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NHC-Ni(0) Catalyzed Diastereodivergent Hydroacylative Enyne Cyclization: Synthesis of Heterocycles bearing γ-Enone

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Abstract. NHC-Nickel(0) catalyzed 1,3- and 1,4-diastereodivergent hydroacylative heteroenyne cyclization with aldehydes was achieved (Syn-:Anti-, switchable from up to 1:99 to 98:2). Both sets of heterocyclic diastereomers are accessible via this route, with a high γ-:α-enone structure ratio. Preliminary DFT investigations indicated that the manipulation of the N-substituent exerts a direct influence on the diastereoselectivity of NHC-nickelacyclopentene formation. The energy differences associated with the endocyclic bond angle (C-Z-C) changes noted in the calculations, might possibly account for the broad scope and high diastereodivergent selectivity observed.

Keywords: Insertion; Olefination; Acylation; Nickel; Heterocycles; N-heterocyclic carbenes

Introduction

Multi-substituted heterocycles are commonly encountered structures that often exhibit important biological activities and have diverse applications. Hence, catalytic stereoselective approaches toward heterocycles continue to be extensively researched.[1] Transition metal-catalyzed cross-cycloaddition and cyclo-isomerization are powerful techniques whereby π-systems are fused to create various cyclic structures.[2] Through the use of aldehydes as reaction partners, highly atom-economical and regioselective hydroacylative enyne cyclizations have been achieved, delivering cyclic products with useful enone structures (Fig. 1a, paths a and b).[3] High *ee*s have been achieved by utilizing various chiral phosphorus ligands,[4] however synthesis of multi-substituted heterocycles with high 1,3- and 1,4-diastereoselectivity (d.r.) remains difficult. For instance, NHC-Ni(0) was found to be effective in 1,3-syn selective carbocycle synthesis and provided α-enones as products, whereby the selectivity was largely governed by the sterically bulky OTBS group on the enyne (Fig. 1b).[3e, 3f][5]

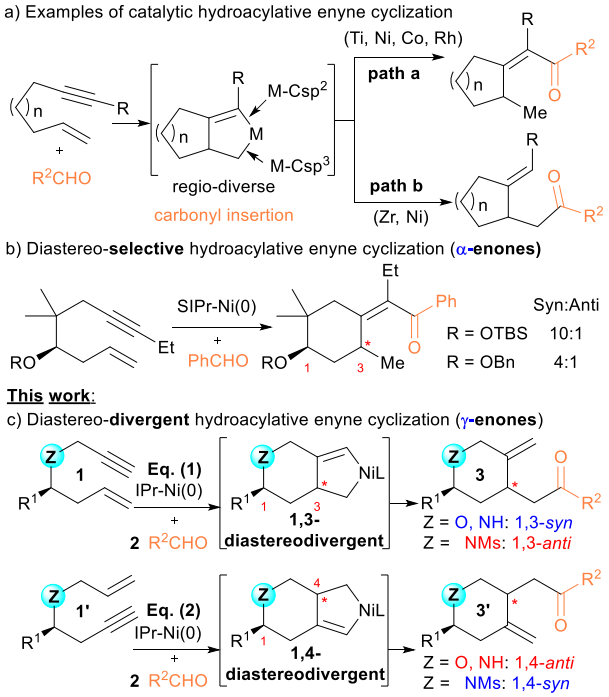
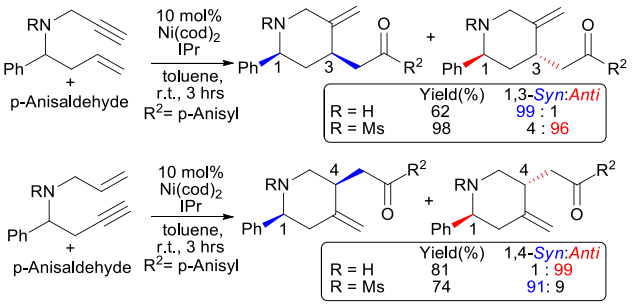


Figure 1. Transition metal-catalyzed hydroacylative enyne cyclization.

