NHC-Ni catalyzed 1,3- and 1,4-diastereodivergent heterocycle synthesis from hetero-substituted enyne

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Diastereodivergent heterocycle synthesis has been recognized as an important tool for drug discovery in recent years, yet strategies based on nickelacycle formation have not been established. Here, we report a NHC-Ni catalyzed highly 1,3- and 1,4-diastereodivergent heterocycle synthesis from enyne, which is achieved by manipulating the enyne N-substituent (allowing switching of selectivity from up to 2:98 to 98:2). The key to success is the efficient diastereodivergent formation of a nickelacyclopentene, with broad enyne scope at mild conditions, which subsequently provides reductive hydroalkenylation, acylation and silylation products on demand. Diastereoisomers which are sterically hard to distinguish or difficult to access by conventional routes are now accessible easily, including those with very similar 4°, contiguous and skipped stereocenters.
Heterocycles bearing multiple stereocenters are common structural motifs in many biologically active molecules. Given that different diastereomers may exhibit diverse bioactivities, synthesis of individual diastereomers is of great importance. Multi-substituted hydropyran and piperidine skeletons with exocyclic olefin are key core structures or precursors in many biologically active natural products and drug molecules. Over the years, various innovative strategies and elegant synthetic methods have been developed for (di)stereodivergent heterocycle synthesis. Substituents in 1,2-, 1,3- or 1,4-diastereodivergent relationships could be built by tailor-made ring closure methods efficiently, which are controlled often by selective facial attack either on prochiral sp² center or on radical acceptors. Some were controlled efficiently by solvent assistance and steric repulsion among substituent Rs on ring closure, or by redesign of reaction pathways or catalysts. Yet, some are limited severely by the choice of nucleophiles and polarized tether structures. Undesired steric repulsion among substituents (mismatch) as well as the high demands of functional group often limited the scope and the efficiency of the process.

Transition-metal-mediated metallacyclopentene formation by using hetero-substituted enyne or related variant is a very powerful technique in catalytic heterocycle synthesis and is a common intermediate for various multi-component coupling. Highly 1,3-syn-diastereoselective synthesis has been achieved in a few examples according to the steric demands of enyne substrates and metallacycle formation. The scope is mostly limited to those equipped with cyclic template, some requires Thorpe-Ingold effect assistance, and no efficient diastereodivergent example has been developed. Developing a novel and general diastereodivergent strategy which is not relied primarily on minimizing undesired steric repulsion among Rs is therefore useful, especially for those sterically less accessible and higher substituted products.

Here, a NHC-Ni catalyzed highly diastereodivergent heterocycle synthetic method is thus developed. That is based on conformational cooperation in the nickelacyclopentene formation step, directed by the choice of N-substituents on the heteroynes, and promoted by NHC-Ni catalyst π-electronic effect. By trapping the NHC-nickelacyclopentenes with alcohol, silane and aldehyde, 1,3- and 1,4-diastereodivergent reductive hydroalkenylation silylation and acylation products are obtained.

**Results**

Optimization for N-substituents directed diastereodivergent reductive hydroalkenylation. Our study commenced with a set of simple 1,7-heteroenynes 1a–f having a racemic stereocenter and terminal propargyl-Z for a study of N-substituents on nickelacyclopentene selective formation (Table 1, entry 1–6, Eq. (1), Z = O, NH or NMs). The condition employed is as simple as an NHC-Ni(0) catalyzed enyne cycloaddition reported in the literature with shorter tethers, except 1-phenylethanol is used as NHC-Ni(0) catalyzed enyne cycloaddition reported in the literature with shorter tethers. The condition employed is as simple as an NHC-Ni(0) catalyzed enyne cycloaddition reported in the literature with shorter tethers, except 1-phenylethanol is used as NHC-Ni(0) catalyzed enyne cycloaddition reported in the literature with shorter tethers. The condition employed is as simple as an NHC-Ni(0) catalyzed enyne cycloaddition reported in the literature with shorter tethers. The condition employed is as simple as an NHC-Ni(0) catalyzed enyne cycloaddition reported in the literature with shorter tethers, except 1-phenylethanol is used as NHC-Ni(0) catalyzed enyne cycloaddition reported in the literature with shorter tethers.

