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(NHC)Ni(II)-catalyzed regioselective hydroalkenylation of norbornene derivatives: fine-tuning of NHC ligands and donor alkenes†

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This study introduced a novel cross-hydroalkenylation approach for addressing a resilient challenge in C5-*exo*-selective norbornene derivative functionalization. The process, guided by mutual interactions among the NHC–Ni catalyst and the substrate pairs, ensured highly chemo- and regio-selective insertion.

Asymmetrically substituted chiral bicycloalkene derivatives are common building blocks and ligands in organic synthesis.[1–3] One of the major limitations of their applications in the subsequent catalytic transformations is the lack of effective means for interacting the catalysts and the remote chiral center on them. Using norbornene derivatives as examples, conventional approaches often fail to selectively functionalize the C5 or C6 olefin positions.[4,5] Mercury-mediated oxymercuration and zirconium-catalyzed carbomagnesation have been effective strategies in this area (Fig. 1a, C6-selective metallation).[6,7] However, the high regioselectivity achieved above is considerably restricted to 2-OH/OR substituted norbornenes. Thus, it is highly desirable to develop a new foundation to extend the unique benefits from those readily available chiral building blocks.

Cross-hydroalkenylation (HA) is an attractive way to functionalize strained alkenes like norbornenes. Since its growth by alkenyl halides/triflates (Fig. 1b), greener alternatives were achieved by using ethylene, unsaturated esters and amides as donors (Fig. 1c).[8–18] Yet, the aforesaid chiral Diels–Alder products are rare olefin acceptors, and the abundant α-olefins are rare donors. Here, we expanded the scope of the norbornene cross-HA and offered a new means for C5-*exo*-alkenylation by a mutual cooperation between NHC and olefin donors (Fig. 1d).[19–22]

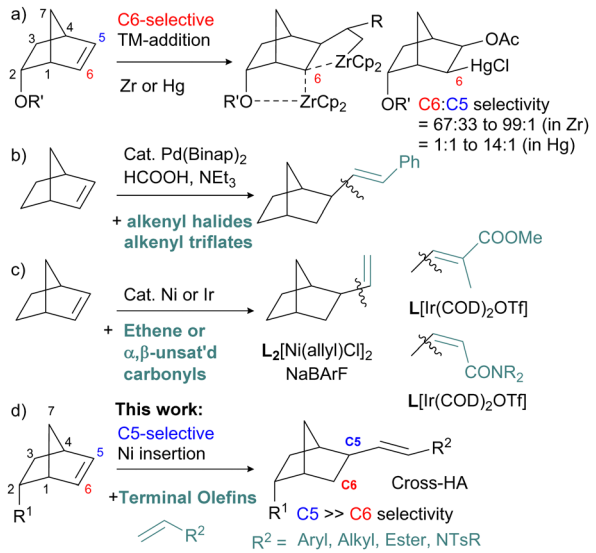

Fig. 1 Remote regio- and stereo-selective functionalization of asymmetric norbornene derivatives and the strategies employed in cross-HA.

We commenced our development using norbornene **1a** and styrene **2a** as a model substrate pair, with 10 mol% of [(NHC)Ni(allyl)Cl]/NaBArF as the catalyst in toluene at r.t. for 12 h (Table 1 and Fig. 2), and several factors that govern the insertion selectivity were revealed. First, this approach revealed a greener synthetic alternative for ***E*-3aa** (*cf.* Fig. 1b). Minor cross-products, like ***Z*-3aa**, **4aa**, and **5aaa**, were minimized by choosing an unsaturated NHC core ($E/Z > 20:1$, entries 2–6 *vs.* 1), using smaller *N*-aryl sizes by changing either the number or size of *N*-aryl *o*-substituents (**3**:**4** $> 20:1$, entries 4–6 *vs.* 2 and 3), and giving more room for β-H elimination (*e.g.* with smaller *N*-aryl *o*-substituents or at least one unsubstituted site, entries 2, 4 and 6). Also, using an optimally sized NHC was found to be crucial to the yield (entries 3 and 5, $<12\%$). Notably, the olefin