However, its effect on 1,7-oxaenyne diastereoselective hydroacylation was not examined, and a cyclic template was employed to assist in diastereoselective azacycle formation. The development of a new hydroacylative strategy that is applicable to the synthesis of diverse heterocycles and can tolerate both small and large substituents for a high d.r. is therefore expected to be essential for further advancement in this

field. Ideally, the strategy should be diastereodivergent, and applicable to the synthesis of both 6- or 7-membered heterocycles from enynes with conformationally less restricted spacers.[6]

As part of our continuing efforts on the use of NHC-Ni as a catalyst for the development of novel hydroalkenylation methods and gem-olefin synthesis,[7] we have recently developed a catalytic reductive hydroalkenylation for the generation of heterocycles, by using hetero-substituted enynes as substrates and 1-phenylethanol as the terminal reductant.[8] By manipulating the N-substitution on enynes, both sets of diastereoisomers could be obtained with high selectivity on demand. Preliminary results indicated that the strategy may also be applicable to simple azaenyne hydroacylative cyclizations if p-anisaldehyde is employed instead of a reductant, which offers higher functionalized heterocycles with γ-enone structures (Scheme 1). However, the reasons for these similarities and high selectivities remain unclear. In this regard, herein we report our recent efforts on the diastereoselective hydroacylative synthesis of heterocycles. We envisage the provision of versatile acyl side chains for further transformations and valuable carbon frameworks via this strategy, improving on previously reported reductive hydroalkenylations. Additionally, through DFT calculations, we hope to offer new insights that are beneficial to rationalizing diastereodivergent transformations.



Scheme 1. Our preliminary results on diastereodivergent hydroacylative cyclization of simple azaenynes[8]

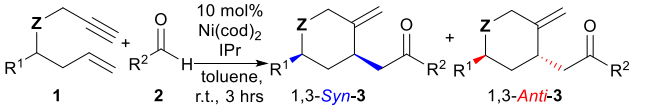
Results and Discussion

Optimization of selective γ-enone synthesis

We commenced our investigation by reacting α-substituted 1,7-oxaenyne **1a** and aldehyde **2**, using the IPr-Ni(0) catalyst in toluene at r.t. (Table 1, Eq. 1). To our delight, the desired oxaenyne hydroacylative cyclization was successful, yielding pyrans with high γ–: α-enone structure ratios and excellent 1,3-d.r.s for the first time (entries 1 – 8, **3aa** – **3ah**, and 1,3-syn-:anti- > 95:5). Electron-rich aldehydes were advantageous for competing with several other undesired, yet commonly observed, reactivities of

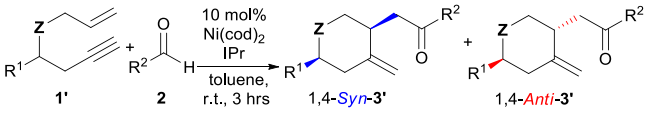
Table 1. Diastereo- and regioselective hydroacylative oxaenyne and azaenyne cyclization. [a,b]

1,3-relations (Eq. 1)



entry	R^1	Z (**1**)	R^2 = (**2**)	**3**	Yield **3** (%)	*Syn*:*Anti* **3**
1	Ph	O (**1a**)	4-OMe-Ph (**2a**)	**3aa**	82 9[d] 20[e]	> 95:5[c]
2			Ph (**2b**)	**3ab**	63	> 95:5[c]
3			4-NMe_2-Ph (**2c**)	**3ac**	84	> 95:5[c]
4			2-NMe-pyrrolyl (**2d**)	**3ad**	80	> 95:5[c]
5			2-Me-4-OMe-Ph (**2e**)	**3ae**	57	> 95:5[c]
6			2-thiophenyl (**2f**)	**3af**	46	> 95:5[c]
7			4-F-Ph (**2g**)	**3ag**	90[f,g]	> 95:5[c]
8			*t*Bu (**2h**)	**3ah**	62	92:8
9	Me	O (**1b**)	4-OMe-Ph (**2a**)	**3ba**	90	> 95:5[c]
10		NH (**1c**)		**3ca**	74	98:2[h]
11		NMs (**1d**)		**3da**	92	11:89
12		NTs (**1i**)		**3ia**	89	36:64
13	Ph	NH (**1e**)	*t*Bu (**2h**)	**3eh**	59[i]	>95:5[c]
14		NMs (**1f**)		**3fh**	90	9:91
15		NMs (**1f**)	4-OMe-Ph (**2a**)	**3fa**	98	4:96[j,k]
16		NTs (**1h**)		**3ha**	92	34:66
17	p-Anisyl	O(**1g**)	4-OMe-Ph (**2a**)	**3ga**	93	>95:5[j]

