Thioether-Directed NiH-Catalyzed Remote γ-C(sp^3)–H Hydroamidation of Alkenes by 1,4,2-Dioxazol-5-ones

Bingnan Du,‡ Yuxin Ouyang,‡ Qishu Chen and Wing-Yiu Yu*

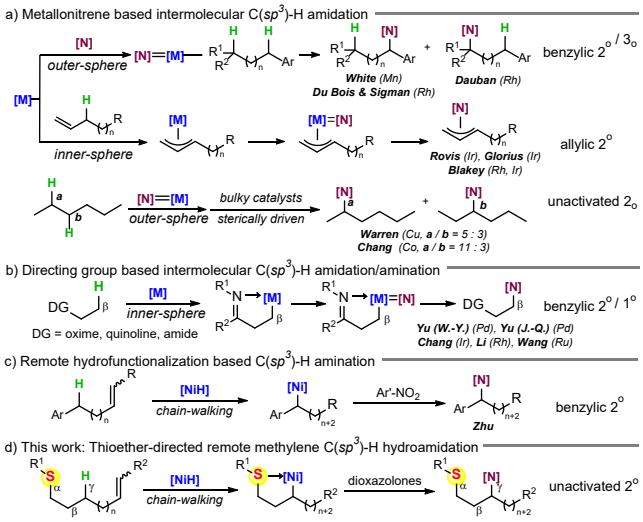
State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong

ABSTRACT: A NiH-catalyzed thioether-directed cyclometalation strategy is developed to enable remote methylene C–H bond amidation of unactivated alkenes. Due to the preference to five-membered nickellacycle formation, the chain-walking isomerization initiated by the NiH insertion to alkene can be terminated at the γ-methylene site remote from the alkene moiety. By employing 2,9-dibutyl-1,10-phenanthroline (**L4**) as ligand and dioxazolones as the reagent, the amidation occurs at the γ-C(sp^3)–H bonds to afford the amide products in up to 90% yield (>40 examples) with remarkable regioselectivity (up to 24:1 rr).

Regiocontrolled catalytic C(sp^3)–H bond amidations have been extensively investigated for atom- and step-economical amine synthesis.[1, 2] Classical metal-nitrene mediated intermolecular amidations can target successfully either benzylic or tertiary C–H bonds by virtue of their relatively weaker bond dissociation energies and unique steric environment (Scheme 1a).[3] The research groups of Rovis,[4] Glorius[5] and Blakey[6] have accomplished regioselective allylic C–H amidations by sequential Ir(III) and Rh(III)-mediated site-selective metalation and migratory insertion to metal-nitrenoid species. Indeed, regioselective functionalization of unactivated methylene C–H bonds remains elusive. Recently, specially designed Cu (Warren)[7] and Co (Chang)[8] catalysts have demonstrated favorable regioselectivity toward amidations of unactivated methylene C–H bonds. However, effective differentiation among the methylene sites with similar chemical environment remains problematic (Scheme 1a). In a separate pursuit, the donor group-guided cyclometalation by electrophilic late transition metals such as Pd(II),[9] Ir(II),[10] Rh(III)[11] and Ru(III)[12] can effect successfully regiocontrolled C(sp^3)–H functionalization for C–C and C–X (X = heteroatom) bond formations.[13] With the balance between steric factor and thermodynamic preference for five-membered metallacycle formation, the cyclometalation strategy is largely limited to primary β-C(sp^3)–H amidations/aminations (Scheme 1b). Indeed, intermolecular regiocontrolled amidation at remote unactivated γ-methylene sites remains a formidable challenge.

Recently, NiH catalysis merging with chain-walking isomerization are proved to be an effective approach for remote C–H functionalization of alkenes.[14, 15] Addition of NiH to alkenes would afford alkyl-Ni complexes, which are prone to chain-walking isomerization through iterative β-hydride elimination/migratory insertion events. The chain-walking process led to migration of the alkyl-Ni groups to some distal positions (either less steric or resonance/heteroatom-stabilized sites) of the hydrocarbon skeleton. Notably, Zhu's group reported a protocol to directly install an arylamine function onto a benzylic C(sp^3)–H site distal from the C=C bond through a relay NiH-mediated hydrometalation-alkene isomerization sequence, followed by reductive coupling with nitroarenes (Scheme 1c).[15h] Inspired by Zhu's work, we anticipated that a donor group pre-installed on the alkene skeleton may stabilize the transient nickellacycle intermediate through chelation and terminate the

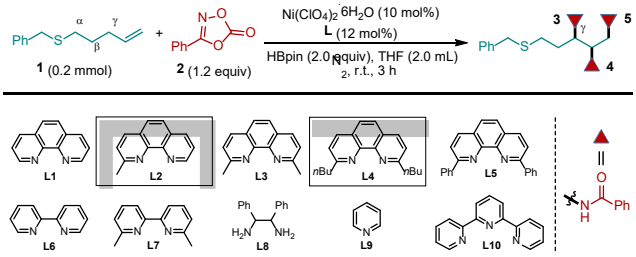
Scheme 1. Strategies for C(sp^3)–H Bond Amidation



alkyl-Ni migration at some non-stabilized methylene sites.[15k, 15m] Indeed, chelation-control strategy has shown successes in regiocontrolled hydroalkylation.[16] Here we report a thioether-directed remote γ-C(sp^3)–H amidation of alkenes using dioxazolones as the amidating reagents (Scheme 1d). When 2,9-dibutyl-1,10-phenathroline (**L4**) was utilized as ligand, the highly γ-selective methylene C(sp^3)–H amidation (up to 24:1 rr) was achieved in up to 90% yield (>40 examples). Recently, dioxazolone has emerged as a versatile reagent for transition metal-catalyzed hydroamidation.[17] However, the use of dioxazolones in NiH-catalyzed alkene functionalization is less established.

