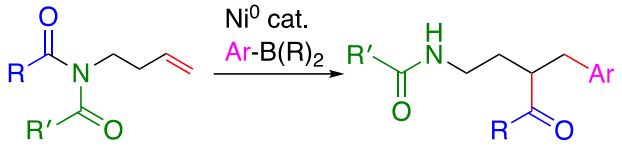
Nickel-Catalyzed Formation of α-Substituted γ-Amino Ketones via Alkene Carboacylation

Austin S. Moore and Levi M. Stanley*

Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States



- Unactivated Alkene
- Regioselective C-N Bond Activation
- 16 examples up to 92% yield

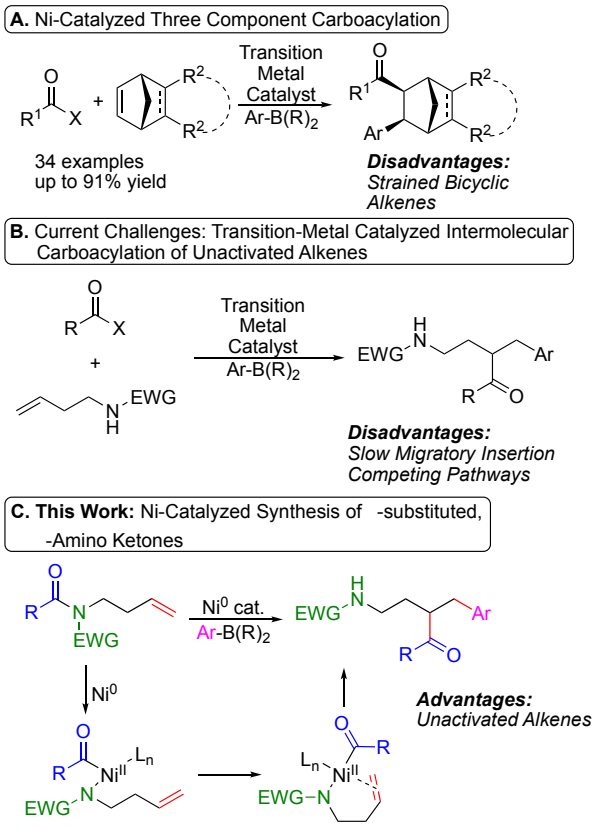
ABSTRACT: Herein we report Ni-catalyzed intramolecular carboacylation of imides containing a tethered alkene and tetraarylborate nucleophiles. Using a nickel-phosphine catalyst system, α-substituted, γ-amino ketones are generated in up to 92% yield with site selectivity. Deprotection and cyclization of the γ-amino ketone product afforded a cyclic imine in 71% yield, and a stereoselective reduction formed the β-substituted, δ-amino alcohol in 66% yield with 2.3:1 d.r. and 94% ee (major diastereomer).

Transition metal-catalyzed dicarbofunctionalization reactions of alkenes are important tools in the development of functionally complex compounds from commercially available feedstocks.[1] Our group and others have focused on the development of arylacylation reactions of alkenes to rapidly generate ketones.[2] These arylacylation reactions fall into two general categories: 1) activation of a C-C bond to form a aryl-metal-acyl intermediate[1a, 2a, 2b, 2d-g, 2i] and 2) direct activation of the C-X bond of a carboxylic acid derivative to form a metal-acyl intermediate.[2h, 2j-l, 2n-p, 2r] The former strategy has been leveraged to make a variety of structurally complex ketones, but this approach requires relatively complex starting materials and/or challenging removal of directing groups. The latter approach has drawn significant interest in recent years due to the variety of readily accessible carboxylic acid derivatives. Our group and the Newman group have reported intramolecular arylacylation reactions of *ortho*-allylbenzamides and *ortho*-allylbenzoate esters with arylboron nucleophiles.[2k, 2l, 2r] These reactions provide proof-of-concept for transition metal-catalyzed arylacylation of alkenes with carboxylic acid derivatives and arylboron nucleophiles. However, these reactions require preorganization of the acyl and alkene coupling partners and are limited to the formation of substituted indanones.

The utility of arylacylation reactions of alkenes would be greatly expanded by the ability to perform intermolecular, three-component couplings of carboxylic acid derivatives, alkenes, and arylboron reagents. To this end, our group and others have shown that intermolecular arylacylation reactions of strained, bicyclic alkenes occur to form functionalized ketones in good-to-excellent yields (Scheme 1A).[1e, 2l] However, these types of intermolecular arylacylation reactions are not general for alkenes beyond those that are strained and bicyclic.

