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Diastereodivergent Hydrosilylative Enyne Cyclization Catalyzed by NHC-Ni(0)

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Dedicated to Department of Chemistry, SUSTech, on the occasion of her 10th founding anniversary.

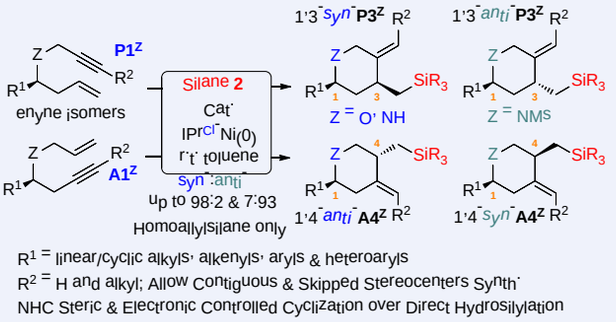
Keywords

N-heterocyclic carbenes | nickel | diastereodivergent synthesis | enyne | silylative hydroalkenylation

Main observation and conclusion

Catalytic diastereodivergent hydrosilylative enyne cyclization with high generality and broad scope was achieved using electronic activated NHC-Ni(0) as a catalyst and R_3SiH as silane (IPr^{Cl}, syn-:anti-selectivity from up to 98:2 to 7:93 by Z = O, NH vs NMs, R^1 = n-pentyl). Heterocycles bearing homoallylsilane rather than vinylsilane was obtained chemoselectively. The undesired yet highly competitive reactivity was suppressed, like direct hydrosilylation of alkene and alkyne concurrently. Optionally, the homoallylsilane products could be reduced further in 1-pot using IPr^{Me} as ligand and $(EtO)_3SiH$ as silane under otherwise the same standard condition as the above, offers practical access to additional stereocenters and more diverse product structures from enynes.

Comprehensive Graphic Content



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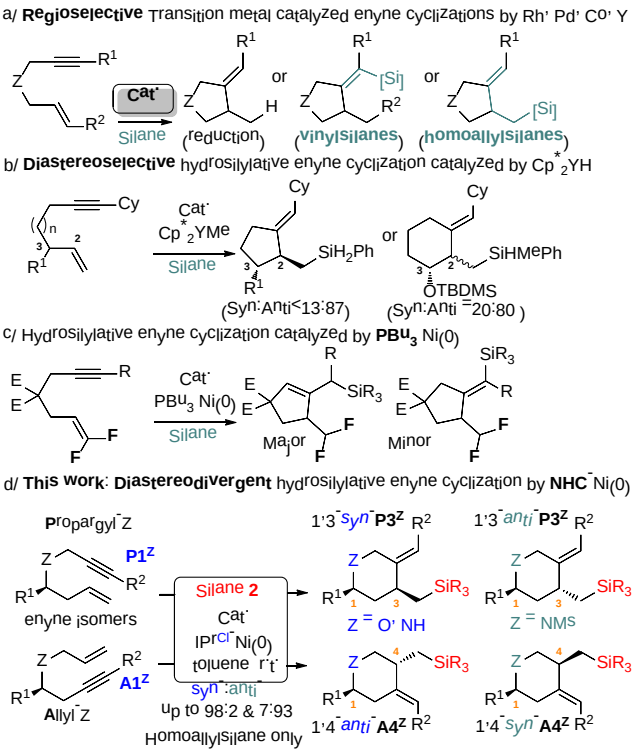
Background and Originality Content