In this work, treating 5-(benzylthio)-1-pentene **1** (0.2 mmol), 3-phenyl-1,4,2-dioxazol-5-one **2** (1.2 equiv) and pinacolborane (2.0 equiv) in the presence of $[Ni(ClO_4)_2]\cdot 6H_2O$ (10 mol%) and **L4** (12 mol%) in THF at room temperature for 3 h furnished γ-selective hydroamidation product **3** in 95% yield, with 4% anti-Markovnikov product **5** formation (24:1 rr). No Markovnikov product **4** was detected (Table 1, entry 1). Poor regioselectivity (2:1 rr) was observed without ligands, with the desired amide **3** formed in only 22% yield (entry 2). While simple 1,10-phenanthroline (**L1**) was ineffective (entry 3), the 2,9-substituents

Table 1. Influence of Ligands



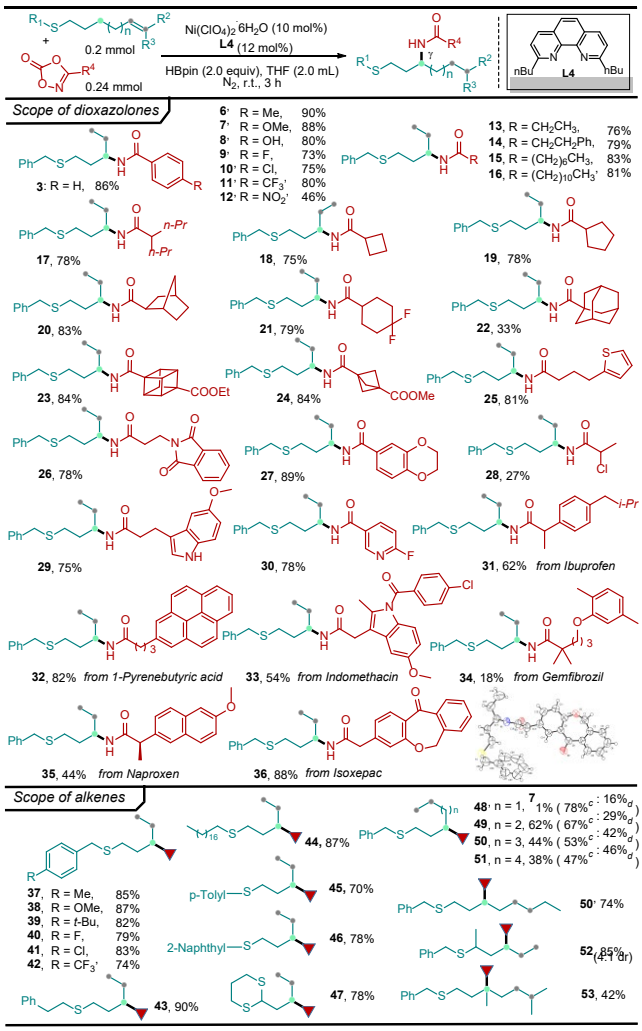
entry	ligand	3 (%)[a]	4 (%)[a]	5 (%)[a]	rr[b]
1	**L4**	**95**	**n.d.**	**4**	**24:1**
2	no ligand	22	35	n.d.	2:1
3	**L1**	12	30	n.d.	3:1
4	**L2**	14 (**6**)[c]	71 (**77**)[c]	3 (**2**)[c]	4:1 (**10:1**)[c]
5	**L3**	74	16	6	3:1
6	**L5**	n.d.	20	20	1:1
7	**L6**	8	21	n.d.	3:1
8	**L7**	73	6	13	4:1
9	**L8**	7	18	n.d.	3:1
10	**L9**	13	28	n.d.	2:1
11	**L10**	8	25	n.d.	3:1

[a]Yields determined by ^{1}H NMR; CH_2Br_2 as internal standard. [b]rr refers to regioisomeric ratio: the major product to the sum of all other isomers (determined by ^{1}H NMR). [c]MeCN instead of THF; 2.0 equiv of **2**.

seemed to be critical for the observed chemoselectivity. Among related ligands (**L2**–**L5**) tested, **L2** bearing a single methyl group furnished the Markovnikov product **4** in 71% yield, with only 14% yield of the chain-walked amide **3** (4:1 rr; entry 4). By switching solvent to MeCN, 10:1 rr was attained with amide **4** as major product (see later section). Yet, **L3** with two methyl groups favored chain-walked amide **3** in 74%, with 16% amide **4** formation (entry 5). Employing bulkier **L5** as ligand led to suppression of amide **3** production, forming amides **4** (20%) and **5** (20%) exclusively (entry 6). Other nitrogen-based ligands such as diamine, pyridine and terpyridine were all ineffective for this transformation (entries 7–11).

Employing the working protocol for the remote hydroamidation, we first turned to dioxazolone scope study (Table 2). Under the optimized conditions, aryl-substituted dioxazolones would effectively couple with the 5-(benzylthio)-1-pentene **1** to give the corresponding amides (**6**–**12**) in good yields. Dioxazolones with EDG gave higher yields (>80%) than those bearing EWG (≤80%). Facile coupling with the dioxazolones containing primary (**13**–**16**) and secondary alkyl groups (**17**–**21**) were also accomplished in good yields (~80%). Presumably due to steric effect, transformation of the dioxazolone bearing an adamantyl group was less successful (**22**: 33%). Surprisingly, dioxazolones containing strained carbocycles such as cubanes and bicyclo[1.1.1]pentanes, afforded **23** and **24** in 84% yields. Furthermore, dioxazolones containing thiophene, phthalimide, ether groups were converted to their amides (**25**–**27**) in good yields. Moreover, the coupling reaction involving the dioxazolone derived from 2-chloropropanoic acid was also successful, and amide **28** was obtained in 27% yield. Here 3-indolepropionic acid and 6-fluoronicotinic acid can be derivatized to the corresponding dioxazolones, and their coupling reactions gave amides **29** (75%) and **30** (78%) effectively. In this work, corresponding amides were also prepared successfully from the analogous reactions of dioxazolones derived from ibuprofen (**31**: 62%), 1-pyrenebutyric acid (**32**: 82%), indomethacin (**33**: 54%), gemfibrozil (**34**: 18%), naproxen (**35**: 44%) and isoxepac (**36**: 88%). The molecular structure of **36** has been confirmed by X-ray crystallography.