1,4-relations (Eq. 2)



entry	R^1	Z (**1′**)	R^2 = (**2**)	**3′**	Yield **3′**(%)	*Syn*:*Anti* **3′**
18	Ph	O (**1′a**)	4-OMe-Ph (**2a**)	**3′aa**	61	6:94
19	Me	O (**1′b**)		**3′ba**	55	14:86
20	Me	NH (**1′c**)	4-OMe-Ph (**2a**)	**3′ca**	58	9:91
21		NMs (**1′d**)		**3′da**	81	> 95:5[c]
22	Ph	NH (**1′e**)	*t*Bu (**2h**)	**3′eh**	79	<5:95[c]
23		NMs (**1′f**)		**3′fh**	61	90:10

[a] 0.5 mmol **1** or **1′** and 0.75 mmol **2** in 1 mL toluene was gradually added to 0.05 mmol NHC-Ni(0) catalyst in 2 mL toluene at 2 mL/hr, and the mixture was stirred at r.t. for 3 h before work up. [b] Products are shown in relative configurations. [c] Minor stereoisomer was not observed in the ^{1}H NMR spectra, and was not separable/ detected in GCMS. [d] IMes was used. [e] 20 mol% Ni, Ni:PCy_3 = 1:2. [f] 20 mol% catalyst, **1a**:**2g** = 1:1.2. [g] R^2 = 4-CF_3-Ph failed. [h]

By GCMS. [i] Ran at 0.04 M of **1e**. [j] Structure determined by XRD. [k] Data collected from ref. 8.

structurally flexible terminal enynes.[9] Possible side reactions, including alkyne oligomerization,[10] aldehyde,[11] or enyne[12] homo-dimerization and alkene or alkyne hydroacylation,[13] were all inhibited in the absence of gem-substitution assistance (use of α-R^1 has a limited impact on the 1,7-enyne conformation (discussed later).

Notably, the use of significantly smaller R^1 vs. Ph likewise delivered high 1,3-syn-:anti- d.r.s under the same conditions (entries 1 and 9), indicating that the size of R^1 is not the most critical factor in determining the d.r. Moreover, a high d.r. was also observed when smaller ligands were employed (entry 1, IPr vs. IMes and PCy_3). Although the yield was lowered dramatically, such a comparison clearly indicated that the high d.r. was not controlled by the ligand size.[14] In addition, when **1′** was used instead of **1** (Fig. 1c, allyl- vs. propargyl-Z), the synthesis of pyrans with high 1,4-anti-:syn- d.r.s and high γ-:α-enone structure ratios was accomplished (Table 1, Eq. 2, entries 18-19). The new stereocenter formed at C4 is further away from R^1 than in the 1,3- heterocycles, suggesting that the highly diastereoselective synthesis was not a direct result of minimizing the steric repulsion between R^1 and ligand substituents.

Azaenynes with Z = NH provided similar results to the corresponding oxaenynes in the synthesis of both 1,3- and 1,4-diastereomers (entries 9 and 10, 19, and 20). More interestingly, inverse diastereoselectivity was observed when Z = NMs (entries 11, 14, 15, 21, and 23). This outcome appears to be common for a variety of R^1 and R^2, as it was observed for both aromatic and aliphatic substituents (entries 11 and 15; entries 14 and 15). However, the use of a bulkier sulfonyl group (NTs vs. NMs) caused a dramatic drop in d.r. (entry 11 vs. 12; 15 vs. 16), which is unexpected in view of the steric considerations and thus deserves further investigation (see later DFT calculations).