Transition metal-catalyzed hydrosilylative cyclization is a renowned strategy to prepare key intermediates for more complicated products.[1-4] Notable methodologies have been developed over the years to utilize those silylated products, in which Hiyama coupling[5-9] and Fleming-Tamao oxidations are often exploited.[10-12] In particular, the catalytic hydrosilylative enyne cyclizations have received a lot of attention over decades and efficiently construct various carbo-/hetero-cycles (Scheme 1a).[13-15] Unlike the hydrosilylative diyne cyclization, most of the enyne mechanism's first step is the corresponding metal hydride or metal silyl insertions to the alkyne rather than metalacycle formation. That is because of the relatively lower oxidative cyclization reactivity of the enyne and the somewhat easier oxidative addition of silane.[16,17] After subsequent insertion and reductive elimination steps, homoallyl-/vinyl-silanes products are formed, and the catalyst is regenerated accordingly. Common complications are those related to premature reductive elimination after alkyne insertion, competitive intermolecular alkyne versus alkene insertions, as well as reductive cyclization without silyl group incorporation (Scheme 1a, reduction).[18, 19] Therefore, many well-designed catalysts and strategies have been developed recently in order to cope with different enyne structural characteristics for high regioselectivity. For example, $Rh_4(CO)_{12}$,[20, 21] $Rh_2Co_2(CO)_{12}$,[20, 21] NHC–Rh,[22] Rh-Co nanoparticle[23] and PBu_3-Ni[24] complexes for products with vinylsilane and allyl silane, while Cp^*_2Y[25-27], $IP.CoCl_2$[28] and a few π-allyl-Pd[29] complexes for homoallylsilane derivatives (Scheme 1a-c). Asymmetric and diastereoselective versions have also been achieved using chiral Rh and Y catalysts.[30, 31] Yet, diastereodivergent synthesis development has been limited often by the delicate balance of the above highly competitive reactivity, especially when unfavorable or ineffective steric repulsions are involved.[32-34] In cases of 1,n-enynes without a cyclic template or quaternary center in Ni(0) catalysis, non-selective oligomerization may lower the yield and selectivity further sometimes (e.g. n = 7).[35-37] Overall, there is a great demand to develop a new methodology to meet the new challenges in the catalytic hydrosilylative enyne cyclization and quickly provide products with more diverse substitution patterns.

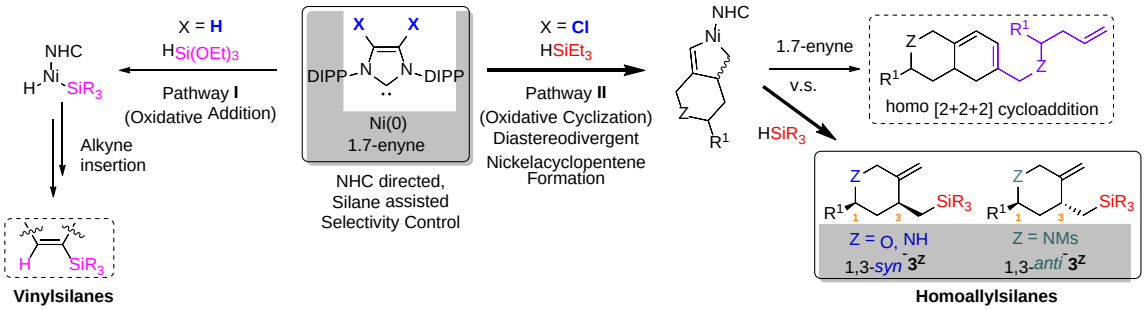
We have recently achieved a diastereodivergent 1,n-aza-enynes reductive hydroalkenylation[38] and hydroacylation[39] using IPr–Ni(0) as catalysts. Alcohols and aldehydes have been used as reductants and hydroacylating reagents, respectively. Our mechanistic study has shown that nickelacyclopentene formation is crucial in those reactions. Electronic manipulations of the 1,n-enyne's hetero-substituent can work with 1,3-allylic strain and govern the heterocycles' C-Z-C bond angles as shown in our DFT calculation.[39] As a result, the product's preferred configurations can be controlled logically.

Next, we envisioned a diastereodivergent hydrosilylative enyne cyclization that could be achieved by trapping the nickelacyclopentene with a suitable silane (Scheme 1d). Yet, the above complications involved silanes and enynes can be very significant. Key challenges ahead are the highly competitive NHC-Ni(0) catalyzed alkyne or alkene hydrosilylations through NHC-Ni(II)H(SiR_3) formation at r.t. (Scheme 2, pathway **I**).[41, 42] Indeed, unless a gem-difluoromethylene was used as alkene terminus, the hydrosilylative enyne cyclization was unable to proceed with Ni(0) (Scheme 1c).[24] Moreover, the silane needs to be more reactive than the enyne in the nickelacyclopentene ring-opening step to avoid undesired enyne homo-reaction (Scheme 2, pathway **II**). At the same time, it has to be less reactive toward the Pathway **I**.



