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Intermolecular, Branch-Selective and Redox-Neutral Cp*Ir^{III}-Catalyzed Allylic C–H Amidation

Tobias Knecht[+], Shobhan Mondal[+], Jian-Heng Ye, Mowpriya Das, and Frank Glorius*

Dedicated to Yitzhak Apeloig on the occasion of his 75th birthday

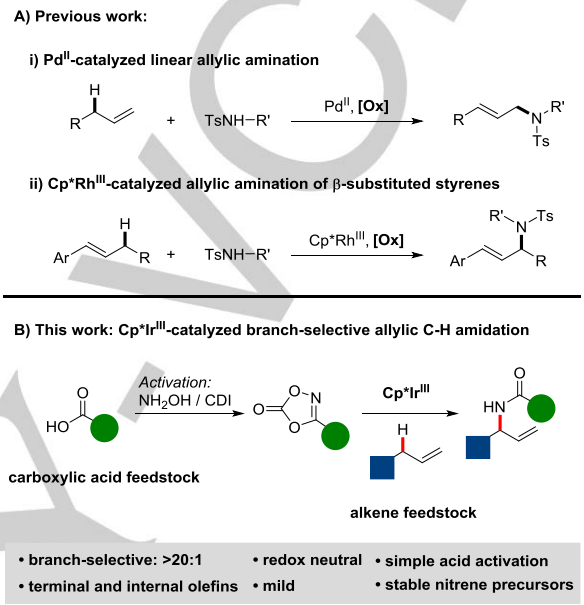
Abstract: Herein, we report the redox-neutral, intermolecular and highly branch-selective amidation of allylic C–H bonds enabled by Cp*Ir^{III} catalysis. A variety of readily available carboxylic acids were converted into their corresponding dioxazolones and efficiently coupled with terminal and internal olefins in high yields and selectivities. Mechanistic investigations support the formation of a nucleophilic Ir^{III}–allyl intermediate rather than the direct insertion of an Ir-nitrenoid species into the allylic C–H bond.

Nitrogen moieties are present in many of the most privileged structures found in pharmaceutical science.[1] Methods for the formation of aliphatic carbon–nitrogen bonds, such as by reductive amination or N-alkylation, are therefore naturally among the most commonly used transformations in drug discovery.[2] Furthermore, amide bond formation is another class of reaction that is essential to medicinal chemistry.[3] However, these reactions all typically require the synthesis of pre-functionalized starting materials.

The interconversion of allylic C–H to C–N bonds by the insertion of a metal-nitrenoid species into a C–H bond is a direct approach to streamline the synthesis of aminated compounds, but these methods often suffer from low regio- and chemoselectivity.[4] Alternatively, White, Liu and others have demonstrated that linear allylic amination can be selectively promoted through the coupling of terminal olefins with tosylamides using palladium-catalysis (Scheme 1A(i)).[5] In a complementary fashion, Blakey reported the allylic amination of β-substituted styrenes using Cp*Rh^{III} as the catalyst (Scheme 1A(ii)).[6] A common drawback of these processes is that the use of amine nucleophiles generally involves a reductive elimination pathway and thus, stoichiometric amounts of oxidants are required to regenerate the catalyst.[7]

More recently, Chang has introduced dioxazolones as stable nitrene-precursors for the redox-neutral *ortho*-directed C–H amidation of arenes avoiding Curtius-type rearrangements which are known to be problematic in metal-nitrene chemistry.[8,9]

Based on our experience in Cp*Rh^{III}-catalyzed allylic C–H functionalization reactions, we assumed that a Rh^{III}–allyl-intermediate might have ambiphilic characteristics.[10]



Scheme 1. General outline of allylic amination protocols via C–H activation.

Whereas several reports describe the electrophilic nature of Cp*Rh^{III}–allyl intermediates, which can be intercepted by nucleophilic coupling reagents, the insertion of the allyl–metal bond into an electrophile has yet to be described.[6,10] We aimed to couple dioxazolones, derived from naturally abundant and bioactive carboxylic acids with terminal and internal olefin feedstocks by allylic C–H activation (Scheme 1B).[11] Importantly, this electrophilic amidation approach would enable direct alkyl to amide coupling, whilst obviating the need for external oxidants.