Substrate scope of heteroenynes for γ-enones

Next, the substituent effect of the hetero-substituted enynes on this hydroacylative enyne cyclization was studied under our standard conditions using IPr-Ni(0) as a catalyst at r.t. (Table 2). First, the size of the α-substituent (R^1) and the effects of the β-substituent were evaluated (Set A). The results indicated that not only phenyl, but also cyclic and linear alkyl chains can be utilized to provide the desired reactivity and selectivity (high γ-:α-enone ratio, high d.r., and a reliable trend in diastereodivergent selectivity). Moreover, both syn- and anti-substituents at the β-position were tolerated, which allows for a general strategy for the assembly of well-defined 1,2,3-contagious stereocenters with high selectivity in 6-membered heterocycles bearing a γ-enone.

Second, in addition to being applicable to enynes with propargyl-Z, the above-discussed strategy was also valid for enynes with allyl-Z (Set B), as exemplified in Table 1 Eq. 2. This finding complements the above 1,3-diastereodivergent synthesis by offering access to structurally analogous heterocycles with well-defined 1,2,4-skipped stereocenter substitution patterns. Third, in addition to its applicability to acyclic 1,7-enynes, the method was found to be practical for cyclic enynes and 1,8-enynes (Table 2, Sets C and D). Although a higher catalyst loading was required for hetero-cycloheptene synthesis, the diastereodivergent synthetic efficiency was nonetheless remarkable considering these challenging examples. The preferred relative configuration of 1,8-enyne stereocenters was directed again by Z, however it was opposite to that observed for 1,7-enynes.

In summary, the hydroacylative cyclizations generally proceeded with high yields and exhibited a broad scope. The exocyclic gem-olefin was found to be stable under mild hydroacylative cyclization conditions. No further hydroacylation, isomerization or carbonyl-ene reactions were noted by NMR spectroscopy, hence a versatile handle is provided for subsequent manipulations and for generating new stereocenters. In addition, the high γ-:α-enone ratio, high d.r., and the diastereodivergent selectivity trend were well-preserved in all the cases examined. This generality highlighted the competitiveness and unique advantage of our strategy for preparing highly substituted heterocycles, which avoids catalyst redesign and synthetic route revision for the generation of the opposite isomer.

Rationale for diastereodivergence

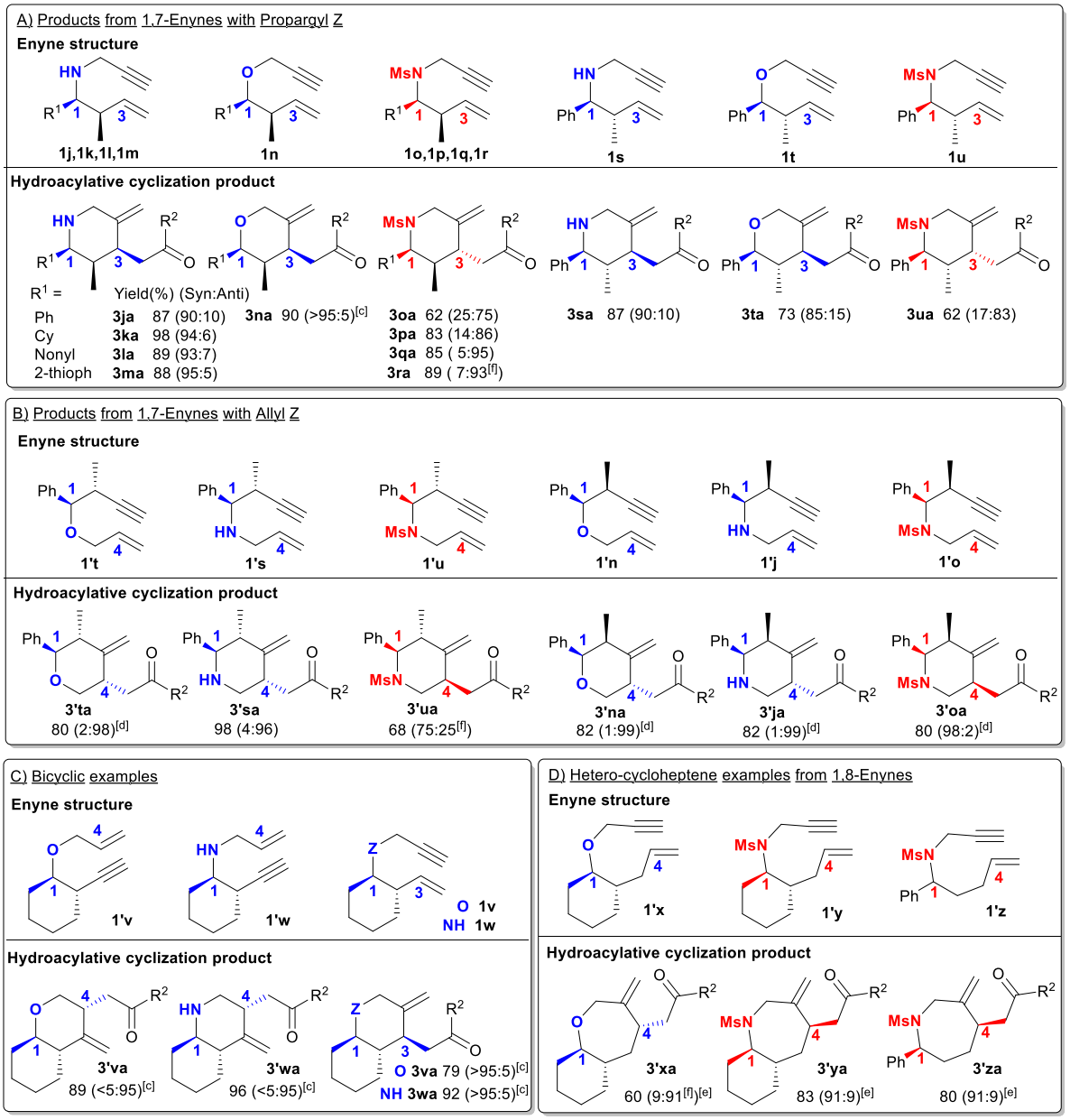
Although Z could possibly affect the enyne conformational preference, conformational analysis of **1c** and **1d** via DFT calculations suggested that the enynes remain very flexible and do not display a single dominant conformation irrespective of Z, implying that the diastereodivergence did not arise from a conformational constraint on the enyne.[15] While the prevailing 1,3-allylic strain model[16] could possibly explain the axial preference of α-Me with NMs enynes and therefore the d.r. switch, the lower d.r.s observed with sterically bulkier NTs compared to NMs cases, as noted in Table 1 (entry 11 vs. 12, and 15 vs. 16), were intriguing and led us to pursue a new model, supplementary to the explanation based on the 1,3-allylic strain.