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**Fig. 1** Bioactive targets. Examples of bioactive multi-substituted heterocycles involved exocyclic olefin precursors.

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**Fig. 2** Strategy for catalytic diastereodivergent/selective heterocycle synthesis from π-systems. a) By condition modification. b) By cyclic template. c) By steric substituents. d) By hetero-substituted enynes.

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**ARTICLE COMMUNICATIONS CHEMISTRY | https://doi.org/10.1038/s42004-020-0299-9 | www.nature.com/commschem**
configuration directed by allyl-Z was found different from the propargyl-Z cases (Tables 1 and 2, e.g., allyl-NMs favored 1,4-syn-, propargyl-NMs favored 1,3-anti-).

At first, one might consider the steric difference in Z is sufficient to explain the above diastereodivergent synthesis. Yet, very similar efficiency among enynes having different sizes of R1 in both Eqs. (1) and (2) caught our attention. That made us suspected it was not just directed by simple steric interaction, so Z with different steric and electronic property was evaluated next (Supplementary Table 2). First, using sterically bulkier Z than NMs were found not helpful in favoring anti-selectivity further but led to a drop in selectivity (Table 1, N-Ms vs -Ts and -Bn, entry 5, 7 and 8). This is unusual since a larger Z like NTs or NBn is expected to favor a stronger steric repulsion among R1 and Z for more anti-product. Second, using a bulky N-Bn could favor the syn-product as N-H did (Table 1, entry 3, 8). These 2 sets of results are in sharp contrast to the former rationale that based on steric effect increment on Z from NH to NMs alone. Altogether, the diastereodivergent synthesis as noted above was attributed mainly to the use of Z with different electronic property. Yet, the size of Z is still critical in terms of diastereodivergent efficiency, in which using small Z could avoid competing steric interactions. Overall, the diastereodivergent synthesis efficiency and preference did not follow the order of the Z sizes to change gradually (Size: N-H < Ms < Bn~Ts, while the Syn:Anti-ratio ranged from 96:4 to 6:94 in order of N-H > Bn > Ts > Ms). Similar phenomenon was noted in Table 2, Eq. (2), entry 3 and 5.

Ligand effect on diastereoselectivity. The above results prompted us to screen ligands with different steric and electronic properties by using 1a, 1c and 1e as well as 2a, 2c and 2e

### Table 1 Substituent effects on NHC-Ni catalyzed diastereodivergent reductive hydroalkenylation of enyne with propargyl Z.°

| Entry | Z   | R1 | Ligand | Product | Syn:Anti 3:3 | Sy n:Anti 4:4 | Yield (%) |
|-------|-----|----|--------|---------|--------------|--------------|-----------|
| 1     | 1a  | O  | Ph     | 3a      | 95:5         | n.a.         | 74        |
|       |     |    |        |         |              |              |           |
| 2     | 1b  | Me | IPr   | 3b      | 95:5         | n.a.         | 78        |
| 3     | 1c  | NH | Ph     | 3c      | 96:4°        | n.a.         | 81        |
| 4     | 1d  | Me | IPr   | 3d      | 95:5         | n.a.         | 62        |
| 5     | 1e  | NMs| Ph     | 4'e     | n.a.         | 6:94°        | 84        |
| 6     | 1f  | NMs| Me     | 4'd     | n.a.         | 12:88°       | 58        |
| 7     | 1g  | NTs| Ph     | 4'g     | n.a.         | 40:60°       | 30        |
| 8     | 1h  | NBn| IPr   | 3i      | 88:12°       | n.a.         | 48        |

* a See Methods section for procedure. Homo-dimerization and oligomerization were obtained in some ineffective cases. Products were shown in relative configuration only.