We began our studies using 1-octene (**1a**) and methyl dioxazolone (**2a**) as the substrates with $[Cp^*RhCl_2]_2$ as the catalyst and AgOAc as the base at 80 °C in DCE (Table 1). To our delight we found that the product **3aa** was formed in 62% yield and with a 4:1 branch/linear (B/L) ratio (Table 1, entry 1). Upon switching the catalyst from Cp*Rh^{III} to Cp*Ir^{III}, the yield was increased to 86% and perfect branch-selectivity was observed (entry 2). The amount of AgOAc was decreased to 10 mol% and the reaction temperature was lowered to mild 40 °C without influencing the reaction outcome (entry 3-4).[12]

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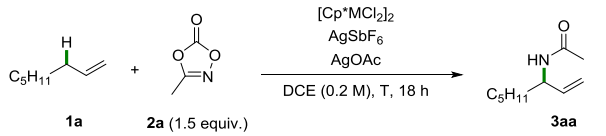
Table 1. Reaction optimization.[a]



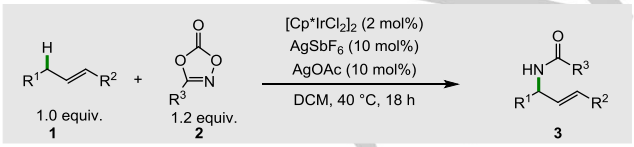
1a **2a** (1.5 equiv.) **3aa**

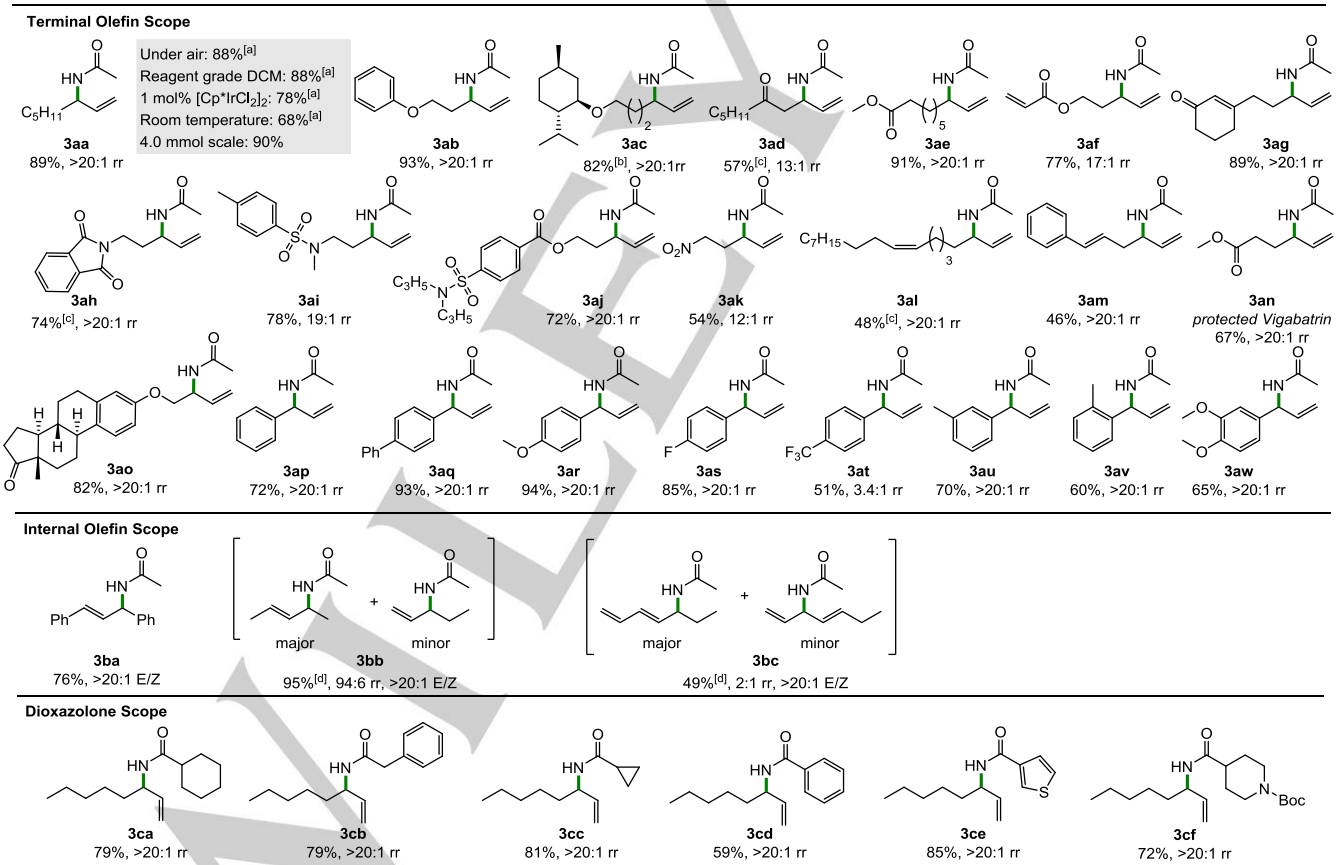
Entry	Catalyst	$AgSbF_6$	AgOAc	T	B/L	Yield[b]
1	[Rh] 5%	20%	200%	80 °C	4:1	62%
2	[Ir] 2.5%	10%	200%	80 °C	>20:1	86%
3	[Ir] 2.5%	10%	10%	80 °C	>20:1	90%
4	[Ir] 2.5%	10%	10%	40 °C	>20:1	90%
5[c]	[Ir] 2%	10%	10%	40 °C	>20:1	86%
6[d]	[Ir] 2%	10%	10%	40 °C	>20:1	90%