We envisioned identifying a catalyst system capable of coupling a

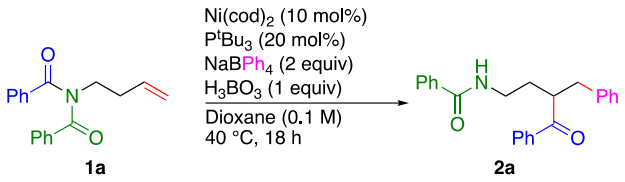
Scheme 1. Arylacylation Reactions



range of alkenes with acyl electrophiles and aryl nucleophiles. In particular, we targeted reactions of homoallylic amines with carboxylic acid derivatives and an arylboron nucleophile as a novel entry to the γ-amino ketone motif found in a variety of pharmaceuticals and biologically active compounds (Scheme 1B).[3] Based on our preliminary studies, these types of intermolecular arylacylation reactions are challenging because the rate of migratory insertion of unactivated alkenes into the acyl-metal bond is slow relative to catalyst decomposition and competing reaction pathways.

We sought to address these limitations by designing a reactant for pseudo-intermolecular alkene arylacylation (Scheme 1C). Our knowledge of imide activation[2k, 2l, 2n] led us to evaluate *N*-homoallylimides in which activation of the acyl C-N bond leads to cleavage of the homoallylic amine unit from the acyl coupling partner. This approach would provide rapid access to γ-amino ketones via a formal intermolecular coupling of a carboxylic acid derivative, a homoallylic amine, and an aryl nucleophile. Moreover, we hypothesize this strategy will mitigate the need for strained, bicyclic alkenes that lead to fast migratory insertion by pre-organizing the acyl and alkene units within the same Ni(II) complex. This pre-organization has the potential to limit the impact of competing reaction pathways and improve the rate of migratory insertion of an unactivated alkene into the Ni-C(acyl) bond.

Table 1. Optimization Studies



Entry	Deviation from Standard Conditions	Yield (%)[a]
1	none	92[b,c]
2	95 °C	41
3	rt	20
4	5 mol% $Ni(cod)_2$, 10 mol% P^tBu_3	72
5	10 mol% P^tBu_3	85
6	No H_3BO_3	26
7	2 equiv H_3BO_3	65
8	2 equiv BPh_3 instead of $NaBPh_4$	0
9	2 equiv BPh_3, no $NaBPh_4$ or H_3BO_3	0
10	20 mol% BPh_3	48
11	20 mol% BPh_3, no H_3BO_3	0

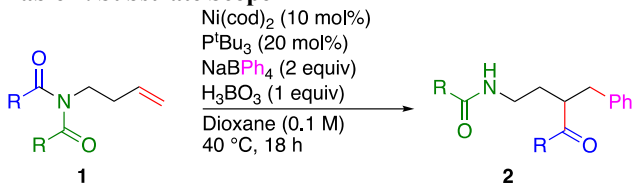
[a]Determined by ^1H NMR spectroscopy using dibromomethane as internal standard. [b]Isolated Yield. [c]Reaction Conditions: **1a** (0.100 mmol), $NaBPh_4$ (0.200 mmol), H_3BO_3 (0.100 mmol), P^tBu_3 (0.020 mmol), $Ni(cod)_2$ (0.010 mmol), 1,4-dioxane (1 ml), 18 h at 40°C.

We began our investigation by evaluating the reactivity of *N*-benzoyl-*N*-(but-3-en-1-yl)benzamide **1a** as a model substrate (Table 1). The reaction of **1a** with sodium tetraphenylborate ($NaBPh_4$) in the presence of boric acid and a catalyst generated from $Ni(cod)_2$ and tri-*tert*-butylphosphine (P(*t*-Bu)$_3$) formed amino ketone **2a** in 92% yield (entry 1). We found the following reactions parameters led to the formation of amino ketone **2a** in high yield: a 1:2 ratio of catalyst to ligand; 2 equivalents of the $NaBPh_4$ nucleophile; and 1 equivalent of boric acid at 40 °C in 1,4-dioxane.

During optimization studies, we found the reaction temperature significantly impacts the yield of amino ketone **2a**. Increasing the reaction temperature resulted in lower yields of **2a** due to decarbonylation from the intermediate acylnickelamidate species followed by transmetalation and reductive elimination to generate biphenyl (entry 2). Lowering the reaction temperature to room temperature led to low yield of **2a** (20%) with nearly quantitative recovery of the balance of the mass as starting material **1a** (entry 3). Lowering the catalyst loading and changing the ratio of Ni:ligand from 1:2 to 1:1 led to slight decreases in the yield of **2a** (entries 4 and 5). Eliminating the boric acid additive from the reaction leads to a significant decrease in the yield of **2a** (entry 6). However, increasing the loading of boric acid is also detrimental to the yield of the reaction (entry 7).