Scheme 1 Catalytic Hydrosilylative Enyne Cyclizations.

Herein, we report our continuous effort in diastereodivergent heterocycle synthesis, illustrating the scope and selectivity further by the practical catalytic synthesis of structurally more diverse heterocycles bearing homoallylsilanes (Scheme 1d, c.f. preliminary study: R^1 = Ph, R^2 = H, Z = NH and NMs[38,40]). Interestingly, the optimization showed that the exocyclic olefin on the heterocycle could be hydrogenated using a suitable combination of catalyst and siliane in one-pot. That discovery offers an option to access an additional stereocenter for structurally more diverse product structures at high efficiency.



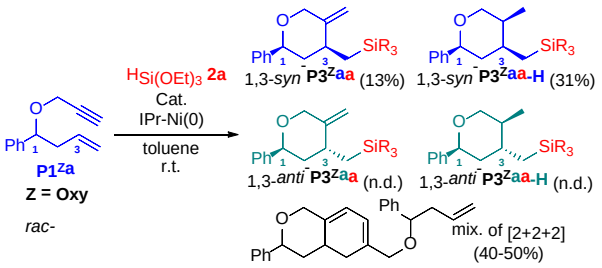
Scheme 2 Competitions in NHC-Ni(0) Catalyzed Enyne Hydrosilylation Cyclizations.

Results and Discussion

Our study commenced with enyne **P1^{Oxy}a** as a substrate and a methoxylsilane **2a** as a hydrosilylating reagent (Scheme 3). Unfortunately, this initial attempt using IPr-Ni(0) catalyst did not offer good chemoselectivity and yield. Direct hydrosilylation of alkyne[41, 43] and non-selective [2+2+2] cycloaddition[44] occurred significantly as the literature implied. The desired hydrosilylative enyne cyclization product 1,3-*syn*-**P3^{Oxy}aa** was formed only in a small amount, yet the diastereoselectivity and homoallylsilane formation selectivity were remarkably high (no 1,3-*anti*-**P3^{Oxy}aa** and no vinylsilane by ^{1}H NMR). Interestingly, an unexpected exocyclic methylene reduction of 1,3-*syn*-**P3^{Oxy}aa** was observed and resulted in a significant amount of 1,3-*syn*-**P3^{Oxy}aa-H** product.

Notable advances in yield and selectivity came by screening ligands and silanes.[45, 46] First, ligand screening was conducted using a less reactive triethylsilane **2b** to avoid those undesired reactivities related to hydrosilane oxidative addition, like exocyclic methylene reduction, as well as direct alkyne and/or alkene hydrosilylations. While very low reactivity and basically no improvement were observed using PCy_3, SIPr and IMes,[24] much better results were observed using sterically bulkier NHCs like IPr^{Me} and IPr^{Cl} than the IPr itself (Table 1, entry 1-4). Since the difference in V%$_{bur}$ of IPr^{Me} and IPr^{Cl} is relatively small,[45-48] the better and higher catalyst reactivity obtained from IPr^{Cl} was attributed mainly to the electronic property change (entry 3 and 4). That could result in a more selective nickelacyclopentene opening with **2b** over [2+2+2] reactivity. It should be noted that the IPr^{Cl} catalyst has a lower alkyne hydrosilylation reactivity than IPr, as evidenced by a model study using a terminal alkyne for a comparison (see SI), which may also help the desired pathway. To our delight, the use of IPr^{Cl} also provided good results in the synthesis of azacycle 1,3-*syn*-**P3^{NH}ab** (entry 5). Yet, the decisive improvement brought by the use of IPr^{Cl} is even more apparent in the synthesis of azacycle 1,3-*anti*-**P3^{NMs}ab** (entry 6-9). With the key NHC identified, other combinations of R_3SiH with various steric and electronic properties could be used (Table 2). Desired products could be obtained in reasonably good yield, high d.r. and homoallyl-:vinyl-silane selectivity in general (*syn*-:*anti*- > 95:5 for Z = O and NH; > 5:95 for Z = NMs).