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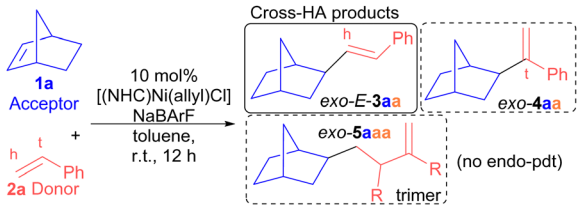
Table 1 Screening of NHC for cross-HA of norbornene and styrene



	NHC	Conv. 1/2%[a]	HA yield %	3 : 4	*E*/*Z*-3	(3+4) : 5
1	**L1**	100/82	69	7.7 : 1	14 : 1	6 : 1
2	**L2**	100/90	76	12 : 1	> 20 : 1	4.3 : 1
3	**L3**	40/5	11	2.3 : 1	> 20 : 1	n.d.
4	**L4**	78/51	43	> 20 : 1	> 20 : 1	8.5 : 1
5	**L5**	33/31	12	> 20 : 1	> 20 : 1	n.d.
6	**L6**	100/100	69	> 20 : 1	> 20 : 1	10 : 1

Olefin acceptor **1a** (0.25 mmol) and olefin donor **2a** (0.3 mmol) were added to the [(NHC)Ni(allyl)Cl]/NaBArF catalyst (10 mol%) and 1-octene (40 mol%) in toluene (2 mL) at r.t. and stirred for 12 h.[24] No *endo*-product was observed in all cases. Conversion, yield, cross/oligo-, and cross-HA regio-selectivity were determined by crude ^{1}H NMR using CH_3NO_2 as a standard. *E*/*Z*-**3** was determined by GCMS. The relative configuration and structures of **3–5** were confirmed by isolation. [a] Non-selective oligomerization of **1a** was observed.

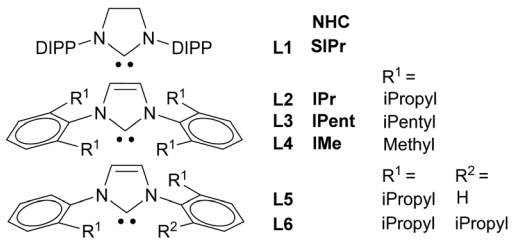


Fig. 2 NHC employed in this work.

ring-strain alone was found to be insufficient for guiding the chemoselective hydrometallation (HM), as the undesired consumption of the smaller-sized olefin was still effective when the size of NHC was not optimized. Finally, the screening result above also indicated the prospect of a selective cross-trimerization development.[23]

Next, the scope of the olefin donor was investigated (Table 2). In set 1, the **3 : 4** selectivity was improved from 12 : 1 to 17–20 : 1 by adding substituents on the vinylarenes. Higher yield of **5** was achieved with more electron-rich styrene. Electron-rich vinylarene proved to be the most efficient choice in competing with hydrometallated norbornene for carbometallation to yield **3**.

The method proved applicable for non-aromatic donors (set 2–4), despite initially resulting in a mixture of olefin isomerization and oligomerization products. Ring-strain relief was crucial in controlling chemoselective HM but insufficient against smaller, linear olefins like **2e** with a NHC catalyst, leading to faster undesired olefin consumption. Aliphatic branched α-olefins (**2f–g**) and *O*/*N*-substituted allyl and homoallyl olefins (**2h–r**) gave us better selectivity for **3 : 4** and *E*/*Z*-**3** with lower catalyst loading (decreasing from 10 mol% for 12 h in set 1 and 2 to 1–5 mol% for 0.5–3 h in set 3 and 4). They minimized side reactions, and aided the productive HM and the irreversible carbometallation steps by an extended donor structure with high steric demand (*e.g.* tosylamides > carbonates > ethers). Matching steric demands between **L** and the donor proved essential for high cross-HA reactivity, where bulkier **L2** suited smaller donors while smaller **L6** suited larger ones. Activated terminal olefins like **2t** and **2s** proved viable substrates (set 5), offering a redox-neutral strategy suitable for both electron-rich and deficient olefin donors by eliminating constraints associated with C–H oxidative addition and π-system cross-oxidative cyclization challenges (Fig. 1c). In set 6, high yields and selectivity were maintained with fused aryl and *exo*-substituted cases, while the *endo* case showed marked reduction, suggesting stronger steric repulsion by *endo* substituents and greater demand for chemo- and regio-selective insertion.