Our intial hypothesis was that the beneficial effects of boric acid were likely a result of reaction with sodium tetraphenylborate to generate triphenylborane during the course of the reaction. The triphenylborane could serve to activate the imide substrate **1a** or serve as the active organoboron nucleophile in the reaction.[21] In an effort to identify the active organoboron nucleophile, we conducted our model reaction with 2 equiv of triphenylborane instead of sodium tetraphenylborate in the presence and absence of boric acid (entries 8 and 9). These reactions did not lead to the formation of amino ketone **2a**, suggesting that triphenylborane is not the active organoboron nucleophile. In fact, addition of catalytic quantities of triphenylborane as an additive is detrimental to the yield of amino ketone **2a** (entries 10 and 11). Taken together, these results suggest that boric acid plays a role in activation of the imide substrate and that sodium tetraphenylborate is likely the active organoboron nucleophile.

Table 2. Substrate Scope[a]



Entry	R	Product	Yield (%)
1	C_6H_5	2a	92 (92)[b]
2	p-$CH_3C_6H_4$	2b	86
3	p-FC_6H_4	2c	71
4	p-$OCH_3C_6H_4$	2d	70
5	m-$CH_3C_6H_4$	2e	77
6	C_6H_{11}	2f	61
7	p-$CF_3C_6H_4$	2g	10[c]
8	m-$OCH_3C_6H_4$	2h	24[c]
9	o-$CH_3C_6H_4$	2i	16[c]
10	o-FC_6H_4	2j	21[c]
11	CH_3	2k	0[c]

[a]Reaction Conditions: **1a** (0.200 mmol), $NaBPh_4$ (0.400 mmol), H_3BO_3 (0.200 mmol), P^tBu_3 (0.040 mmol), $Ni(cod)_2$ (0.020 mmol), 1,4-dioxane (2 ml), 18 h at 40°C. Yields of **2a-f** are isolated yields

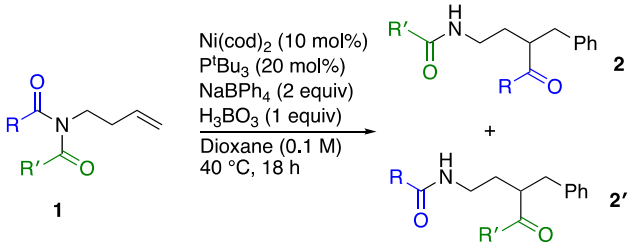
after column chromatography. [b]Reaction run at 1 mmol scale. [c]Yields determined by ^{1}H NMR spectroscopy using dibromomethane as internal standard.

Unfortunately, the scope of the reaction with respect to sodium tetraarylborate nucleophiles is limited to sodium tetraphenylborate. As shown in Table 1, entry 1, the model reaction of **1a** with commercial sodium tetraphenylborate purchased from Sigma-Aldrich) led to the formation of **2a** in 92% yield (see Table S1, entry 2). The reaction of **1a** with sodium tetraphenylborate synthesized from phenylmagnesium bromide and sodium tetrafluroborate formed **2a** in 91% yield.[4] However, reactions of sodium tetra(*p*-tolyl)borate, sodium tetra(4-methoxyphenyl)borate, and sodium tetra(4-fluorophenyl)borate, prepared from the appropriate Grignard reagent and sodium tetrafluoroborate, with **1a** in the presence of the nickel catalyst did not lead to the formation of the corresponding amino ketone products (see Table S1, entries 3-5).

With practical reactions conditions in hand, we investigated reactions of a range of substituted *N*-benzoyl-*N*-(but-3-en-1-yl)benzamides (Table 2). Reactions of *N*-benzoyl-*N*-(but-3-en-1-yl)benzamides containing electron-donating and mildly electron-withdrawing substituents at the para position formed products **2b-2d** in 70-86% yield. The reaction of *N*-(but-3-en-1-yl)-3-methyl-*N*-(3-methylbenzoyl)benzamide formed product **2e** in 77% yield. In addition, the reaction of *N*-(but-3-en-1-yl)-*N*-(cyclohexanecarbonyl)cyclohexancarboxamide formed γ-amino ketone **2f** in 61% yield.

Unfortunately, reactions of symmetrical *N*-benzoyl-*N*-(but-3-en-1-yl)benzamides do not form γ-amino ketones in high yields in many instances (Table 2). For example, *N*-benzoyl-*N*-(but-3-en-1-yl)benzamides containing electron-withdrawing groups react to form γ-amino ketones in low yields (10-24%). Reactions of *N*-benzoyl-*N*-(but-3-en-1-yl)benzamides containing ortho substitution are inefficient and lead to the corresponding γ-amino ketones in 16-21% yield. In addition, *N*-acetyl-*N*-(but-3-en-1-yl)acetamide was unreactive. Imides containing *N*-allyl, *N*-bis-homoallyl and substituted homoallyl groups did not generate the corresponding amino ketone products.