[a] Conditions: **1a** (0.10 mmol), **2a** (0.15 mmol) in 1,2-dichloroethane (DCE) under argon. [b] Yields determined by calibrated GC-FID analysis using mesitylene as internal standard. [c] Using 1.2 equiv. of **2a**. [d] Reaction run in dichloromethane (DCM) and using 1.2 equiv. of **2a.**

The loading of iridium pre-catalyst could also be lowered to 2 mol% when using 1.2 equiv. of **2a** (entry 5). Additionally, the solvent could be changed to dichloromethane (entry 6).

Whilst linear-selective allylic amination has been well explored, branch-selective C–H amination has only been realized: i) in an intramolecular fashion,[11,13] ii) through C–H oxygenation/allylic substitution[14] or iii) by employing a sulfurdiimide reagent which undergoes an ene-reaction followed by a Pd-catalyzed rearrangement.[15] This manuscript describes the direct intermolecular branch-selective amidation of allylic C–H bonds. With the optimized conditions in hand, we next analyzed the sensitivity of this reaction protocol (Scheme 2). Pleasingly, the product **1a** could also be isolated in the same yield (89%) when the reaction was conducted under air or standard reagent grade CH_2Cl_2 was used.





Scheme 2. Scope of the branch-selective allylic C–H amidation. Reaction performed on a 0.4 mmol scale in 2.0 mL of DCM under an argon atmosphere. Isolated yields of major isomers reported. Boc = *tert*-butyloxycarbonyl. [a] Reaction performed on a 0.1 mmol scale. Yield determined by GC-FID analysis using mesitylene as internal standard. [b] Product obtained in a 1:1 diastereomeric ratio. [c] 2.0 equiv. of **2** were used and the reaction time was 48 h. [d] 1.5 equiv. of **1** and 1.0 equiv. of **2** were used.

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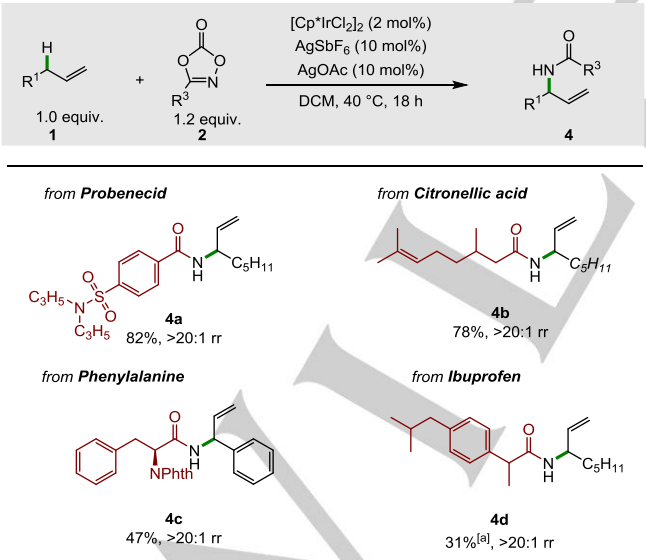
At reduced catalyst loading (1 mol%) the product was still formed in 78% yield. Performing the reaction at room temperature reduced the yield of the product to 68%. Finally, the reaction was scaled up to 4.0 mmol and no erosion in yield was observed (90%, 609 mg).