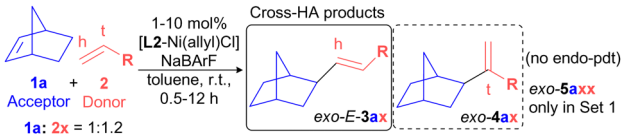
The dramatic reactivity change in set 6 inspired us to pick asymmetric *endo*-substituted norbornene as a substrate to solve the C5-metallation selectivity problem by steric repulsion (Table 3). This achieved highly C5-selective cross-HA for the first time, using *endo*-alkyl ether substituted norbornene **1e** and an allylether **2h** under mild conditions. Further increase in the C5/C6-ratio was achieved simply by using *endo*-COOMe **1f** (8 : 1 to 10 : 1), while *exo*-COOMe or NTs (*exo*-**1f–g**) showed inferior C5/C6-ratio as expected.[25–28] The method proved useful for other representative olefin donors shown in Table 2, such as aryl and hetero-substituted olefins (**3fx**, C5/C6 = 5–10 : 1, *E*/*Z*-**3** up to 20 : 1).

The traditional cross-HA cycle of norbornene relied on ring-strain relief-directed chemoselective HM, followed by steric repulsion-directed carbometallation. Steric repulsion among the NHC ligand and the 2-*endo*-substituted norbornene predicted a high C5/C6-ratio, potentially overcoming classic δ^- charge at the C6-position in other electrophilic transition-metal systems (Fig. 1a). Although using a smaller NHC (**L6**) showed a C5/C6-selectivity drop, the proposed irreversible bimolecular HM model involving norbornene and the catalyst failed to explain the C5/C6-ratio variations from 4 : 1 to 10 : 1 relative to the donor structural changes, and higher ratio with smaller donors (allyl ether/amide > styrene). Thus, the conventional models were inadequate to explain all the observations, prompting investigation of additional factors.

Initially, we aimed to determine the basic C5/C6-selectivity achievable through the hypothesized ring-strain relief-directed HM step in the absence of a donor (see ESI†). Surprisingly, this intended HM using a stoichiometric amount of 2-*endo*-substituted norbornene and NHC catalyst was unsuccessful or non-irreversible (for 30 min, repeated 3 times). Efforts to trap the hydrometallated species with D_2O before backward elimination also failed, with minimal 2-*endo*-substituted norbornene conversion (< 5% by ^{1}H NMR) even after extended stirring for 30 min. This result accounted for the rapid consumption of linear olefins **2e–f** in Table 2 and underscored the ring strain's inadequacy in directing highly chemoselective HM, suggesting that acceptor HM was assisted by the donor, yielding minimal inherent C5/C6-selectivity *via* typical HM (see ref. 34).

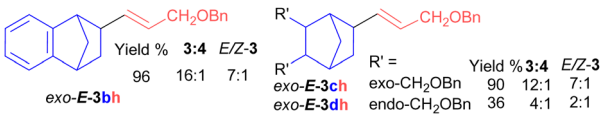
One logical explanation for the donor effect on C5/C6-selectivity at this stage was based on the differences between two highly competing HM pathways identified earlier in related