Table 2. Substrate Scope Study[a-b]

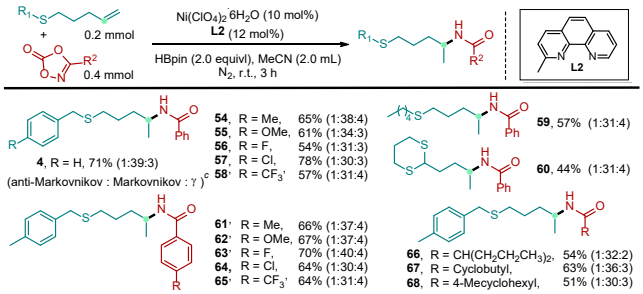


[a]Reaction conditions: alkenes (0.2 mmol), dioxazolones (0.24 mmol), $[Ni(ClO_4)_2]\cdot 6H_2O$ (10 mol%), **L4** (12 mol%), HBpin (2.0 equiv), THF (2.0 mL), N_2, r.t., 3 h. [b]Isolated yield. [c]Product yields determined by ^{1}H NMR; CH_2Br_2 as internal standard. [d]Anti-Markovnikov by-product yields determined by ^{1}H NMR; CH_2Br_2 as internal standard.

The synthetic versatility of this reaction was further explored with a collection of structurally diversified alkenes (Table 2). With 3-phenyl-1,4,2-dioxazol-5-one, alkenes with functionalized aryl rings (**37**–**42**) produced the corresponding amides in ~80% yields. As expected, alkenes with modified thioether group are effective to bring about the γ-C–H amidation products **43**–**46**. Interestingly, hydroamidation of dithiane-substituted alkenes was also accomplished (**47**: 78%). Adding methylene units between the sulfur and the C=C termini was somehow tolerated, albeit with reduced selectivities on longer migrating distance. This can be attributed to the diminished chelation effects toward the initial NiH hydrometallation. The reactions of internal alkene and alkenes with alkyl branching at the α- and γ- position gave also high γ-selectivity (**50**, **52**–**53**). The lower yield of **53** is presumably due to increased steric effect of the tertiary center.

As mentioned earlier, employing **L2** as ligand for the Ni-catalyzed hydroamidation has diverted the regioselectivity to the Markovnikov amide **4** formation (Table 1, entry 4).[18] Upon reaction optimization (see Supporting Information), we found

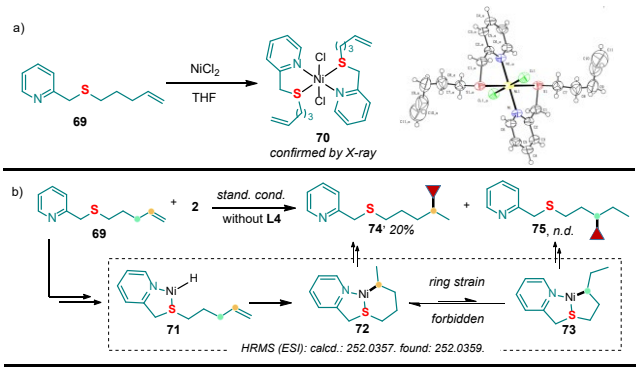
Table 3. Ni-Catalyzed Markovnikov Hydroamidation[a-b]



[a]Reaction conditions: alkenes (0.2 mmol), dioxazolones (0.4 mmol), $[Ni(ClO_4)_2]\cdot 6H_2O$ (10 mol%), **L2** (12 mol%), HBpin (2.0 equiv), MeCN (2.0 mL), N_2, r.t., 3 h. [b]Isolated yield. [c]The ratio of products was determined by ^1H NMR; CH_2Br_2 as internal standard.

that performing the reaction in MeCN solvent along with 2.0 equiv of **2** would afford predominantly the Markovnikov amide **4**. Similar observation has been reported by Hong and co-workers.[19] As depicted in Table 3, the hydroamidation of alkenes with substituents on the aryl ring produced **54**–**58** in moderate yields with regioselectivity of ~10:1 rr. Aliphatic sulfide (**59**) and bisulfide (**60**) were also effective substrates. A series of dioxazolones bearing both aryl and alkyl groups furnished the desired amides **61**–**68** in remarkable selectivity.

Scheme 2. Binding Mode Study of The Thioether Group[a-b]

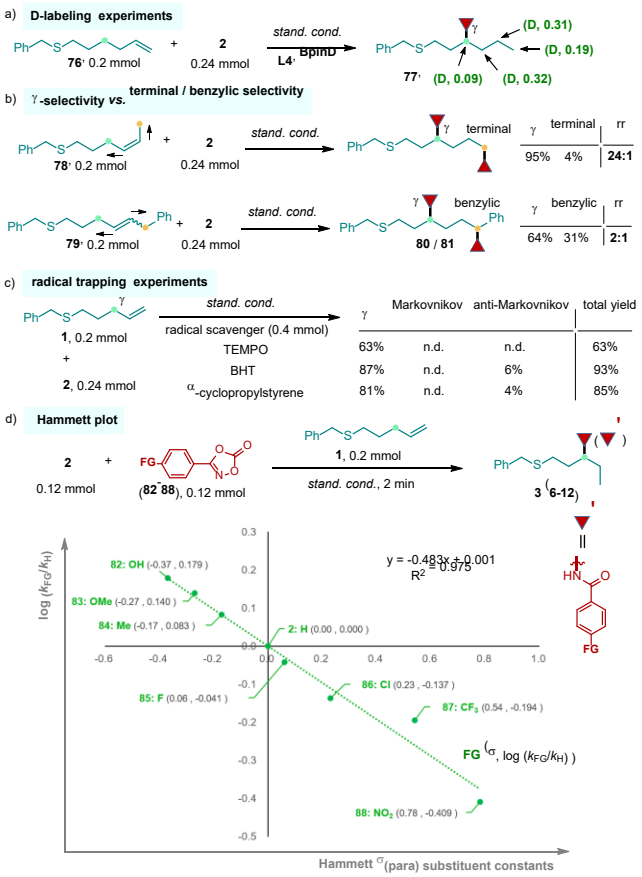


[a]Standard conditions: **69** (0.2 mmol), **2** (0.24 mmol), $[Ni(ClO_4)_2]\cdot 6H_2O$ (10 mol%), **L4** (12 mol%), HBpin (2.0 equiv), THF (2.0 mL), N_2, r.t., 3 h. [b]Yields determined by ^1H NMR; CH_2Br_2 as internal standard.