Given that comparable d.r.s were obtained irrespective of the partners employed (alcohol or aldehyde), we reasoned that the effective inversion of diastereoselectivity was determined solely by the nickelacyclopentene intermediate. This is supported by DFT calculations of the relative stability of *syn*- and *anti*-nickelacyclopentene intermediates with a simplified NHC (Table 3),[17] which successfully predicted the inversion of diastereoselectivity with a different Z in both propargyl and allyl heteroenynes

(Fig. 1c, Eq. 1 and 2). Whereas O or NH enynes favor intermediates with equatorial α-R^1 (Me), NMs enynes favor intermediates with axial α-R^1 (Me).

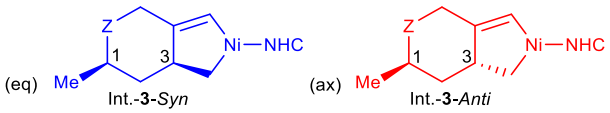
We reasoned that the slight difference in the hybridization of N in Z could modify the natural preference of the endocyclic C-Z-C angle (Fig. 2a). As the N lone pair becomes more delocalized, the p-character of the lone pair increases and the p-character of the N-C orbital decreases correspondingly, leading to a preference for expanding the endocyclic C-Z-C angle (Fig. 2a). In addition, α-R^1 can also affect the nearby endocyclic angle (Fig. 2b), with axial R^1 increasing the angle to a larger extent, presumably to reduce undesired 1,3-diaxial interactions. Thus, we propose that for NMs enynes, axial α-R^1 will reinforce the expansion of the endocyclic angle and is hence favored over the alternative intermediate with equatorial α-R^1. In contrast, for O and NH enynes, which prefer a smaller endocyclic angle, intermediates with equatorial α-R^1 are favored.