Next, such an NHC and silane cooperation effect in preparing sterically more challenging and diversely substituted heterocycles was tested (Table 3). Even though the changes in enyne substituents could cause undesired steric repulsions and reactions, the desired selectivity and reactivity were maintained very well. First, highly consistent 1,3-*syn*-/*anti*-configuration preferences and high homoallyl-:vinyl-silane ratio were observed in general among enynes with various R^1, like linear/cyclic alkyls, alkenyls, and (hetero-)aryls (Set 1a, 1,7-enyne **P1^Z** with propargyl-Z). Moreover, the method was found equally effective in the catalytic preparation of 1,4-diastereomers using 1,7-enynes **A1^Z** with allyl-Z (Set 1b, *syn*-:*anti*- > 5:95 for Z = O and NH; > 95: 5 for Z = NMs). This switch of the product's syn-/anti-configurations preference resembled well with our former diastereodivergent reductive hydroalkenylation and hydroacylation. Enynes with internal alkenes were found incompatible due to the more apparent terminal alkyne oligomerization. On the other hand, enynes with internal alkynes are decent substrates under our condition (Set 2a-b). That serves as a new method to synthesize stereodefined trisubstituted homoallylsilane on the ring. Finally, the method helps set up contiguous/skipped stereocenters on heterocycles (Set 3-4). The preferred outcomes in these hydrosilylative enyne cyclizations still follow the choice of Z selected as indicated above.

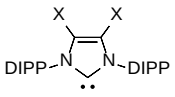


Scheme 3 Initial attempt in catalytic hydrosilylative oxaenyne cyclization (product structures are shown in relative configurations).

Table 1 Screening of Ligands for Hydrosilylative Enyne Cyclization.[a]

entry	1	2	Ligand	P3^Z	yield (%)	Syn:Anti[d]	P3^Z-H
1[b]	P1^{Oxy}a	2b	PCy_3	P3^{Oxy}ab	18	n.d.	< 5
2[c]			IPr		53	**> 95**:5	< 5
3[c]			IPr^{Me}		68	**> 95**:5	<5
4			**IPr^{Cl}**		**84**	**> 95**:5	< 5
5	**P1^{NH}a**	**2b**	**IPr^{Cl}**	**P3^{NH}ab**	**71**	**97**:3[d]	< 5
6	P1^{NMs}a	2b	PCy_3	P3^{NMs}ab	32	13:87	< 5
7			IPr		35	10:90	< 5
8			IPr^{Me}		56	8:92	< 5

9	**IPr^{Cl}**		**87**	6:**94**	< 5



NHC [=]	X [=]	V%$_{Bur}$[e] [=]	(Aver) υco [f][=]
IPr	H	34.9	2023.9
IPr^{Me}	Me	35.7	2021.3
IPr^{Cl}	Cl	35.5	2028.3

[a] See scheme 3 for the reaction equation, enyne and product structures. See Experimental Section for procedure except otherwise indicated. [b] 2 equiv. of PCy_3. [c] 20 mol% catalyst. [d] By GCMS. [e] From [(NHC)$AuCl_3$].[47] [f] From [$IrCl(CO)_2$(NHC)].[50]

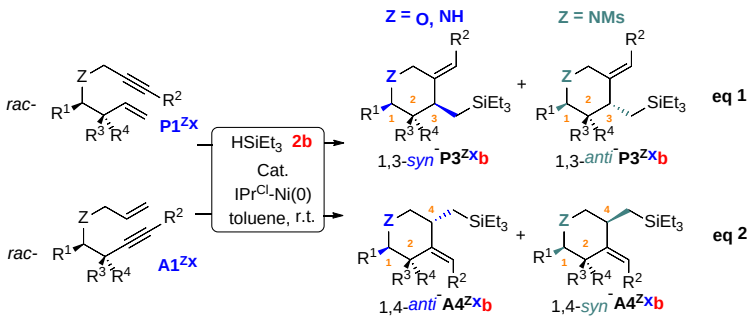
Table 2 Screening of Silanes for Hydrosilylative Enynes Cyclization.[a]