Table 3. Unsymmetric Imide Substrate Scope



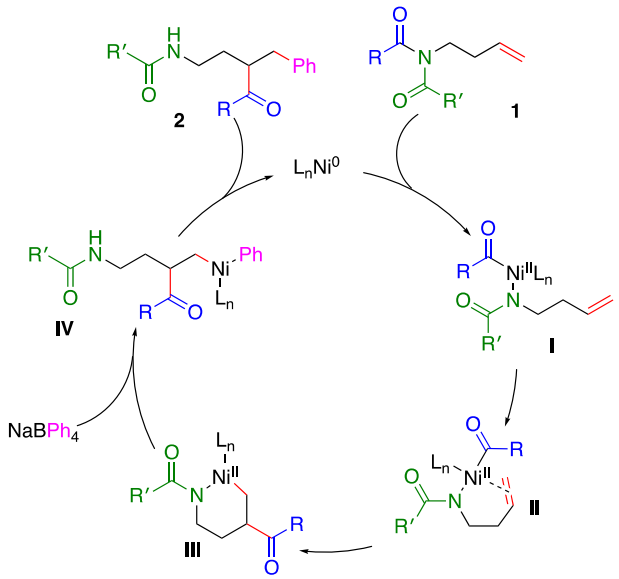
R	R´	Product	Yield (%)	**2**:**2′** Ratio
C_6H_5	p-$CF_3C_6H_4$	2l	75	1.9:1
p-$OCH_3C_6H_4$	p-$CF_3C_6H_4$	2m	90	4:1
p-$CF_3C_6H_4$	o-$CH_3C_6H_4$	2n[a]	44	>20:1
p-$CF_3C_6H_4$	Mes	2o	40	>20:1
p-$CF_3C_6H_4$	o-$OCH_3C_6H_4$	2p[a]	60	>20:1
m-$OCH_3C_6H_4$	o-$OCH_3C_6H_4$	2q[a]	62	>20:1
Ac	o-$OCH_3C_6H_4$	2r[a]	25	>20:1
C_6H_5	Cy	2s[a]	68	>20:1

[a]Reaction run at 60 ºC.

Following studies on the scope of reactions with symmetrical *N*-benzoyl-*N*-(but-3-en-1-yl)benzamides, we sought to leverage the lack of reactivity observed with *N*-benzoyl-*N*-(but-3-en-1-yl)benzamides containing strongly electron-deficient aryl groups or *ortho*-substituted aryl groups to facilitate selective C-N bond activation in unsymmetrical *N*-homoallylimide substrates (Table 3). By pairing the *p*-trifluoromethyl substituted benzoyl group with the electron-neutral phenyl and electron-rich *p*-methoxybenzoyl derivatives, we found that *N*-benzoyl-*N*-(but-3-en-1-yl)-4-(trifluoromethyl)benzamide and *N*-(but-3-en-1-yl)-4-methoxy-*N*-(4-(trifluoromethyl)benzoyl)benzamide generated 1.9:1 and 4:1 mixtures of two γ-amino ketone regiomers in 75% and 90% yield, respectively (Table 3, products **2l** and **2m**). These regioisomeric mixtures indicate that selective reaction of the imide C-N bond of the more electron-rich benzoyl group is favored.

We next sought to investigate the impact of sterics on imide activation as a way to improve on the modest selectivity observed by differentiating the electronic properties of the benzoyl groups present in the unsymmetrical *N*-homoallylimide substrates. Reactions of unsymmetrical *N*-homoallylimides containing a 4-trifluoromethylbenzoyl group and an *ortho*-substituted benzoyl group led to greater than >20:1 selectivity favoring C-N bond activation of the less hindered benzoyl group (products **2n-p**). For example, the reaction of *N*-(but-3-en-1-yl)-2-methoxy-*N*-(4-(trifluoromethyl)benzoyl)benzamide forms product **2p** in 60% yield with greater than >20:1 regioselectivity. This result is remarkable as the ketone product is formed in good yield despite the requirement for selective reaction of an electron-deficient benzoyl group which proved problematic in the context of symmetrical *N*-homoallylimide substrates.