To examine the binding mode of the sulfur donor,[20] we prepared a N, S-bidentate-tethered alkene substrate **69**. Treating **69** with a stoichiometric amount of $NiCl_2$ afforded a stable metallacyclic complex **70**, and its structure has been confirmed by X-ray crystallographic study (Scheme 2a). When subjecting **69** to the Ni-catalyzed conditions, Markovnikov amide **74** was obtained exclusively in 20% yield. Assuming a Ni-H intermediate, this result suggests that a preferred formation of a 5,6-bicyclic alkyl-Ni complex (**72**) (Scheme 2b). Presumably, the 5,6-bicyclic structure (**72**) is thermodynamically more stable than the analogous 5,5-bicyclic structure (**73**), thereby suppressing the chain-walking process.[21] By HRMS analysis of the reaction mixture, molecular ion cluster peaks corresponding to **71**–**73** have been detected (see Supporting Information), supporting the bicyclic alkyl-Ni complex formation. These results are consistent with the nickallacycle formation involving the thioether group.

To explore the underlying mechanism of the chain-walking process, deuterium labeling experiments with **76** as substrate

Scheme 3. Mechanistic Study[a-c]

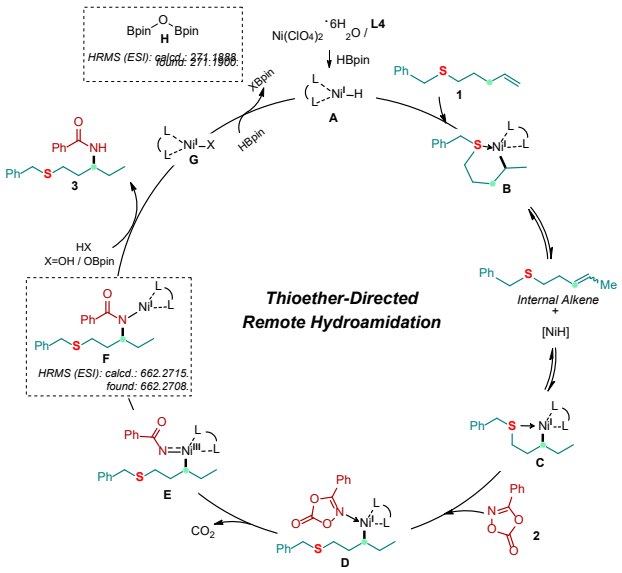


[a]Standard conditions: alkenes (0.2 mmol), dioxazolones (0.24 mmol), $[Ni(ClO_4)_2]\cdot 6H_2O$ (10 mol%), **L4** (12 mol%), HBpin (2.0 equiv), THF (2.0 mL), N_2, r.t., 3 h. [b]Yields determined by ^1H NMR; CH_2Br_2 as internal standard. [c]rr was determined by ^1H NMR.

were performed. With DBpin as hydride source, deuterium incorporation was found at all positions from the terminal to the γ-position (Scheme 3a). This result supports the 1,2-hydride shift mechanism for the chain-walking isomerization.[14b] Subjecting disubstituted alkene **78** to the standard conditions furnished predominantly the γ-C–H amidation product (95%). While the terminal amide product was obtained, the high regioisomeric ratio (24:1 rr) for the γ-amidation product indicates that the thioether-directed nickellacycle formation should prevail over steric effect in determining the direction of the chain-walking isomerization (Scheme 3b). Moreover, a competition study with **79** as substrate afforded a 2:1 mixture of **80** and **81** as products. This confirmed that the thioether-metallacycle formation is a stronger factor than the π-conjugation in determining the regioselectivity (Scheme 3b). In agreement with our earlier experiment with **78** as substrate, the metallacycle formation serves as the regio-determining step for this reaction.

Radical scavengers such as TEMPO, BHT and α-cyclopropylstyrene were employed to probe the involvement of radical intermediates (Scheme 3c). Under the standard conditions, BHT and α-cyclopropylstyrene exerted negligible effect to the formation of **3**, suggesting that radical-mediated reaction pathways are untenable. However, formation of **3** was suppressed (61%) in the presence of TEMPO. This could be attributed to the oxidation of the low valent nickel intermediate by TEMPO, resulting in catalyst deactivation.[22]

Scheme 4. Proposed Mechanism

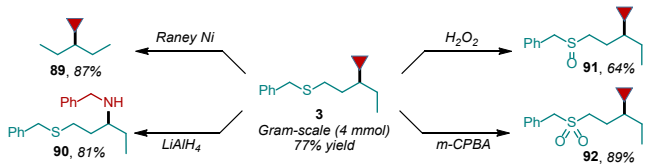


In this work, we have also conducted a Hammett correlation study using a series of *para*-substituted aryl dioxazolones (**82**–**88**) under competition conditions, and the yields were determined by ^{1}H NMR. Plotting the log(k_{FG}/k_H) values with the Hammett σ(para) substituent constants resulted a linear plot with a slope of -0.48 ($R^2 = 0.975$) (Scheme 3d). The observed negative reaction constant suggests that the product-determining step is likely to be the "dioxazolone + alkyl-Ni", which would be promoted by electron-donating substituents on the dioxazolone reagent.[23]