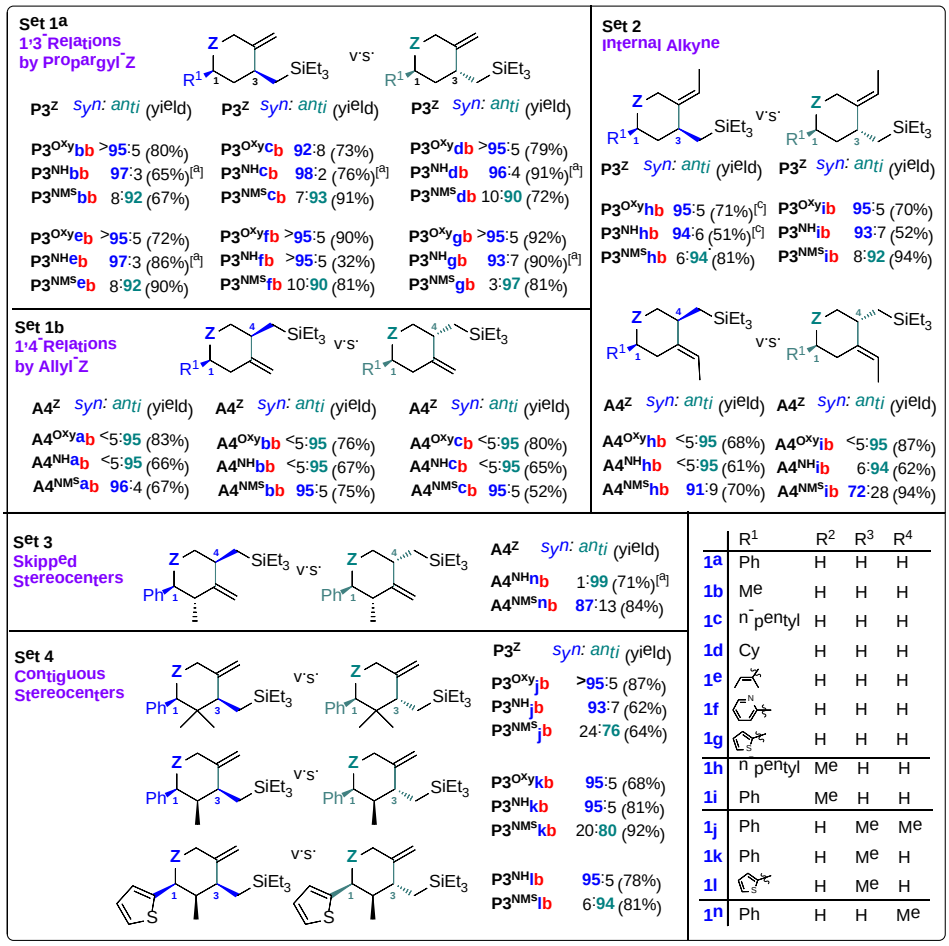
entry	**P1^{Z}**	Silane **2**	**P3^{Z}**	yield (%)	Syn:Anti
1		$(EtO)_3SiH$ **2a**	**P3^{Oxy}aa**	66	**> 95**:5
2		$BnMe_2SiH$ **2c**	**P3^{Oxy}ac**	68	**> 95**:5
3	**P1^{oxy}a**	$PhMe_2SiH$ **2d**	**P3^{Oxy}ad**	71	**> 95**:5
4		Ph_3SiH **2e**	**P3^{Oxy}ae**	67	**> 95**:5
5		*t*$BuMe_2SiH$ **2f**	**P3^{Oxy}af**	61	**> 95**:5
6	**P1^{NH}a**	$(EtO)_3SiH$ **2a**	**P3^{NH}aa**	68	**98**:2[b]
7	**P1^{NMs}a**		**P3^{NMs}aa**	83	5:**95**[b]
8	**P1^{NH}a**	Ph_3SiH **2e**	**P3^{NH}ae**	65	**> 95**:5
9	**P1^{NMs}a**		**P3^{NMs}ae**	82[c]	8:**92**

See scheme 1d for the reaction equation, enyne and product structures. See Experimental Section for procedure except otherwise indicated. [a] IPr^{Cl} was used as ligand. [b] Determined by GC-MS. [c] Major product structure was confirmed by XRD.