Scheme 2. Proposed Mechanism



A plausible reaction mechanism is presented in Scheme 2. Oxidative addition of *N*-homoallylimide **1** in the presence of the Ni(0) catalyst leads to the formation of acyl-nickel-amidate

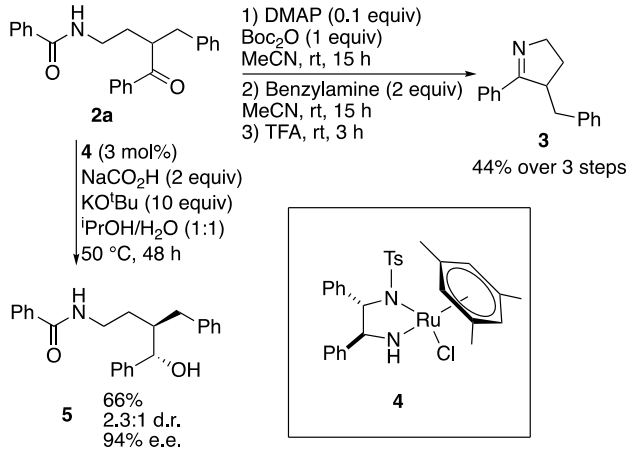
intermediate **I**. Subsequent isomerization of the acyl and amidate ligands and coordination of the alkene generates intermediate **II**. Migratory insertion of the alkene into the Ni-C(acyl) bond forms intermediate **III**. Transmetalation of intermediate **III** with $NaBPh_4$ in the presence of boric acid generates intermediate **IV**. Reductive elimination from intermediate **IV** liberates the γ-amino ketone product and regenerates the Ni(0) catalyst.

The results of reactions of symmetrical imides containing electron-deficient acyl groups in combination with the reactivity and selectivity observed in reactions of the unsymmetrical imides provide insight into the requirements for efficient carboacylation reactions. The reaction of symmetrical *N*-(but-3-en-1-yl)-4-(trifluoromethyl)-*N*-(4-(trifluoromethyl)benzoyl)benzamide **1g** leads to 40% conversion of the imide starting material but only 10% yield of the γ-amino ketone product **2g** (Table 2, entry 7).[2j] This result suggests oxidative addition to form the corresponding acyl-nickel-amidate intermediate **I** is feasible. The low product yield may result from dissociation of the electron-deficient amidate ligand leading to relatively slow migratory insertion and a significant rate of decarbonylation of the Ni-acyl intermediate. It is also possible that migratory insertion into the Ni-acyl bond of an electron-deficient acyl group is slow relative to migratory insertion into the Ni-acyl bond of an electron-rich acyl ligand.[2c, 2n, 5] The reaction of *N*-(but-3-en-1-yl)-4-methoxy-*N*-(4-(trifluoromethyl)benzoyl)benzamide proceeds selectively through an acyl-nickel-amidate intermediate containing an electron-deficient amidate ligand and an electron-rich acyl ligand (Table 3, product **2m**). The carboacylation reaction occurs in high yield. This result is consistent with faster rates of migratory insertion into Ni-C(acyl) bonds with electron-rich acyl groups. However, the electronic differentiation between a *p*-methoxybenzoyl group and a *p*-trifluoromethylbenzoyl group does not lead to synthetically useful regioselectivity. Oxidative addition of *N*-(but-3-en-1-yl)-2-methoxy-*N*-(4-(trifluoromethyl)benzoyl)benzamide occurs selectively into the more electron-deficient acyl group to generate an acyl-nickel-amidate intermediate containing an electron-rich amidate ligand and an electron-deficient acyl ligand. The corresponding carboacylation reaction occurs to form the ketone product in 60% yield despite migratory insertion occurring into a Ni-C(acyl) bond with an electron-deficient acyl group. This result is consistent with more electron-rich amidate ligands leading to faster relative rates of migratory insertion. The relatively faster rates of migratory insertion may result from an equilibrium favoring association of the amidate ligand to the metal center in conjuction with electron-rich amidate ligands leading to relatively slow rates of decarbonylation of the Ni-acyl intermediate.

The ability to selectively activate C-N bonds in unsymmetrical *N*-homoallylimide substrates and an understanding of the factors that lead to productive carboacylation led us to validate this approach in a selection of additional unsymmetrical *N*-homoallylimides. The reactions of *N*-(but-3-en-1-yl)-2-methoxy-*N*-(3-methoxybenzoyl)benzamide and *N*-acetyl-*N*-(but-3-en-1-yl)-2-methoxybenzamide formed ketones **2q** and **2r** in 62 and 25% yield, respectively (products **2q** and **2r**). These results contrast the poor yields observed in reactions of symmetrical *N*-homoallylimide substrates containing either 3-methoxybenzoyl or acetyl groups. The reaction of *N*-(but-3-en-1-yl)-*N*-(cyclohexanecarbonyl)benzamide containing one aromatic acyl group and one aliphatic acyl group generated the aromatic ketone product in 68% yield with >20:1 selectivity.