### Table 2 Substituent effects on NHC-Ni catalyzed diastereodivergent reductive hydroalkenylation of enyne with allyl Z.°

| Entry | Z   | R1 | Ligand | Product | Syn:Anti 5:5 | Syn:Anti 6:6 | Yield (%) |
|-------|-----|----|--------|---------|--------------|--------------|-----------|
| 1     | 2a  | O  | Ph     | 5'a     | 8:92         | n.a.         | 78        |
|       |     |    |        |         |              |              |           |
| 2     | 2b  | Me | IPr   | 5'b     | 11:89        | n.a.         | 64        |
| 3     | 2c  | NH | Ph     | 5'c     | 9:97°        | n.a.         | 51        |
| 4     | 2d  | Me | IPr   | 5'd     | 7:93         | n.a.         | 76        |
| 5     | 2e  | NMs| Ph     | 6e      | n.a.         | 93:7°        | 73        |
| 6     | 2f  | Me | IPr   | 6f      | n.a.         | 85:15°       | 21        |

* a See Methods section for procedure. Homo-dimerization and oligomerization were obtained in some ineffective cases. Products were shown in relative configuration only.

b By GCMS.
In general, using bulky NHC is one of the keys to obtain desired reactivity. Indeed, non-selective oligomerization and dimerization was noted in IMes and PCy3 (Table 1, entry 5). More interestingly, the NHC electronic effect has a strong impact on the diastereodivergent efficiency in both equations and IPr performed much better than SIPr in general (Table 1, entry 1, 5; Table 2, entry 1, 5), in which dramatic drops were observed when using Z=NMMe and SIPr. This result suggested that the use of NHC with lower π-accepting ability is highly desirable for higher diastereodivergent efficiency, given that IPr and SIPr are very similar in size and σ-donating power.34,35

Also, it showed that the above is not entirely a Z controlled process.

Substrate scope of diastereodivergent reductive hydroalkenylation. The fine-tuned reductive hydroalkenylation reactivity, which was brought by propargyl-/allyl-Z, 2° alcohol and NHC-Ni cooperation, also came with a broad scope of 1 and 2 (Fig. 3). It provided a general access to functionalized hydroalkenylation products (3 and 6, 4’ and 5’) in one step by simply using an in situ generated catalyst from over-the-counter sources. Enynes with aryl and alkyl substitutions (Set 1), with internal alkenes and alkynes (Set 2 and 3), with nearby stereocenter interference at 2-position (Set 4), with gem-disubstituted alkenes (Set 5) and with a longer chain length (Set 6) are all good substrates for this reductive hydroalkenylation (Eqs. (1) and (2)).

Fig. 3 Scope of the diastereodivergent reductive hydroalkenylation of enyne by NHC-Ni(0) catalyst and 1-phenylethanol. See Methods section for hydroalkenylation procedure; see Tables 1 and 2 for Eqs. (1) and (2). Product syn:anti-selectivity was determined by NMR, yield of desired product in relative configuration is in parenthesis. a By GC/MS. b 2 h addition, to suppress oligomerization. c 20 mol% catalyst. d IPrMe was used instead of IPr. e enyne: alcohol = 1:1.5, to avoid undesired enyne direct reduction. f 3 equiv. of NaBH₄, to avoid acetophenone insertion (from the 1-phenylethanol).
organometallic reagents, the rearrangement of side chains or the stoichiometric catalysts, the traditional steric approaches, the cyclic products as well as isomers. Overall, it complements to having marginal steric differences are hard to make selectively (Set 1, Eqs. (1) and (2)). Several notable results deserve further comment. First, the switching is not primarily on steric repulsion (Set 1, Eqs. (1) and (2)). Second, the method can still perform even when interfered by an extra 2-substituent at syn/anti-relative configuration (Set 4). This indicated that such gauche interactions are not competitive enough to the desired preference directed by our strategy (e.g., Z directed nickelacyclopentene forming step at the start (a 3 x C bond).

Discussion
The precise mechanism for our desired reactivity and the diastereodivergent strategy are still under investigation, yet some insights were obtained from the studies that used CD3OH, ArCHO and TESH instead of 1-phenylethanol (Fig. 4). First, using CD3OH in the reductive hydroalkenylation of ketone, and (ii) Acyclic alkenol (Supplementary Methods).

The robust reactivity also came along with moderate to excellent 1,3- and 1,4-diastereodivergent efficiency (e.g., from up to 2:98 to 98:2). Several notable results deserve further comment. First, the diastereodivergent synthesis efficiency is excellent even in cases with substituents as small as Me. It highlighted that the basis of this robust reactivity is not primarily on steric repulsion (Set 1, Eqs. (1) and (2)). Second, the method can still perform even when interfered by an extra 2-substituent at syn/anti-relative configuration (Set 4). This indicated that such gauche interactions are not competitive enough to the desired preference directed by our strategy (e.g., Z directed nickelacyclopentene forming step at the start (a 3 x C bond).