Overall, the product's syn-/anti-configurations control here is consistent with the related examples that we noted before. So, we surmised that the diastereodivergent hydrosilylative enyne cyclization went through the same set of nickelacyclopentenes successfully when we employed a suitable choice of electronic activated bulky NHC and silane (Scheme 2, the pathway **I** vs **II**). Next, it might involve a regioselective silane metathesis at the nickelacyclopentene Csp^3-Ni over the Csp^2-Ni site according to the product structure we obtained. That high regioselectivity was similar to the regioselective hydroacylation. That was presumably a result of the longer Csp^3-Ni bond and the steric repulsion control based on NHC and silane substituents. The undesired oligomerization and [2+2+2] reactivity was suppressed mainly by the NHC electronic and steric properties as shown in Table 1.

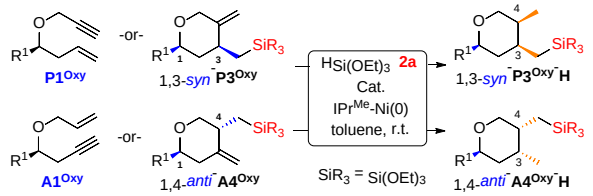
Table 3 Scope of the diastereodivergent hydrosilylative enyne cyclization by IPr^{Cl}-Ni(0) catalyst and Et_3SiH **2b**.[a]





e Experimental Section for general procedure, structures are shown in relative configuration. *Syn*-:*Anti*-selectivity and yield (in parenthesis) were determined by NMR and isolation except otherwise indicated. [a] By GCMS. [b] 20 mol% catalyst.

Table 4 Diastereoselective reduction and effect of R^1 by using IPr^{Me}-Ni(0) catalyst and $(EtO)_3SiH$ **2a**.



entry	R^1	starting materials	product	yield (%)	3,4- *syn*:*anti*
1	Ph	**P1^{Oxy}a**		61%	88:12[a]
2		1,3-*syn*-**P3^{Oxy}aa**	1,3-*syn*-**P3^{Oxy}aa-H**	69%	87:13[b]
3		1,3-*syn*-**P3^{Oxy}aa**		67%	**67**:33[c]
4	Ph	**A1^{Oxy}a**		71%	83:17[a]
5		1,4-*anti*-**A4^{Oxy}aa**	1,4-*anti*-**A4^{Oxy}aa-H**	87%	83:17[b]
6		1,4-*anti*-**A4^{Oxy}aa**		64%	12:**88**[c]
7	n-pentyl	**P1^{Oxy}c**	1,3-*syn*-**P3^{Oxy}ca-H**	82%	90:10[a]
8		**A1^{Oxy}c**	1,4-*anti*-**A4^{Oxy}ca-H**	76%	75:25[a]
9	Cy	**P1^{Oxy}d**	1,3-*syn*-**P3^{Oxy}da-H**	77%	90:10[a]
10		**A1^{Oxy}d**	1,4-*anti*-**A4^{Oxy}da-H**	68%	80:20[a]

Structures are shown in relative configuration, selectivity was determined by NMR. [a] one-pot reaction by using **P1^{Z}** or **A1^{Z}** and **2a** as substrates. [b] Reduction by using isolated cyclization products **P3^{Z}** or **A4^{Z}**. [c] Reduction of the isolated cyclization products **P3^{Z}** or **A4^{Z}** by using cat. Pd/C H_2.

Given the above proposed mechanism, a one-pot reduction was examined to provide an additional stereocenter from the exocyclic olefin (Table 4). Again, **P1^{Oxy}a** and **A1^{Oxy}a** were selected as model substrates for such a development, but at this time $(EtO)_3SiH$ **2a** and IPr^{Me} were used to provide the right balance in enyne oxidative cyclization and the silane oxidative addition reactivities for later on reduction. To our delight, that could be done easily under otherwise the same condition except for 24 hrs reaction time (entry 1 and 4).[49] This discovery offered an new option to prepare vicinal side chains at 3,4-positions with high *syn*-diastereoselectivity. That selectivity was presumably a direct result of minimizing undesired steric repulsions between the silylated side chain and the NHC-Ni catalyst. Additional control experiments using isolated 1,3-*syn*-**P3^{Oxy}aa** and 1,4-*anti*-**A4^{Oxy}aa** as substrates showed highly comparable reduction selectivities as the one-pot hydrosilylative enyne cyclization-reduction (Table 4, entry 1, 2, 4, 5), indicating that the reduction might occur independently and after the primary catalytic cycle. Interestingly, our reduction showed a much stronger 3,4-*syn*-selectivity preference than the traditional Pd/C catalyzed hydrogenation, showing a

strong catalyst control character of our reduction (entry 3 and 6). Finally, enynes with different R^1 were examined briefly in the catalytic one-pot diastereoselective reduction (entry 1, 4, 7-9). The reactions proceeded smoothly, and the 3,4-*syn*-selectivity in **P1^{Oxy}** was higher than **A1^{Oxy}** in general.