We then investigated two synthetic applications of the γ-amino ketone product: (1) amine deprotection followed by imine condensation to generate a 3,4-dihydro-2*H*-pyrrole and (2) asymmetric transfer hydrogenation in conjunction with dynamic kinetic resolution[6] to generate chiral β-substituted, δ-amino alcohols (Scheme 3). A sequence of activation of **2a**, cleavage of the benzyl protecting group,[7] and treatement with TFA[8] generated 3,4-dihydro-2*H*-pyrrole **3** in 44% yield over 3 steps. Asymmetric transfer hydrogenation of **2a** in the presence of catalytic RuCl(mesitylene)[(*S*,*S*)-Ts-DPEN)] **4** formed β-substituted, δ-amino alcohol **5** in 66% yield with 2.3:1 dr and 94% ee (major diasteromer) and 93% ee (minor diastereomer).

Scheme 3. Applications



In summary, we report the intramolecular carboacylation of imides containing a tethered unactivated alkene to generate α-substituted, γ-amino ketones. This transformation allows for expedited access to a challenging amino ketone motif in up to 92% yield. We also demonstrate the ability to transform unsymmetric imides into α-substituted, γ-amino ketones by selective activation of one C(acyl)-N bond over another. Electronic differentiation of the imide acyl groups leads to modest selectivity. However, steric differentiation of the imide acyl groups enables selective activation of the more accessible C(acyl)-N bond and the formation of the corresponding α-substituted, γ-amino ketones with >20:1 regioselectivity. We also demonstrate the utility of this synthetic method via deprotection and cyclization to form a 3,4-dihydro-2*H*-pyrrole and asymmetric transfer hydrogenation to generate a chiral, non-racemic β-substituted, δ-amino alcohol.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supplementary material.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterization data, and spectral data (PDF)

AUTHOR INFORMATION

Corresponding Author

Levi M. Stanley – *Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States;* orcid.org/0000-0001-8804-1146; Email: lstanley@iastate.edu

Authors

Austin S. Moore – *Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States*

Funding Sources

The authors thank the National Science Foundation for CHE Grant 1955529 that supported this work.

Notes

The authors declare no competing financial interest

ACKNOWLEDGMENT

The authors gratefully acknowledge Prof. Junqi Li (Iowa State University) for discussions and suggestions related to this study.

REFERENCES

(1) (a) Liu, L.; Ishida, N.; Murakami, M., Atom- and Step-Economical Pathway to Chiral Benzobicyclo[2.2.2]octenones through Carbon–Carbon Bond Cleavage. *Angew. Chem. Int. Ed.* **2012,** *51*, 2485-2488. (b) Xu, T.; Ko, H. M.; Savage, N. A.; Dong, G., Highly Enantioselective Rh-Catalyzed Carboacylation of Olefins: Efficient Syntheses of Chiral Poly-Fused Rings. *J. Am. Chem. Soc.* **2012,** *134*, 20005-20008. (c) Xu, T.; Dermenci, A.; Dong, G., Transition Metal-Catalyzed C–C Bond Activation of Four-Membered Cyclic Ketones. In *C-C Bond Activation*, Dong, G., Ed. Springer Berlin Heidelberg: Berlin, Heidelberg, 2014; pp 233-257. (d) Busch, M.; Wodrich, M. D.; Corminboeuf, C., A Generalized Picture of C–C Cross-Coupling. *ACS Catal.* **2017,** *7*, 5643-5653. (e) Dhungana, R. K.; KC, S.; Basnet, P.; Giri, R., Transition Metal-Catalyzed Dicarbofunctionalization of Unactivated Olefins. *Chem. Rec.* **2018,** *18*, 1314-1340. (f) Shu, W.; García-Domínguez, A.; Quirós, M. T.; Mondal, R.; Cárdenas, D. J.; Nevado, C., Ni-Catalyzed Reductive Dicarbofunctionalization of Nonactivated Alkenes: Scope and Mechanistic Insights. *J. Am. Chem. Soc.* **2019,** *141*, 13812-13821. (g) Derosa, J.; Apolinar, O.; Kang, T.; Tran, V. T.; Engle, K. M., Recent developments in nickel-catalyzed intermolecular dicarbofunctionalization of alkenes. *Chem. Sci.* **2020,** *11*, 4287-4296. (h) Qi, X.; Diao, T., Nickel-Catalyzed Dicarbofunctionalization of Alkenes. *ACS Catal.* **2020,** *10*, 8542-8556. (i) Zhu, J.-W.; Zhou, B.; Cao, Z.-Y.; Liang, R.-X.; Jia, Y.-X., Stereoselective 1,2-Dicarbofunctionalization of Trisubstituted Alkenes by Palladium-Catalyzed Heck/Suzuki or Heck/Sonogashira Domino Sequence. *CCS Chem.* **2021,** *3*, 2340-2349. (j) Wang, H.; Liu, C.-F.; Martin, R. T.; Gutierrez, O.; Koh, M. J., Directing-group-free catalytic dicarbofunctionalization of unactivated alkenes. *Nat. Chem.* **2022,** *14*, 188-195.