Table 2 Scope of the cross-hydroalkenylation



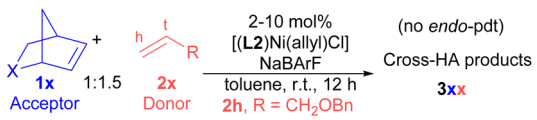
2	R	Yield %	3 : 4	*E*/*Z*-3	(3+4) : 5	2	R	Yield %	3 : 4	*E*/*Z*-3
Set 1 Vinylarene[a]						**Set 2** Simple alky[a]				
2a	Ph	76	12 : 1	20 : 1[h]	4.3 : 1	**2e**	nhex	13 (*E*-3)	n.d.	n.d.
2b	2-Naphthalene	52	17 : 1	20 : 1[h]	20 : 1	**2f**	Bn	42[e]	n.d.	n.d.
2c	(4-CF_3)-C_6H_4	27	>20 : 1	20 : 1[h]	20 : 1	**2g**	Cy	22 (*E*-3)	n.d.	n.d.
2d	(4-OMe)-C_6H_4	80	18 : 1	20 : 1[h]	6 : 1					
Set 3 Heterosub-O[d]						**Set 4** Heterosub-N[bf]				
2h	CH_2OBn	96	17 : 1	5 : 1		**2o**	CH_2NTsMe	58[ag]	17 : 1	20 : 1
2i	CH_2OCy	91	14 : 1	4 : 1				77	20 : 1	20 : 1
2j	CH_2OnBu	95	>20 : 1	4.6 : 1		**2p**	CH_2NTsEt	83	20 : 1	20 : 1
2k	$(CH_2)_2OBn$	84	15 : 1	10 : 1[i]		**2q**	$(CH_2)_2NTsMe$	57	18 : 1	20 : 1
2l	$(CH_2)_2OPh$	50	>20 : 1	10 : 1[i]		**2r**	CH_2NHTs	24	20 : 1	20 : 1
2m	$CH_2OCOOMe$	62	19 : 1	14 : 1				80[g]	20 : 1	20 : 1
		65[f]	>20 : 1	16 : 1						
		86[cf]	>20 : 1	18 : 1		**Set 5** Activated[af]				
2n	$CH_2OCOOPh$	73[cf]	>20 : 1	16 : 1		**2s**	COOMe	50[g]	20 : 1	1 : 1
								91	20 : 1	3 : 1
						2t	NPhth	76[b]	20 : 1	20 : 1

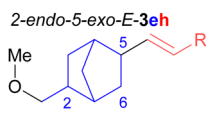
Set 6 Symmetrically substituted norbornene derivatives[aj]



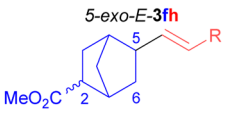
General procedure: olefin acceptor **1** (0.5 mmol) and olefin donor **2x** (0.6 mmol) were added to the [(**L2**)Ni(allyl)Cl]/NaBArF catalyst (*n* mol%) and 1-octene (4 × *n* mol%) in toluene (2 mL) at r.t. No *endo*-product was observed in all cases examined. Conversion, yield and selectivity were determined by crude ^{1}H NMR using CH_3NO_2 as standard. The structure of **3** was confirmed by isolation and is shown in relative configuration. In set 2–5, no **5** and cross-homoallylic HA product **3′** were observed by ^{1}H NMR unless otherwise indicated. [a] 10 mol% cat., 12 h. [b] 5 mol% cat., 3 h. [c] 3 mol% cat., 2 h. [d] 1 mol% cat., 0.5 h. [e] **3** : **3′** = 1 : 1. [f] **L6**. [g] **L2**. [h] Determined by GCMS. [i] Determined after isolation. [j] Acceptor : donor = 1 : 2.