Second, by using ArCHO or TESH as enyne reaction partners in place of alcohol, several sets of highly efficient diastereodivergent acylations or silylations were achieved, respectively (Fig. 4b, c)25-26. The excellent diastereodivergent synthesis efficiency and trend noted at here are comparable with the above reductive hydroalkenylation (Tables 1, 2, Fig. 3). This strongly suggested the strategy is related to a common diastereodivergent nickelacyclopentene formation step, and not by an in situ generated Ni(II)H from NHC-Ni (0) and 2° alcohol. Thus, the diastereodivergent synthesis could be a Z directed nickelacyclopentene formation with a suitable choice of NHC, not on choices of partners41-43. Synthetically, the exocyclic-olefin also links up many useful organic transformations (Fig. 5), which broaden the impacts and the applications of this hydroalkenylation.

In summary, an efficient 1,3- and 1,4-diastereodivergent heterocycle synthesis strategy was established by tuning property of Z on enynes under NHC-Ni catalysis (switch from up to 2:98 to 98:2). It was demonstrated by a reductive hydroalkenylation of enynes using 2° alcohol as reductant. Highly competing side reactions were suppressed and broad scope was achieved simultaneously. Unlike a number of former diastereodivergent approaches that based on facial selection at the latter stage of the catalytic cycle, here the diastereodivergent efficiency is governed by Z directed nickelacyclopentene forming step at the start (a 3 x bonds formation event, including 1 x C=C and 2 x Ni=C bond). Moreover, that can be promoted by choice of NHC ligand (IPr vs SIPr). That feature makes the preferred diastereodivergent outcome highly predicatable and tunable, which in turn makes it less dependent on steric interactions among external reaction partners and substituents on the tether. Products packed densely with diastereocenters which is difficult to be made by conventional steric approaches (either sterically unfavorable or hardly distinguishable, e.g., preparation of 1,2,3-contagious and skipped stereocenters, and new 4° center with Me vs Et). Products obtained from the studies that used CD3OH, ArCHO and TESH instead of 1-phenylethanol (Fig. 4). First, using CD3OH in the reductive hydroalkenylation of ketone, and (ii) Acyclic alkenol (Supplementary Methods).

Discussion
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based on nickelacyclopentenones and related species for broader scope. Exploration along this line is now underway.

**Methods**

Preparation of hetero-substituted enynes: See Supplementary Methods. Determination of diastereoselectivity: See Supplementary Methods, Supplementary Figs. 4–10. Acylation procedure: See Supplementary Methods. Synthesis procedure: See Supplementary Methods. Products characterization: See Supplementary Data 1. Standard reductive hydroalkenylation procedure: (0.05 mmol each) were dissolved in toluene (2 mL) and stirred at 30 °C in glovebox for 1 h. An enyne and 1-phenylethanol (0.5: 1.5 mmol) toluene solution (1 mL) were added dropwise to the above catalyst in 0.5 h, and was stirred at 30 °C for 3 h. After work up, the yield, structure and selectivity were determined by 1HNMR, NMR, NOESY, isolation and GCMS (average of two runs). Mesylation of NH products were carried out for direct comparison of the isomers when necessary (Supplementary Method A).

**Data availability**

The authors declare that all the other data supporting the findings of this study are available within this paper, its Supplementary Information file and Supplementary Data 1.

Received: 23 March 2020; Accepted: 3 April 2020; Published online: 30 April 2020

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**Acknowledgements**

C.Y.H. thanks R. H. Grubbs (Shenzhen Nobel Prize Scientists Laboratory Project (17783101), SZ research fund (C17701701045157), Guangdong Provincial Key Laboratory of Catalysis (2020B121201002) and NSFC (21602099). We thank Dr. Elvis W. H. Ng for useful discussion.

**Author contributions**

The manuscript was achieved through contributions of all authors. X.Y. designed and conducted the experiments. W.G. participated in the reductive hydroalkenylation section. X.L. contributed to preparation of substrates. C.Y.H. supervised the project.
Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s42004-020-0299-9.

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