(2) (a) Dreis, A. M.; Douglas, C. J., Catalytic Carbon−Carbon σ Bond Activation: An Intramolecular Carbo-Acylation Reaction with Acylquinolines. *J. Am. Chem. Soc.* **2009,** *131*, 412-413. (b) Wentzel, M. T.; Reddy, V. J.; Hyster, T. K.; Douglas, C. J., Chemoselectivity in Catalytic C–C and C–H Bond Activation: Controlling Intermolecular Carboacylation and Hydroarylation of Alkenes. *Angew. Chem. Int. Ed.* **2009,** *48*, 6121-6123. (c) Arndt, M.; Salih, K. S. M.; Fromm, A.; Goossen, L. J.; Menges, F.; Niedner-Schatteburg, G., Mechanistic Investigation of the Ru-Catalyzed Hydroamidation of Terminal Alkynes. *J. Am. Chem. Soc.* **2011,** *133*, 7428-7449. (d) Rathbun, C. M.; Johnson, J. B., Rhodium-Catalyzed Acylation with Quinolinyl Ketones: Carbon−Carbon Single Bond Activation as the Turnover-Limiting Step of Catalysis. *J. Am. Chem. Soc.* **2011,** *133*, 2031-2033. (e) Lutz, J. P.; Rathbun, C. M.; Stevenson, S. M.; Powell, B. M.; Boman, T. S.; Baxter, C. E.; Zona, J. M.; Johnson, J. B., Rate-Limiting Step of the Rh-Catalyzed Carboacylation of Alkenes: C–C Bond Activation or Migratory Insertion? *J. Am. Chem. Soc.* **2012,** *134*, 715-722. (f) Xu, T.; Dong, G., Rhodium-Catalyzed Regioselective Carboacylation of Olefins: A C–C Bond Activation Approach for Accessing Fused-Ring Systems. *Angew. Chem. Int. Ed.* **2012,** *51*, 7567-7571. (g) Souillart, L.; Parker, E.; Cramer, N., Highly Enantioselective Rhodium(I)-Catalyzed Activation of Enantiotopic Cyclobutanone C□C Bonds. *Angew. Chem. Int. Ed.* **2014,** *53*, 3001-3005. (h) Tatsumi, K.; Fujihara, T.; Terao, J.; Tsuji, Y., Palladium-catalyzed formal arylacylation of allenes employing acid chlorides and arylboronic acids. *Chem. Commun.* **2014,** *50*, 8476-8479. (i) Lu, G.; Fang, C.; Xu, T.; Dong, G.; Liu, P., Computational Study of Rh-Catalyzed Carboacylation of Olefins: Ligand-Promoted Rhodacycle Isomerization Enables Regioselective C–C Bond Functionalization of Benzocyclobutenones. *J. Am. Chem. Soc.* **2015,** *137*, 8274-8283. (j) Szostak, R.; Meng, G.; Szostak, M., Resonance Destabilization in N-Acylanilines (Anilides): Electronically-Activated Planar Amides of Relevance in N–C(O) Cross-Coupling. *J. Org. Chem.* **2017,** *82*, 6373-6378. (k) Walker, J. A.; Vickerman, K. L.; Humke, J. N.; Stanley, L. M., Ni-Catalyzed Alkene Carboacylation via Amide C–N Bond Activation. *J. Am. Chem. Soc.* **2017,** *139*, 10228-10231. (l) Kadam, A. A.; Metz, T. L.; Qian, Y.; Stanley, L. M., Ni-Catalyzed Three-Component Alkene Carboacylation Initiated by Amide C–N Bond Activation. *ACS Catal.* **2019,** *9*, 5651-5656. (m) Xu, S.; Wang, K.; Kong, W., Ni-Catalyzed Reductive Arylacylation of Alkenes toward Carbonyl-Containing Oxindoles. *Org. Lett.* **2019,** *21*, 7498-7503. (n) Koeritz, M. T.; Burgett, R. W.; Kadam, A. A.; Stanley, L. M., Ni-Catalyzed Intermolecular Carboacylation of Internal Alkynes via Amide C–N Bond Activation. *Org. Lett.* **2020,** *22*, 5731-5736. (o) Wang, L.; Wang, C., Nickel-Catalyzed Three-Component Reductive Alkylacylation of Electron-Deficient Activated Alkenes. *Org. Lett.* **2020,** *22*, 8829-8835. (p) Banovetz, H. K.; Vickerman, K. L.; David, C. M.; Alkan, M.; Stanley, L. M., Palladium-Catalyzed Intermolecular Alkene Carboacylation via Ester C–O Bond Activation. *Org. Lett.* **2021,** *23*, 3507-3512. (q) Jin, Y.; Fan, P.; Wang, C., Nickel-Catalyzed Reductive Asymmetric Aryl-Acylation and Aryl-Carbamoylation of Unactivated Alkenes. *CCS Chem.* **2022**, *4*, 1510-1518. (r) Zheng, Y.-L.; Xie, P.-P.; Daneshfar, O.; Houk, K. N.; Hong, X.; Newman, S. G., Direct Synthesis of Ketones from Methyl Esters by Nickel-Catalyzed Suzuki–Miyaura Coupling. *Angew. Chem. Int. Ed.* **2021,** *60*, 13476-13483.