Table 3 C5-selective cross-HA of asymmetric 2-*endo*-substituted Diels–Alder products



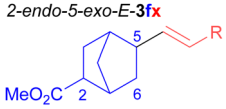


Yield	86%[a]
C5/C6	**8 : 1**
3 : 4	6 : 1
E/*Z*-3	10 : 1
(3+4) : 5	>20 : 1



Yield	2-*endo* >95%[a]	2-*exo* 82%[a]
C5/C6	**10 : 1**	**2 : 1**
3 : 4	10 : 1	9 : 1
E/*Z*-3	8 : 1	10 : 1
(3+4) : 5	>20 : 1	>20 : 1

Yield	80%[b]
C5/C6	**1.7 : 1**
3 : 4	7 : 1
E/*Z*-3	20 : 1
(3+4) : 5	>20 : 1



	R	Ph[c]	Ph[c,g]	Nphth[c]	COOMe[c]	CH_2NMeTs[bf]
	Yield	25%	24%	>95%	78%	62%
	C5/C6	5 : 1	**4 : 1**	**5.6 : 1**	**8.8 : 1**	**10 : 1**
	3 : 4	5 : 1	20 : 1	>20 : 1	>20 : 1	15 : 1
	E/*Z*-3	3.4 : 1	20 : 1	3 : 1[d]	1 : 1.3[e]	>20 : 1
	(3+4) : 5	1.6 : 1	5 : 1	>20 : 1	>20 : 1	>20 : 1

General procedure applied. [a] 0.5 h. [b] 5 mol% cat. [c] 10 mol% cat. [d] *E*/*Z*-selectivity of the C6 product is 3.5 : 1. [e] *E*/*Z*-selectivity of the C6 product is 1 : 1. [f] 3 h. [g] By **L6**.

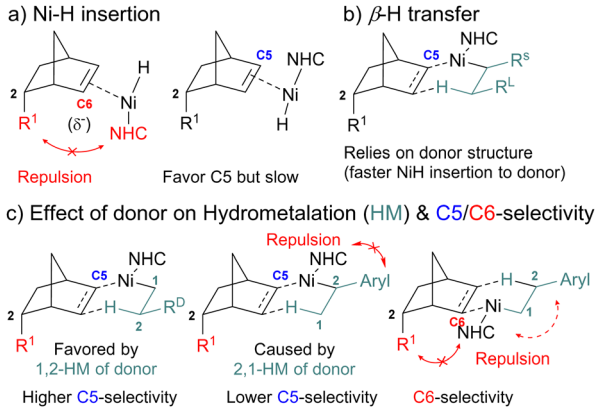


Fig. 3 Hydrometallation (HM) pathway competitions.

(NHC)Ni-catalyzed HA (Fig. 3a and b: NiH insertion or β-H transfer).[29–31] As the repulsion between the NHC and acceptor increased, the acceptor-to-donor HM ratio decreased. Consequently, this may favor a β-H transfer pathway and lead to a correlation of the donor structure and C5/C6-selectivity (styrene < vinylphthalimide < acrylate < allyl ether and amide). For instance, among the two possible C5-selective pathways, the benzylic stabilization of **2a** directed the 2,1-HM over the heteroatom of **2h** directed 1,2-HM (*i.e.* add Ni at the 2- *vs.* 1- or (*int-vs. ter-*) position of the terminal alkene) (Fig. 3c), causing a relatively less favorable β-H transfer transition state by steric repulsion. Hence, one of the C5-selective cross-HA paths was suppressed, and a lower C5/C6-selectivity was observed.[32–34]

In summary, we first expanded the scope of norbornene cross-HA using a well-defined (NHC)Ni(allyl)Cl as a catalyst. This method first directly used terminal olefins as olefin donors, saved the efforts in preparing alkenyl halides, and yielded the corresponding exocyclic olefins with high chemo-, regio-, and *E-exo*-selectivity.