Table 2. Heteroenyne scope for diastereodivergent hydroacylative cyclizations with aldehydes.[a], [b]

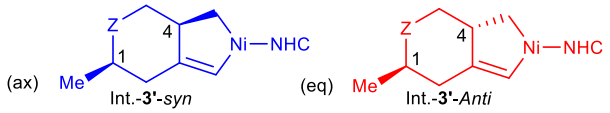


[a] Standard procedure was followed. Enyne and cyclization products are shown in relative configurations. [b] Yields refer to the major stereoisomer only, and the *syn*-:*anti*-selectivity is shown in parenthesis. [c] Minor stereoisomer was not observed in NMR, and was not separable/ detected in GCMS. [d] By GCMS. [e] 20 mol% catalyst. [f] Structure determined by XRD.

Table 3. Relative stabilities of NHC-nickelacyclopentene intermediates from α-methyl heteroenynes **1b**, **1c**, **1d** and **1′b**, **1′c**, **1′d**.



entry	Z	1,3-***Syn***, ***Anti*** Rel. G (kcal/mol) [a]	1,3-***Syn***:***Anti*** Hydroacylative	Reductive [b]
1	O	**0**, +2.9	**95**:5	**95**:5
2	NH	**0**, +2.3	**98**:2	**95**:5
3	NMs	+3.0, **0**	11:**89**	12:**88**



entry	Z	1,4-***Syn***, ***Anti*** Rel. G (kcal/mol) [a]	1,4-***Syn***:***Anti*** Hydroacylative	Reductive [b]
4	O	+2.2, **0**	14:**86**	11:**89**
5	NH	+1.7, **0**	9:**91**	3:**97**
6	NMs	**0**, +3.7	**96**:4	**94**:6

[a] Level of theory: SMD(toluene)-B3LYP-D3(BJ)/def2-TZVPP//B3LYP-D3(BJ)/6-31G*-SDD.[18] [b] Data were collected from hydroalkenylation products in ref. 8.

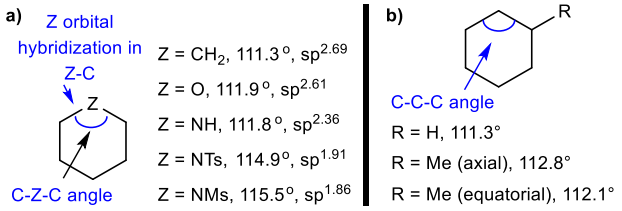


Figure 2. Effect of Z and α-R on the C-Z-C angle. **a)** Endocyclic C-Z-C angle and hybridization of the Z-centered orbital that is engaged in endocyclic Z-C bond formation (from NBO analysis[19] at B3LYP-D3(BJ)/6-31G*). **b)** Effect of axial and equatorial Me on the endocyclic angle.

Indeed, the endocyclic C-Z-C angles of the nickelacyclopentene intermediate from DFT calculations appear to be consistent with the above proposal (Fig. 3). For Z = O or NH, the intermediate with a smaller C-Z-C angle is favored, as it is closer to the natural preference of the C-Z-C angle and additionally minimizes 1,3-diaxial interactions. For Z = NMs, the intermediate with a larger C-N-C angle is favored, as it better accommodates the higher p-character of N. In fact, the X-ray structures of the cyclization products indicated a large C-Z-C angle for **3fa** with Z = NMs (114.7°) and a small C-Z-C angle for **3ga** with Z = O (111.5°) (Fig. 4). Furthermore, the endocyclic angle widening effect of the α-R^1 group diminishes rapidly with distance; whereas the *ortho-endocyclic* angle in methylcyclohexane is increased by 1.5° by axial-Me, the *meta-endocyclic* angle is decreased only by 0.1°, which is practically negligible. Correlation of the bond angle changes according to α-substitution and Z, therefore, implies their significantly higher impact on the d.r., compared to that of the β-position, and hence the stereochemistry at the β-position has a relatively small effect on the diastereoselectivity. Based on DFT calculations and analysis of the endocyclic C-Z-C angle, a proposed catalytic cycle and mechanism for Z-directed 1,3- and 1,4-diatereodivergent hydroacylative enyne cyclizations are presented in Figure 5.[3f] First, the selected choices of Z and enyne direct an intramolecular diastereodivergent enyne oxidative cyclization with NHC-Ni(0) as discussed above.[20] Subsequent aldehyde insertion to the Ni-Csp^3 center gives the corresponding oxanickelacycloheptenes. Finally, typical β-H elimination followed by reductive elimination of H and alkenyl groups on Ni provides the desired products and regenerates the catalyst.