Scheme 4 depicts a plausible mechanism for this transformation.[19, 24] The reaction is likely to be initiated by the generation of [NiH] (**A**) from $Ni(ClO_4)_2{\cdot}6H_2O$, **L4** and HBpin.[15j, 25] Hydrometalation of alkene **1** by **A** should give a 6-membered metallacycle **B** as an immediate product.[16, 19] Complex **B** should undergo spontaneous reversible *β*-hydride elimination/migratory insertion processes to afford a more stable 5-membered metallacycle **C**.[26] It is plausible that the isomerized internal alkene intermediate may have dissociated from the Ni center prior to sequential hydrometallation to form **C**. Coordination of dioxazolone **2** to **C** should form a Ni-complex **D**, which would transform further to some electrophilic metal-nitrenoid **E** through releasing a CO_2 molecule. Facile nitrene insertion should afford a Ni-amide complex **F**, which is readily protonated to give amide **3** and **G** for turnovers.[17c] The proposed mechanism lends it support from the HRMS study of the reaction mixture with intermediates **B**, **C**, **F** and **H** being observed (see Supporting Information).

The reported protocol is amenable to gram-scale operation, obtaining amide **3** in 77% yield. Moreover, the synthetic versatility of **3** was also explored. Successful desulfurization with Raney Ni gave **89** in 87% yield. Reduction with $LiAlH_4$ furnished **90** in 81% yield. Controlled oxidation with H_2O_2 and *m*-CPBA furnished sulfoxide **91** and sulfone **92** in 64% and 89% yields respectively (Scheme 5).

Scheme 5. Synthetic Transformations of Amide 3[a]



[a]Isolated yield.

In conclusion, we developed a NiH-catalyzed thioether-directed nickellacycle formation strategy for targeting remote *γ*-methylene C–H bond amidation of unactivated alkenes. The preferred five-membered nickelacycle formation effectively terminate the chain-walking isomerization at specific *γ*-methylene site. This cyclometalation-control approach offers remarkable regio-differentiation of multiple methylene C–H sites of similar chemical environment on the hydrocarbon chain. We envision that this catalytic hydroamidation protocol would serve more than a synthetic tool for diverse amide synthesis but also offer insights for development of regiocontrolled C–N bonds construction on unactivated aliphatic alkanes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at

Screening and optimization study, mechanistic study, experimental details, characterization of new compounds and crystallographic data (PDF)

Accession Codes

CCDC 2079172 and 2079166 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*wing-yiu.yu@polyu.edu.hk

ORCID

Bingnan Du: 0000-0001-5503-3916

Yuxin Ouyang: 0000-0001-5453-513X

Qishu Chen: 0000-0003-0472-2388

Wing-Yiu Yu: 0000-0003-3181-8908

Author Contributions

‡B.D. and Y.O. contributed equally.

ACKNOWLEDGMENT

We are grateful to the financial support from the Hong Kong Research Grants Council (PolyU153152/16P, PolyU153023/17P; PolyU153017/19P) and the State Key Laboratory for Chemical Biology for Drug Discovery.

REFERENCES

(1) For selected reviews via transition metal-nitrene approach, see: (a) Davies, H. M. L.; Manning, J. R. Catalytic C–H Functionalization by Metal Carbenoid and Nitrenoid Insertion. *Nature* **2008**, *451*, 417-424. (b) Collet, F.; Dodd, R. H.; Dauban, P. Catalytic C–H Amination: Recent Progress and Future Directions. *Chem. Commun.* **2009**, *34*, 5061-

5074. (c) Zalatan, D. N.; Bois, J. D. Metal-Catalyzed Oxidations of C−H to C−N Bonds. *Top. Curr. Chem.* **2009**, *292*, 347-378. (d) Ramirez, T. A.; Zhao, B.; Shi, Y. Recent Advances in Transition Metal-Catalyzed sp^3 C–H Amination Adjacent to Double Bonds and Carbonyl Groups. *Chem. Soc. Rev.* **2012**, *41*, 931-942. (e) Park, Y.; Kim, Y.; Chang, S. Transition Metal-Catalyzed C–H Amination: Scope, Mechanism, and Applications. *Chem. Rev.* **2017**, *117*, 9247-9301. (f) Hayashi, H.; Uchida, T. Nitrene Transfer Reactions for Asymmetric C–H Amination: Recent Development. *Eur. J. Org. Chem.* **2020**, *2020*, 909-916. (g) Trowbridge, A.; Walton, S. M.; Gaunt, M. J. New Strategies for the Transition-Metal Catalyzed Synthesis of Aliphatic Amines. *Chem. Rev.* **2020**, *120*, 2613-2692.

(2) For selected reviews via other approaches, see: (a) Stateman, L. M.; Nakafuku, K. M.; Nagib, D. A. Remote C–H Functionalization via Selective Hydrogen Atom Transfer. *Synthesis* **2018**, *50*, 1569-1586. (b) Zhao, Y.; Xia, W. Recent Advances in Radical-based C–N Bond Formation via Photo-/Electrochemistry. *Chem. Soc. Rev.* **2018**, *47*, 2591-2608. (c) Yang, Y.; Arnold, F. H. Navigating the Unnatural Reaction Space: Directed Evolution of Heme Proteins for Selective Carbene and Nitrene Transfer. *Acc. Chem. Res.* **2021**, *54*, 1209-1225.

(3) For selected review, see: (a) Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. The Essential Role of Bond Energetics in C–H Activation/Functionalization. *Chem. Rev.* **2017**, *117*, 8622-8648. For selected recent examples, see: (b) Bess, E. N.; DeLuca, R. J.; Tindall, D. J.; Oderinde, M. S.; Roizen, J. L.; Du Bois, J.; Sigman, M. S. Analyzing Site Selectivity in $Rh_2(esp)_2$-Catalyzed Intermolecular C–H Amination Reactions. *J. Am. Chem. Soc.* **2014**, *136*, 5783-5789. (c) Clark, J. R.; Feng, K.; Sookezian, A.; White, M. C. Manganese-Catalysed Benzylic C(sp^3)–H Amination for Late-Stage Functionalization. *Nat. Chem.* **2018**, *10*, 583-591. (d) Brunard, E.; Boquet, V.; Van Elslande, E.; Saget, T.; Dauban, P. Catalytic Intermolecular C(sp^3)–H Amination: Selective Functionalization of Tertiary C–H Bonds vs Activated Benzylic C–H Bonds. *J. Am. Chem. Soc.* **2021**, *143*, 6407-6412.