(3) (a) Michael, J. P., Indolizidine and quinolizidine alkaloids. *Natural Product Reports* **2008,** *25*, 139-165. (b) Daly, J. W.; Spande, T. F.; Garraffo, H. M., Alkaloids from Amphibian Skin: A Tabulation of Over Eight-Hundred Compounds. *J. Nat. Prod.* **2005,** *68*, 1556-1575.

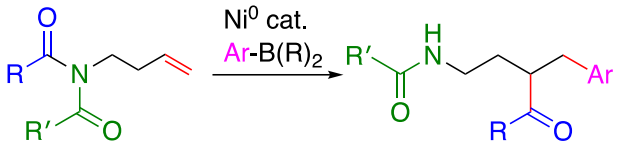
(4) Vasu, D.; Hausmann, J. N.; Saito, H.; Yanagi, T.; Yorimitsu, H.; Osuka, A., Robust Palladium-Catalyzed Arylation of Catalyst-Poisoning ortho-Sulfanyl Aryl Halides with Tetraarylborates and Its Application to Synthesis of π-Extended Dibenzothiophenes. *Asian Journal of Organic Chemistry* **2017,** *6*, 1390-1393.

(5) Aharonovich, S.; Botoshansky, M.; Balazs, Y. S.; Eisen, M. S., Elucidation of Substituent Effects in the Polymerization of Propylene Promoted by Titanium Amidinates. *Organometallics* **2012,** *31*, 3435-3438.

(6) (a) Zheng, D.; Zhao, Q.; Hu, X.; Cheng, T.; Liu, G.; Wang, W., A dynamic kinetic asymmetric transfer hydrogenation–cyclization tandem reaction: an easy access to chiral 3,4-dihydro-2H-pyran-carbonitriles. *Chem. Commun.* **2017,** *53*, 6113-6116. (b) Wu, X.; Li, X.; King, F.; Xiao, J., Insight into and Practical Application of pH-Controlled Asymmetric Transfer Hydrogenation of Aromatic Ketones in Water. *Angew. Chem. Int. Ed.* **2005,** *44*, 3407-3411. (c) Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J., Accelerated asymmetric transfer hydrogenation of aromatic ketones in water. *Org. Biomol. Chem.* **2004,** *2*, 1818-1821. (d) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R., Ruthenium(II)-Catalyzed Asymmetric Transfer Hydrogenation of Ketones Using a Formic Acid−Triethylamine Mixture. *J. Am. Chem. Soc.* **1996,** *118*, 2521-2522. (e) Wu, L.; Jin, R.; Li, L.; Hu, X.; Cheng, T.; Liu, G., A Michael Addition–Asymmetric Transfer Hydrogenation One-Pot Enantioselective Tandem Process for Syntheses of Chiral γ-Secondary Amino Alcohols. *Org. Lett.* **2017,** *19*, 3047-3050.

(7) Rahman, M. M.; Li, G.; Szostak, M., Metal-Free Transamidation of Secondary Amides by N–C Cleavage. *J. Org. Chem.* **2019,** *84*, 12091-12100.

(8) Giovannini, A.; Savoia, D.; Umani-Ronchi, A., Organometallic ring-opening reactions of N-acyl and N-alkoxycarbonyl lactams. Synthesis of cyclic imines. *J. Org. Chm.* **1989,** *54*, 228-234.



- **Unactivated Alkene**
- **Regioselective C-N Bond Activation**
- **16 examples up to 92% yield**