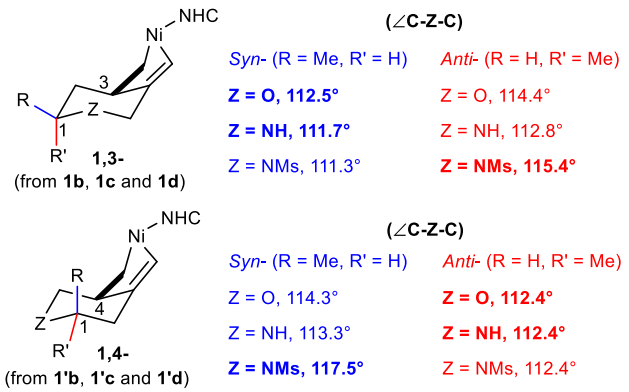


Figure 3. Endocyclic C-Z-C angle for the NHC-nickelacyclopentene intermediates. [a]

[a] The more stable intermediate is denoted in bold. From DFT calculations at SMD(toluene)-B3LYP-D3(BJ)/def2-TZVPP//B3LYP-D3(BJ)/6-31G*-SDD(Ni).[18]

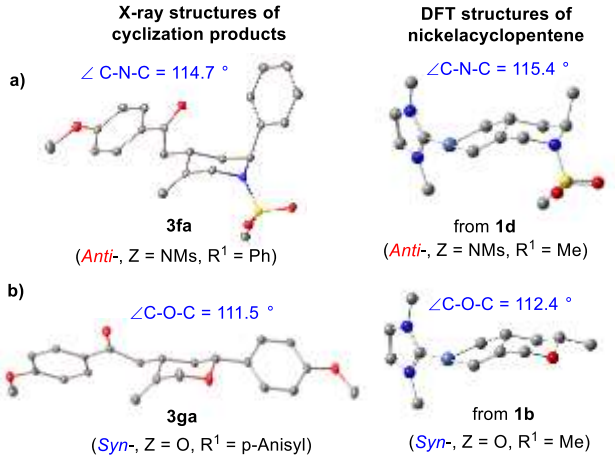


Figure 4. X-ray structures of the cyclization products and DFT structures of NHC-nickelacyclopentene intermediates.