We began scoping studies with respect to the olefin coupling partner. Ether moieties and a γ,δ-unsaturated ketone were well tolerated under the reaction conditions and the corresponding products were isolated in moderate to high yields (**3ab**–**3ad**) [16] Esters, acrylates and an unsaturated ketone reacted smoothly to afford the desired products with no side reactions observed (**3ae**–**3ag**). The products of differently protected amines (**3ah**, **3ai**) and of the sulfonamide bearing Probenecid scaffold (**3aj**) were obtained in high yields. An electron withdrawing aliphatic nitro-group was also tolerated and (**3ak**) was isolated in moderate 54% yield. It should be noted that diminished yields were generally observed when conversions of both starting materials were low. Compounds bearing multiple double bonds were selectively amidated at the terminal allyl moiety (**3al**, **3am**). We also synthesized the protected drug Vigabatrin in a single step in 67% yield (**3an**). Additionally, an Estrone derivative was successfully amidated (**3ao**). Subsequently, we applied our reaction protocol to different allylarenes, which were all well tolerated under the reaction conditions (**3ao**–**3av**). However, electron-poor arenes reacted more sluggish than electron-rich arenes (**3aq**, **3as**). Interestingly, when using an electron deficient CF_3-substituted arene the regioselectivtiy (B/L) decreased to 3.4:1. Besides the functionalization of terminal olefins, internal olefins were also investigated as substrates.



Scheme 3. Functionalization of dioxazolones derived from complex carboxylic acids. Products obtained in a 1:1 diastereomeric ratio. [a] 1.0 equiv of **1** and 2 equiv. of **2** were used.

By employing (*E*)-1,3-diphenylpropene the product **3ba** was obtained in 76% yield. Even the highly volatile (*E*)-2-pentene could be utilized to afford **3bb** in 95% yield. A conjugated diene could also be used to obtain **3bc** in a moderate yield and regioisomeric ratio. The scope of the dioxazolone coupling partner was next investigated. Cyclohexyl, benzyl, cyclopropyl and piperidine substituted dioxazolones reacted smoothly to afford the desired products with no loss in selectivity (**3ca**–**3cc, 3cf**). Product **3cd** was obtained in a modest yield, presumably due to *ortho*-directed C–H amidation side reactions. We next applied the developed reaction protocol to naturally occurring and bioactive carboxylic acids (Scheme 3). Probenecid could be easily activated to form the amidated product **4a** in 82% yield. In addition, the dioxazolones derived from Citronellic acid and Ibuprofen could be used to afford the corresponding products (**4b**, **4d**) in 78% and 31% yield, respectively. Pleasingly, we were also able to couple a protected amino acid with allylbenzene to afford **4c** as a 1:1 mixture of diastereoisomers in 47% yield. The utilization of internal olefins and complex dioxazolones are complementary results to a fundamental work by Rovis that appeared just prior to submission of this manuscript.[17]

We then investigated the reaction mechanism. Considering that Ir-netrenoid species are known to undergo C–H insertion[4,11,18], we envisaged two mechanistic pathways: i) proceeding via C–H activation and the formation of a metal–allyl species, or ii) the direct insertion of a metal-nitrenoid species into the allyllic C–H bond (Scheme 4). We started our investigations by comparing the reaction outcome of allylbenzene (**1ao**) and (*E*)-β-methylstyrene (**1ao'**) (Scheme 4A). In both cases the branch-amidated product was formed, indicating that either the mechanism proceeds through a metal–allyl species or isomerization is followed by C–H insertion. Furthermore, we examined the reaction outcome using (*E*)-4-octene (**1bd**) as the substrate, which led to the formation of both products (**3bd**, **3bd'**) in a 1:1 regiosiomeric ratio. According to a C–H insertion pathway, only a single product would be expected due to the symmetry of **1bd** (Scheme 4B, upper pathway). However, through the formation of a metal–allyl species, the substrate becomes unsymmetrical and two different products (**3bd**, **3bd'**) would be expected (Scheme 4B, lower pathway). Based on these results we propose the following catalytic cycle (Scheme 4C). The pre-catalyst $[Cp^*IrCl_2]_2$ is activated through the abstraction of the halogen atoms by $AgSbF_6$ and AgOAc to form the cationic catalyst **I**. The olefin substrate associates to the metal center (**II**) followed by C–H activation to form the allyl–Ir-complex **III**. This complex then undergoes oxidative addition into the N–O bond, followed by the extrusion of CO_2 to form allyl–Ir-nitrenoid species (**IV**).[8b] The product is then obtained after reductive elimination and proto-demetalation, which concomitantly regenerates **I**.