(4) (a) Lei, H.; Rovis, T. Ir-Catalyzed Intermolecular Branch-Selective Allylic C–H Amidation of Unactivated Terminal Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 2268-2273. (b) Lei, H.; Rovis, T. A Site-selective Amination Catalyst Discriminates between Nearly Identical C–H Bonds of Unsymmetrical Disubstituted Alkenes. *Nat. Chem.* **2020**, *12*, 725-731.

(5) Knecht, T.; Mondal, S.; Ye, J.-H.; Das, M.; Glorius, F. Intermolecular, Branch-Selective, and Redox-Neutral Cp^*Ir^{III}-Catalyzed Allylic C−H Amidation. *Angew. Chem., Int. Ed.* **2019**, *58*, 7117-7121.

(6) (a) Burman, J. S.; Harris, R. J.; Farr, C. M. B.; Bacsa, J.; Blakey, S. B. Rh(III) and Ir(III)Cp* Complexes Provide Complementary Regioselectivity Profiles in Intermolecular Allylic C–H Amidation Reactions. *ACS Catal.* **2019**, *9*, 5474-5479. (b) Kazerouni, A. M.; Nelson, T. A. F.; Chen, S. W.; Sharp, K. R.; Blakey, S. B. Regioselective Cp*Ir(III)-Catalyzed Allylic C–H Sulfamidation of Allylbenzene Derivatives. *J. Org. Chem.* **2019**, *84*, 13179-13185. (c) Farr, C. M. B.; Kazerouni, A. M.; Park, B.; Poff, C. D.; Won, J.; Sharp, K. R.; Baik, M.-H.; Blakey, S. B. Designing a Planar Chiral Rhodium Indenyl Catalyst for Regio- and Enantioselective Allylic C–H Amidation. *J. Am. Chem. Soc.* **2020**, *142*, 13996-14004.

(7) Bakhoda, A.; Jiang, Q.; Badiei, Y. M.; Bertke, J. A.; Cundari, T. R.; Warren, T. H. Copper-Catalyzed C(sp^3)−H Amidation: Sterically Driven Primary and Secondary C−H Site-Selectivity. *Angew. Chem., Int. Ed.* **2019**, *58*, 3421-3425.

(8) Lee, J.; Jin, S.; Kim, D.; Hong, S. H.; Chang, S. Cobalt-Catalyzed Intermolecular C–H Amidation of Unactivated Alkanes. *J. Am. Chem. Soc.* **2021**, *143*, 5191-5200.

(9) (a) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. Intermolecular Amidation of Unactivated sp^2 and sp^3 C−H Bonds via Palladium-Catalyzed Cascade C−H Activation/Nitrene Insertion. *J. Am. Chem. Soc.* **2006**, *128*, 9048-9049. (b) Iglesias, Á.; Álvarez, R.; de Lera, Á. R.; Muñiz, K. Palladium-Catalyzed Intermolecular C(sp^3)–H Amidation. *Angew. Chem., Int. Ed.* **2012**, *51*, 2225-2228. (c) He, J.; Shigenari, T.; Yu, J.-Q. Palladium(0)/PAr_3-Catalyzed Intermolecular Amination of C(sp^3)–H Bonds: Synthesis of *β*-Amino Acids. *Angew. Chem., Int. Ed.* **2015**, *54*, 6545-6549.

(10) (a) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. Iridium-Catalyzed Intermolecular Amidation of sp^3 C–H Bonds: Late-Stage Functionalization of an Unactivated Methyl Group. *J. Am. Chem. Soc.* **2014**, *136*, 4141-4144. (b) Zhang, T.; Hu, X.; Dong, X.; Li, G.; Lu, H. Iridium-Catalyzed Unreactive C(sp^3)–H Amination with 2,2,2-Trichloroethoxycarbonyl Azide. *Org. Lett.* **2018**, *20*, 6260-6264. (c) Han, J.-L.; Qin, Y.; Zhao, D. C(sp^3)–H Bond Arylation and Amidation of Si-Bound Methyl Group via Directing Group Strategy. *ACS Catal.* **2019**, *9*, 6020-6026.

(11) (a) Wang, H.; Tang, G.; Li, X. Rhodium(III)-Catalyzed Amidation of Unactivated C(sp^3)−H Bonds. *Angew. Chem., Int. Ed.* **2015**, *54*, 13049-13052. (b) Dong, Y.; Chen, J.; Xu, H. Rhodium(III)-Catalyzed Directed Amidation of Unactivated C(sp^3)–H Bonds to Afford 1,2-Amino Alcohol Derivatives. *Chem. Commun.* **2018**, *54*, 11096-11099. (c) Wang, Y.; Liu, H.; Li, B.; Wang, B. Rhodium(III)-Catalyzed Intermolecular Unactivated Secondary C(sp^3)−H Bond Amidation Directed by 3,5-Dimethylpyrazole. *Adv. Synth. Catal.* **2019**, *361*, 1564-1569.

(12) Liu, B.; Li, B.; Wang, B. Ru(II)-Catalyzed Amidation Reactions of 8-Methylquinolines with Azides via C(sp^3)–H Activation. *Chem. Commun.* **2015**, *51*, 16334-16337.