Conclusions

In summary, highly efficient 1,3- and 1,4-diastereodivergent hydrosilylative enyne cyclizations were first established. The electronic effect of the NHC was found to be very crucial for the chemoselectivity (vs. alkene and alkyne direct hydrosilylation, and enyne [2+2+2] cycloadditions). Through the steric and electronic manipulations of the NHC and silane, the silane direct oxidative addition to Ni(0) was mitigated (Pathway **I**), and the enyne oxidative cyclization was preferred (Pathway **II**, NHC = IPr^{Cl}). Such changes in reactivity preference first united our highly diastereodivergent nickelacyclopentene formation strategy and the hydrosilylative enyne cyclization (*syn*-:*anti*- up to 98:2 and 6:94). Also, they formed the heterocycles bearing homoallylsilane (Pathway **II**) rather than vinylsilane (Pathway **I**) by Ni(0) catalyst for the first time (Homoallyl-:Vinyl-silane >95:5). Moreover, that change in reactivity preference has dramatically expanded the scope of the Ni(0) catalyzed hydrosilylative enyne cyclization, which was primarily limited to those with activated difluroalkene side chain and 5-member ring formation before. Finally, a one-pot reduction could occur using suitable NHC and silane (IPr^{Me} and $(EtO)_3SiH$), offering an option for adding additional stereocenter on the ring through NHC-Ni catalyst control. Further exploration along this line is now underway.

Experimental

General procedure for the catalytic hydrosilylative enyne cyclizations: 0.05 mmol IPr^{Cl}-Ni(0) catalyst was generated in situ in a glove box from $Ni(cod)_2$ and IPr^{Cl} in 2 mL toluene at r.t.. 0.5 mmol heteroenyne **P1^{Z}** or **A1^{Z}** and 4 mmol **triethylsilane 2b** in 1 mL toluene was added dropwise to the catalyst in 1 hr and stirred for 3 hrs. The reaction was worked up by following the general workup procedure. Yield and selectivity were determined by NMR except otherwise indicated. The products were obtained and separated by column chromatography. Enyne homo-dimerization, oligomerization, alkyne hydrosilylation, and a small amount of isomerization were obtained in some ineffective cases. No vinylsilane was observed on the heterocycle in general.

General procedure for the catalytic 1-pot reduction of the hydrosilylative enyne cyclizations: Same as the above except IPr^{Me}-Ni(0) was used as catalyst, **triethoxylsilane 2a** was used as silane and extended reaction time to 24 hrs.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx. X-Ray crystallographic data: CCDC 1972918 contain the data for this paper, and can be obtained from Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgement

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Diastereodivergent Hydrosilylative Enyne Cyclization Catalyzed by NHC-Ni(0)

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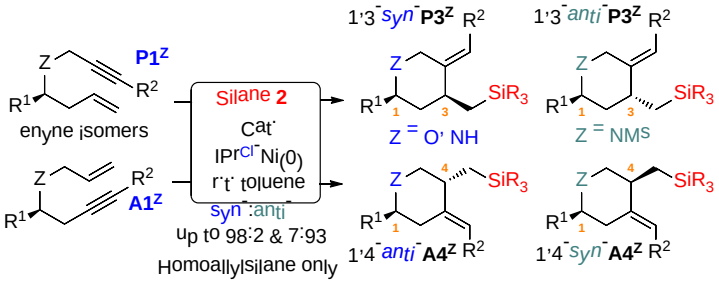

R^1 = linear/cyclic alkyls, alkenyls, aryls & heteroaryls

R^2 = H and alkyl; Allow Contiguous & Skipped Stereocenters Synth.

NHC Steric & Electronic Controlled Cyclization over Direct Hydrosilylation