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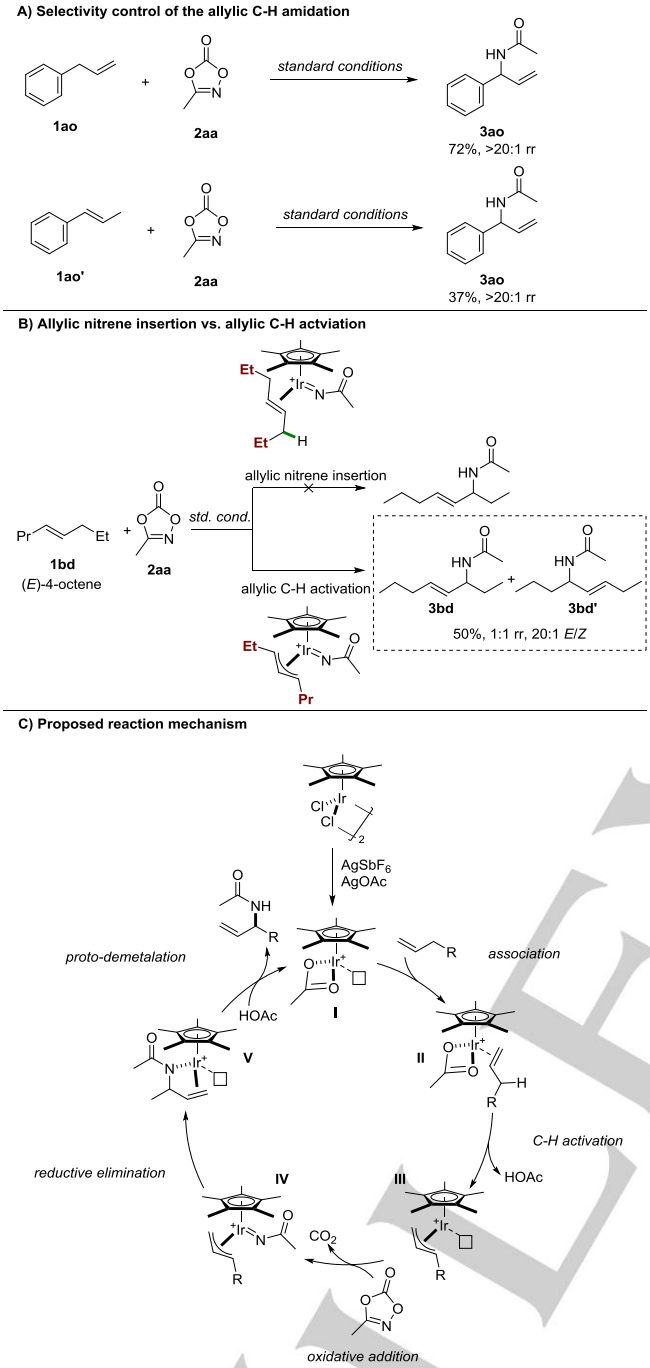

Scheme 4. Mechanistic experiments and proposed reaction mechanism.

In summary, we have developed a mild, intermolecular and highly branch-selective allylic C–H amidation reaction under redox-neutral conditions through the coupling of dioxazolones and olefin feedstocks. The reaction mechanism was investigated and is proposed to proceed through allylic C–H activation. We believe that this method of acid-to-allylamide coupling will be of great interest for the streamlined synthesis of alkylamines in bioactive compounds.

Acknowledgements

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Conflict of Interest

The Authors declare no conflicts of interest.

Keywords: C–H activation • allylic Amination • redox-neutral • branch-selective • carboxylic acids

[1] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257.

[2] S. D. Roughley, A. M. Jordan, *J. Med. Chem.* **2011**, *54*, 3451.

[3] a) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606; b) A. El-Faham, F. Albericio, *Chem. Rev.* **2011**, *111*, 6557.

[4] For selected examples, see: a) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417; b) C. Liang, F. Collet, F. Robert-Peillard, P. Müller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343; c) J. L. Roizen, M. E. Harvey, J. D. Bois, *Acc. Chem. Res.* **2012**, *45*, 911; d) G. Dequirez, V. Pons, P. Dauban, *Angew. Chem. Int. Ed.* **2012**, *51*, 7384; *Angew. Chem.* **2012**, *124*, 7498; e) N. S. Dolan, R. J. Scamp, T. Yang, J. F. Berry, J. M. Schomaker, *J. Am. Chem. Soc.* **2016**, *138*, 14658.