(13) For selected examples employing 3d transition metals, see: (a) Barsu, N.; Rahman, M. A.; Sen, M.; Sundararaju, B. Cp^*Co^{III}-Catalyzed C(sp^3)−H Bond Amidation of 8-Methylquinoline. *Chem. Eur. J.* **2016**, *22*, 9135-9138. (b) Liu, R.-H.; Shan, Q.-C.; Hu, X.-H.; Loh, T.-P. Site-Selective C(sp^3)–H Amination of Thioamide with Anthranils under Cp^*Co^{III} Catalysis. *Chem. Commun.* **2019**, *55*, 5519-5522. (c) Kim, Y; Won, J.; Lee, J.; Kim, J.; Zhou, B.; Park, J.-W.; Baik, M.-H.; Chang, S. Ni-Catalyzed Intermolecular C(sp3)–H Amidation Tuned by Bidentate Directing Groups. *ACS Catal.* **2021**, *11*, 3067-3072.

(14) For selected reviews, see: (a) Vasseur, A.; Bruffaerts, J.; Marek, I. Remote Functionalization through Alkene Isomerization. *Nat. Chem.* **2016**, *8*, 209-219. (b) Sommer, H.; Juliá-Hernández, F.; Martin, R.; Marek, I., Walking Metals for Remote Functionalization. *ACS Cent. Sci.* **2018**, *4*, 153-165. (c) Janssen-Müller, D.; Sahoo, B.; Sun, S.-Z.; Martin, R. Tackling Remote sp^3 C−H Functionalization via Ni-Catalyzed "chain-walking" Reactions. *Isr. J. Chem.* **2020**, *60*, 195-206.

(15) For selected recent examples, see: (a) Lee, W.-C.; Wang, C.-H.; Lin, Y.-H.; Shih, W.-C.; Ong, T.-G. Tandem Isomerization and C–H Activation: Regioselective Hydroheteroarylation of Allylarenes. *Org. Lett.* **2013**, *15*, 5358-5361. (b) Buslov, I.; Becouse, J.; Mazza, S.; Montandon-Clerc, M.; Hu, X., Chemoselective Alkene Hydrosilylation Catalyzed by Nickel Pincer Complexes. *Angew. Chem., Int. Ed.* **2015**, *54*, 14523-14526. (c) Buslov, I.; Song, F.; Hu, X. An Easily Accessed Nickel Nanoparticle Catalyst for Alkene Hydrosilylation with Tertiary Silanes. *Angew. Chem., Int. Ed.* **2016**, *55*, 12295-12299. (d) Juliá-Hernández, F.; Moragas, T.; Cornella, J.; Martin, R. Remote Carboxylation of Halogenated Aliphatic Hydrocarbons with Carbon Dioxide. *Nature* **2017**, *545*, 84-88. (e) He, Y.; Cai, Y.; Zhu, S. Mild and Regioselective Benzylic C–H Functionalization: Ni-Catalyzed Reductive Arylation of Remote and Proximal Olefins. *J. Am. Chem. Soc.* **2017,** *139*, 1061-1064. (f) Chen, F.; Chen, K.; Zhang, Y.; He, Y.; Wang, Y.-M.; Zhu, S. Remote Migratory Cross-Electrophile Coupling and Olefin Hydroarylation Reactions Enabled by in Situ Generation of NiH. *J. Am. Chem. Soc.* **2017**, *139*, 13929-13935. (g) Zhou, F.; Zhu, J.; Zhang, Y.; Zhu, S. NiH-Catalyzed Reductive Relay Hydroalkylation: A Strategy for the Remote C(sp^3)−H Alkylation of Alkenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 4058-4062. (h) Xiao, J.; He, Y.; Ye, F.; Zhu, S. Remote sp^3 C–H Amination of Alkenes with Nitroarenes. *Chem* **2018**, *4*, 1645-1657. (i) Sun, S.-Z.; Börjesson, M.; Martin-Montero, R.; Martin, R. Site-Selective Ni-Catalyzed Reductive Coupling of α-Haloboranes with Unactivated Olefins. *J. Am. Chem. Soc.* **2018**, *140*, 12765-12769. (j) Zhang, Y.; Xu, X.; Zhu, S. Nickel-Catalysed Selective Migratory Hydrothiolation of Alkenes and Alkynes with Thiols. *Nat. Commun.* **2019**, *10*, 1. (k) Zhang, Y.; Han, B.; Zhu, S. Rapid Access to Highly Functionalized Alkyl Boronates by NiH-Catalyzed Remote Hydroarylation of Boron-Containing Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 13860-13864. (l) Sun, S.-Z.; Romano, C.; Martin, R. Site-Selective Catalytic Deaminative Alkylation of Unactivated Olefins. *J. Am. Chem. Soc.* **2019**, *141*, 16197-16201. (m) Qian, D.; Hu, X. Ligand-Controlled Regiodivergent Hydroalkylation of Pyrrolines. *Angew. Chem., Int. Ed.* **2019**, *58*, 18519-18523. (n) Zhang, Y.; He, J.; Song, P.; Wang, Y.; Zhu, S. Ligand-Enabled NiH-Catalyzed Migratory Hydroamination: Chain Walking as a Strategy for Regiodivergent/Regioconvergent Remote C–H

Amination. *CCS Chem.* **2020**, *2*, 2259-2268. (o) Yu, R.; Rajasekar, S; Fang, X. Enantioselective Nickel-Catalyzed Migratory Hydrocyanation of Nonconjugated Dienes. *Angew. Chem., Int. Ed.* **2020**, *59*, 21436-21441 (p) Liu, J.; Gong, H.; Zhu, S. Nickel-Catalyzed, Regio- and Enantioselective Benzylic Alkenylation of Olefins with Alkenyl Bromide. *Angew. Chem., Int. Ed.* **2021**, *60*, 4060-4064. (q) He, Y.; Han, B.; Zhu, S. Terminal-Selective C(sp^3)–H Arylation: NiH-Catalyzed Remote Hydroarylation of Unactivated Internal Olefins. *Organometallics* **2021**, *40*, 2253-2264.

