industry since many biologically active compounds are accessed through use of the Suzuki–Miyaura reaction. However, the efficient coupling of boronic acids with five-membered-ring heteroaryl halides or six-membered-ring heteroaryl chlorides bearing heteroatom substituents has not been well-developed. Catalysts are thought to form inactive complexes with many of these types of substrates, and thus, they typically require high catalyst loadings in order to achieve good yields. Guram's group at Amgen has recently reported the development of an air-stable palladium complex, $(A^{ta}Phos)_2PdCl_2$, for Suzuki–Miyaura cross-coupling reactions. The catalyst is very effective at coupling a wide range of substrates with arylboronic acids, including amino-substituted 2-chloropyridines and five-membered-ring heteroaryl halides. The products are obtained in excellent yields and high turnover numbers (up to 10,000 TON) are typically achieved. A series of new $PdCl_2\{PR_2(Ph\text{-}R')\}_2$ catalysts were developed with various reactivities.



678740



692913



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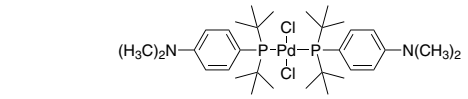
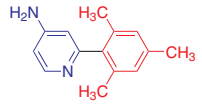
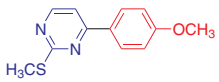


678740

(1 mol %)

K_2CO_3, toluene–water, reflux, 12 h

entry	Product	Yield (%)
1		93
2		98
3		95

References: (1) Singer, R. A. et al. *Tetrahedron Lett.* **2006**, *47*, 3727. (2) Singer, R. A. et al. *Synthesis* **2003**, 1727. (3) Guram, A. S. et al. *Org. Lett.* **2006**, *8*, 1787.

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Palladium(II) [1,3-bis(diphenylphosphino)propane]bis(benzonitrile) bis(tetrafluoroborate)

696617 250 mg

[*175079-12-6*]

$C_{41}H_{36}B_2F_8N_2P_2Pd$

FW: 898.71

(XPhos) palladium(II) phenethylamine chloride

704954 250 mg, 1 g

$C_{41}H_{59}ClNPPd$

FW: 738.76

(SPhos) palladium(II) phenethylamine chloride (1:1 MTBE solvate)

704946 250 mg, 1 g

$C_{39}H_{57}ClNO_3PPd$

FW: 760.72

RuPhos palladium(II) phenethylamine chloride

707589 250 mg

$C_{30}H_{43}O_2P{\cdot}C_8H_{10}ClNPd$

FW: 728.68

***t*-BuXPhos palladium(II) phenethylamine chloride**

708739 250 mg

$C_{37}H_{55}ClNPPd$

FW: 686.69

Bis(di-*tert*-butyl(4-dimethylaminophenyl)phosphine) dichloropalladium(II)

678740 1 g, 5 g

[*887919-35-9*]

$C_{32}H_{56}Cl_2N_2P_2Pd$

FW: 708.07

Bis[(dicyclohexyl)(4-dimethylaminophenyl)phosphine]palladium(II) chloride

692913 250 mg, 1 g

$C_{40}H_{64}Cl_2N_2P_2Pd$

FW: 812.22

Bis[(di-*tert*-butyl)(4-trifluoromethylphenyl)phosphine]palladium(II) chloride

692921 250 mg, 1 g

$C_{30}H_{44}Cl_2F_6P_2Pd$

FW: 757.93

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