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Data availability

The data supporting this article have been included as ESI.†

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 H. B. Kagan and O. Riant, *Chem. Rev.*, 1992, **92**, 1007–1019.
2 S. Kobayashi and K. A. Jorgensen, *Cycloaddition Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, Cambridge, 2002.
3 Y. Hayashi, *Cycloaddition Reactions in Organic Synthesis*, ed. S. Kobayashi and K. A. Jorgensen, 2002, pp. 5–55.
4 T. V. RajanBabu, in *Comprehensive Asymmetric Catalysis*, ed. E. N. Jacobsen, A. Pfaltz and H. Yamamoto, Springer, Berlin, 1999, vol. 1, pp. 417–427.
5 C.-Y. Ho and D. Raja, *Science of Synthesis*, Georg Thieme Verlag KG, 2023, ch. 47.1.9, vol. 2, pp. 307–389.
6 P. Mayo, *et al.*, *J. Org. Chem.*, 2001, **66**, 5182–5191.
7 A. H. Hoveyda, *et al.*, *J. Am. Chem. Soc.*, 1992, **114**, 6692–6697.
8 R. C. Larock and P. L. Johnson, *J. Chem. Soc., Chem. Commun.*, 1989, 1368–1370.
9 A. A. F. Marinelli, *et al.*, *J. Organomet. Chem.*, 1989, **368**, 249–256.
10 F. Ozawa, *et al.*, *J. Chem. Soc., Chem. Commun.*, 1994, 1323–1324.
11 T. V. RajanBabu, *Chem. Rev.*, 2003, **103**, 2845–2860.
12 W. Liu and T. V. RajanBabu, *J. Org. Chem.*, 2010, **75**, 7636–7643.
13 R. Kumareswaran, *et al.*, *Org. Lett.*, 2003, **5**, 4345–4348.
14 Y. Ura, *et al.*, *J. Org. Chem.*, 2005, **70**, 6623–6628.
15 M. Hirano, *ACS Catal.*, 2019, **9**, 1408–1430.
16 M. Hirano and S. Komiya, *Coord. Chem. Rev.*, 2016, 314, 182–200.
17 M. O. Simon and S. Darses, *J. Org. Chem.*, 2013, **78**, 9981–9985.
18 X. Sun, *et al.*, *Organometallics*, 2021, **40**, 2182–2187.
19 Z. Zhang, *et al.*, *Acc. Chem. Res.*, 2023, **56**, 1070–1086.
20 J. Q. Huang, *et al.*, *Nat. Commun.*, 2022, **13**, 4145–4155.
21 J. Q. Huang and C. Y. Ho, *Angew. Chem., Int. Ed.*, 2019, **58**, 5702–5706.
22 J. Q. Huang and C. Y. Ho, *Angew. Chem., Int. Ed.*, 2020, **59**, 5288–5292.
23 L. E. Bowen and D. F. Wass, *Organometallics*, 2006, **25**, 555–557.
24 1-octene was used as a substrate of the [(NHC)Ni(allyl)Cl]/NaBArF precatalyst for forming the Ni(II) hydride catalyst equivalent.
25 B. T. Sargent and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**, 7520–7523.
26 R. S. Glass, *et al.*, *J. Org. Chem.*, 1980, **45**, 3640–3646.
27 A. C. Cope, *et al.*, *J. Am. Chem. Soc.*, 1959, **81**, 2799–2804.
28 It is conceivable that C5-3 with an *exo*-COOMe can be accessed by typical isomerization conditions.
29 J. Joseph, *et al.*, *Organometallics*, 2009, **28**, 3552–3566.
30 Y. Gao, *et al.*, *Org. Biomol. Chem.*, 2017, **15**, 7131–7139.
31 X. Hong, *et al.*, *ACS Catal.*, 2015, **5**, 5545–5555.
32 C. Y. Ho and L. S. He, *Angew. Chem., Int. Ed.*, 2010, **49**, 9182–9186.
33 The R^1 substitutent at the 2-position is known to affect the double bond polarizability as shown in Fig. 1a and ref. 6. It may be a potential way to alter the C5/C6-selectivty in future.
34 In oxidative cyclization attempts using **L2**/Ni(0)$(cod)_2$ or $[(\mathbf{L2})NiCl]_2$ as catalyst, *endo*-**1f** and **2h** or **2s** as substrate pairs are unproductive under the same physical conditions.