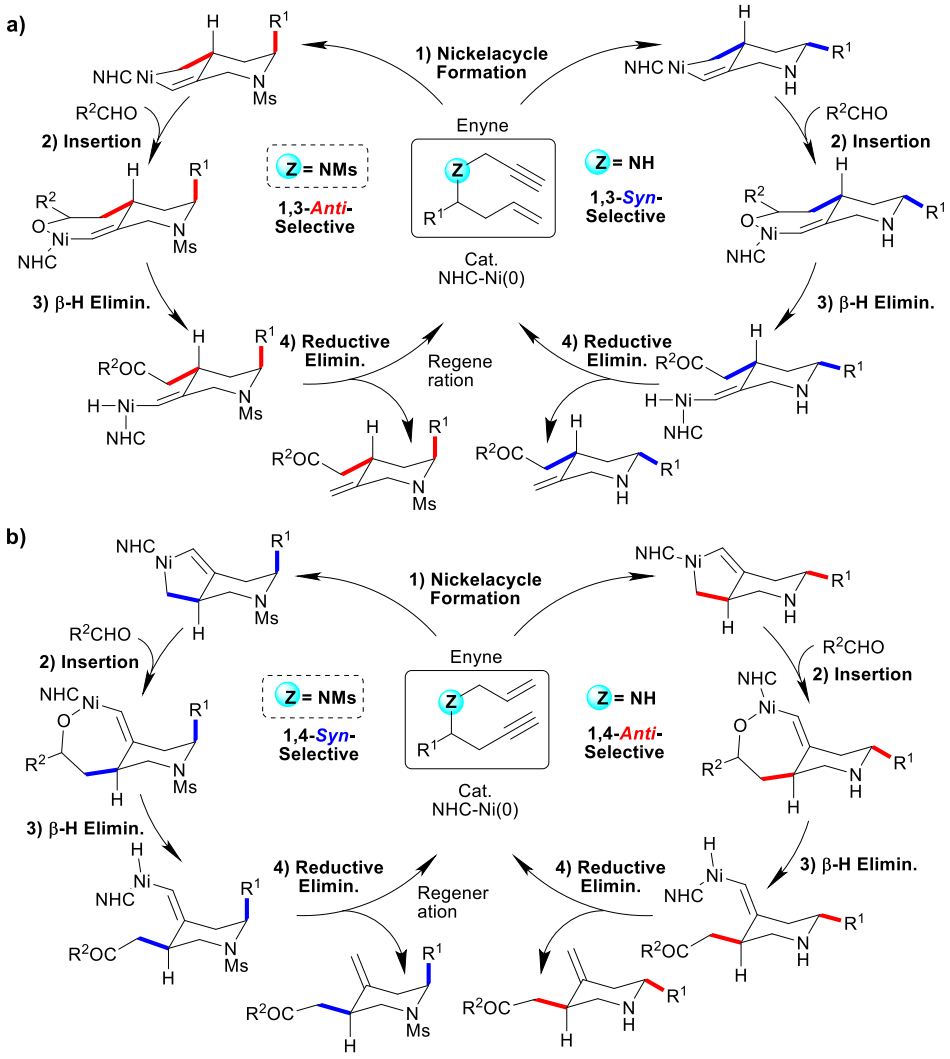


Figure 5. Proposed mechanism for the NHC-Ni(0)-catalyzed diastereodivergent hydroacylative enyne cyclization: **a)** 1,3-relations. **b)** 1,4-relations.

Conclusion

In summary, NHC-Ni(0) catalyzed highly diastereodivergent and regioselective hydroacylative 1,n-heteroenyne cyclizations with aldehydes were achieved. The choice of hetero-substituents on the enyne and that of π–systems (n = 7, 8, switchable from 98:2 to 1:99), provides access to diverse densely substituted heterocycles bearing γ-enone structures. The success of the diastereodivergent synthesis is attributed to the selective formation of a more stable nickelacyclopentene intermediate, revealed with the aid of DFT calculations at this stage, whose stability is strongly affected by the NBO of the nickelacycle and the Z of the selected enone. This feature was found to be highly competitive in terms of changes in energy levels; hence, the methodology could tolerate diverse enyne substitution patterns with variable R sizes and can be implemented for the assembly of contagious and skipped stereocenters on demand. Moreover, as it operates independently of the ensuing intermolecular bond formation events (e.g. carbonyl insertion with aldehyde, and σ-bond metathesis with alcohol), it could serve as a key intermediate for related developments with other coupling partners. In practice, the method is also operationally simple, with a single catalyst being used for a broad range of heterocycle diastereodivergent syntheses. Overall, the strategy is expected to have broad potential applications in other metalacyclopentene-associated cyclizations. Investigations into the utility of this discovery are currently underway.

Experimental Section

Standard Procedure: A solution of **1** and **2** in 1 mL toluene was added to a catalyst mixture of IPr and $Ni(cod)_2$ in 2 mL toluene (0.05 mmol, 10 mol% each) at 2 mL/h. After stirring for 3 h at r.t. and workup, the d.r.s and yields were determined by crude ^1H NMR spectroscopy and isolation. The relative configurations of the major products were determined by NOESY and by comparison with the isomers obtained by other Z groups (see SI for details).

All DFT calculations were carried out at SMD(toluene)-B3LYP-D3(BJ)/def2-TZVPP//B3LYP-D3(BJ)/6-31G*-SDD(Ni) level of theory[18] using the Gaussian 16 program package,[21] and hybridization[19a] was analyzed with NBO 7.0 program[19b] (see SI for details).

X-Ray Crystallographic Data: CCDC-1972921 (**3ga**), 1972922 (**3fa**), 1972925 (**3′ua**), 1972924 (**3ra**), and 1972923 (**3′xa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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NHC-Ni(0) Catalyzed Diastereodivergent Hydroacylative Enyne Cyclization: Synthesis of Heterocycles bearing γ-Enone.

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Diastereodivergent hydroacylative cyclization from enynes and aldehydes by Hetero-Substituent Manipulations