(16) (a) Lv, H.; Kang, H.; Zhou, B.; Xue, X.; Engle, K. M.; Zhao, D. Nickel-Catalyzed Intermolecular Oxidative Heck Arylation Driven by Transfer Hydrogenation. *Nat. Commun.* **2019**, *10*, 5025. (b) Chen, X.; Rao, W.; Yang, T.; Koh, M. Alkyl Halides as Both Hydride and Alkyl Sources in Catalytic Regioselective Reductive Olefin Hydroalkylation. *Nat. Commun*. **2020**, *11*, 5857.

(17) For selected review, see: (a) Hong, S.; Hwang, Y.; Lee, M; Chang, S. Mechanism-Guided Development of Transition-Metal-Catalyzed C–N Bond-Forming Reactions Using Dioxazolones as the Versatile Amidating Source. *Acc. Chem. Res.* **2021**, *54*, 2683-2700. For selected recent examples, see: (b) Zhou, Y.; Eegl, O.; Bandar, J.; Chant, E.; Buchwald, S. CuH-Catalyzed Asymmetric Hydroamidation of Vinylarenes. *Angew. Chem. Int. Ed.* **2018**, *57*, 6672-6675. (c) Lyu, X.; Zhang, J.; Kim, D.; Seo, S.; Chang, S. Merging NiH Catalysis and Inner-Sphere Metal-Nitrenoid Transfer for Hydroamidation of Alkynes. *J. Am. Chem. Soc.* **2021**, *143*, 5867-5877.

(18) For underlying mechanism of Markovnikov selectivity given by **L2**, See Supporting Information for more details.

(19) Jeon, J.; Lee, C.; Seo, H.; Hong, S. NiH-Catalyzed Proximal-Selective Hydroamination of Unactivated Alkenes. *J. Am. Chem. Soc.* **2020**, *142*, 20470-20480.

(20) For selected examples of thioether as directing group, see: (a) Perales, J. B.; Van Vranken, D. L. Thioether-Directed Platinum-Catalyzed Hydrosilylation of Olefins. *J. Org. Chem.* **2001**, *66* , 7270-7274. (b) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. Regio- and Enantioselective Intermolecular Hydroacylation: Substrate-Directed Addition of Salicylaldehydes to Homoallylic Sulfides. *J. Am. Chem. Soc.* **2010**, *132*, 16330-16333. (c) Kona, C. N.; Nishii, Y.; Miura, M. Thioether-Directed C4-Selective C–H Acylmethylation of Indoles Using α-Carbonyl Sulfoxonium Ylides. *Org. Lett.* **2020**, *22*, 4806-4811.

(21) (a) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*, University Science Books, Sausalito, 2006. (b) Xia, G.; Weng, J.; Liu, L.; Verma, P.; Li, Z.; Yu, J.-Q. Reversing Conventional Site-Selectivity in C(sp^3)–H Bond Activation. *Nat. Chem.* **2019**, *11*, 571-577.

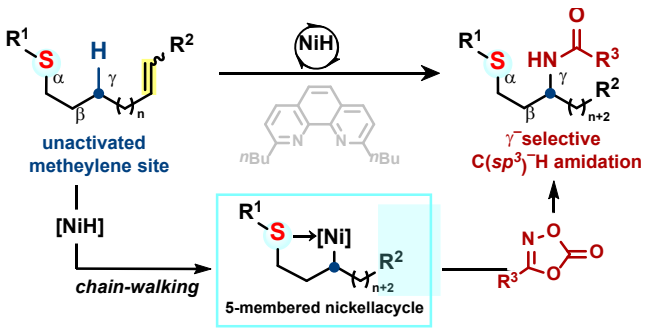
(22) (a) Schley, N.; Fu, C. Nickel-Catalyzed Negishi Arylations of Propargylic Bromides: A Mechanistic Investigation. *J. Am. Chem. Soc.* **2014**, *136*, 16588-16593. (b) Van der Puyl, V.; Derosa, J.; Engle, K. Directed, Nickel-Catalyzed Umpolung 1,2-Carboamination of Alkenyl Carbonyl Compounds. *ACS Catal.* **2019**, *9*, 224-229.

(23) Hammett, L. P. The Effect of Structure upon the Reactions of Organic Compounds Benzene Derivatives. *J. Am. Chem. Soc.* **1937**, *59*, 96-103.

(24) (a) Peng, L.; Li, Z.; Yin, G. Photochemical Nickel-Catalyzed Reductive Migratory Cross-Coupling of Alkyl Bromides with Aryl Bromides. *Org. Lett.* **2018**, *20*, 1880-1883. (b) Li, Y.; Luo, Y.; Peng, L.; Li, Y.; Zhao, B.; Wang, W.; Pang, H.; Deng, Y.; Bai, R.; Lan, Y.; Yin, G. Reaction Scope and Mechanistic Insights of Nickel-Catalyzed Migratory Suzuki–Miyaura Cross-Coupling. *Nat. Commun.* **2020**, *11*, 417.

(25) Eberhardt, N. A.; Guan, H. Nickel Hydride Complexes. *Chem. Rev.* **2016**, *116*, 8373-8426.

(26) (a) Li, W.; Boon, J. K.; Zhao, Y. Nickel-Catalyzed Difunctionalization of Allyl Moieties Using Organoboronic Acids and Halides with Divergent Regioselectivities. *Chem. Sci.* **2018**, *9*, 600-607. (b) Basnet, P.; Dhungana, R. K.; Thapa, S.; Shrestha, B.; Kc, S.; Sears, J. M.; Giri, R. Ni-Catalyzed Regioselective β,δ-Diarylation of Unactivated Olefins in Ketimines via Ligand-Enabled Contraction of Transient Nickellacycles: Rapid Access to Remotely Diarylated Ketones. *J. Am. Chem. Soc.* **2018**, *140*, 7782-7786.


R1
S
H
R2
α
β
γ
n
unactivated
metheylene site
[NiH]
chain-walking
NiH
nBu
N
N
nBu
R1
S
HN
O
R3
R2
n+2
γ-selective
C(sp3)-H amidation
R1
S
[Ni]
R2
n+2
5-membered nickellacycle
N
O
O
O
R3