[5] For selected examples, see: a) S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2008**, *130*, 3316; b) G. Liu, G. Yin, L. Wu, *Angew. Chem. Int. Ed.* **2008**, *47*, 4733; Angew. Chem. **2008**, *120*, 4811; c) M. R. Luzung, C. A. Lewis, P. S. Baran, *Angew. Chem. Int. Ed.* **2009**, *48*, 7025; Angew. Chem. **2009**, *121*, 7159; d) G. Yin, Y. Wu, G. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 11978; e) C. C. Pattillo, I. I. Strambeanu, P. Calleja, N. A. Vermeulen, T. Mizuno, M. C. White, *J. Am. Chem. Soc.* **2016**, *138*, 1265; f) S. R. Vemula, D. Kumar, G. R. Cook, *ACS. Catal.* **2016**, *6*, 5295; g) R. Ma, M. C. White, *J. Am. Chem. Soc.* **2018**, *140*, 3202.

[6] For selected Cp*Rh^{III}-catalyzed allylic functionalization reactions, see: a) T. Cochet, V. Bellosta, D. Roche, J.-Y. Ortholand, A. Greiner, J. Cossy, *Chem. Commun* **2012**, *48*, 10745; b) A. Archambeau, T. Rovis, *Angew. Chem. Int. Ed.* **2015**, *54*, 13337; Angew. Chem. **2015**, *127*, 13535; c) Y. Shibata, E. Kudo, H. Sugiyama, H. Uekusa, K. Tanaka, *Organometallics* **2016**, *35*, 1547; d) J. S. Burman, S. Blakey, *Angew. Chem. Int. Ed.* **2017**, *56*, 13666; *Angew. Chem.* **2017**, *129*, 13854. e) T. A. F. Nelson, S. B. Blakey, *Angew. Chem. Int. Ed.* **2018**, *57*, 14911.

[7] a) F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926; b) T. A. Ramirez, B. Zhao, Y. Shi, *Chem. Soc. Rev.* **2012**, *41*, 931; c) K. Shin, H. Kim, S. Chang, *Acc. Chem. Res.* **2015**, *48*, 1040; d) H. Kim, S. Chang, *ACS. Catalysis* **2016**, *6*, 2341; e) Y. Park, Y. Kim, S. Chang, *Chem. Rev.* **2017**, *117*, 9247.

[8] a) Y. Park, K. T. Park, J. G. Kim, S. Chang, *J. Am. Chem. Soc.* **2015**, *137*, 4534; b) J. Park, S. Chang, *Angew. Chem. Int. Ed.* **2015**, *54*, 14103; *Angew. Chem*. **2015**, *127*, 14309; c) Y. Park, J. Heo, M.-H. Baik, S. Chang, *J. Am. Chem. Soc.* **2016**, *138*, 14020.

[9] For examples showing the practicability of dioxazolones, see: a) Y. Park, S. Jee, J. G. Kim, S. Chang, *Org. Process Rev. Dev.* **2015**, *19*, 1024; b) Y. Hwang, Y. Park, S. Chang, *Chem. Eur. J.* **2017**, *23*, 11147.

[10] a) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9858; b) A. Lerchen, T. Knecht, M. Koy, J. B. Ernst, K. Bergander, C. G. Danilic, F. Glorius, *Angew. Chem. Int. Ed.* **2018**, *57*, 15248; *Angew. Chem.* **2018**, *130*, 15468; c) T. Knecht, T. Pinkert, T. Dalton, A. Lerchen, F. Glorius, *ACS. Catal.* **2019**, *9*, 1253.

[11] S. Y. Hong, Y. Park, Y. Hwang, Y. B. Kim, M.-H. Baik, S. Chang, *Science* **2018**, *359*, 1016.

[12] T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev.* **2016**, *45*, 2900.

10.1002/anie.201901733

[13] For selected examples, see: a) K. J. Frauenhoffer, M. C. White, *J. Am. Chem. Soc.* **2007**, *129*, 7274; b) E. Milczek, N. Boudet, S. Blakey, *Angew. Chem. Int. Ed.* **2008**, *47*, 6825; *Angew Chem.* **2008**, *120*, 6931; c) D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 9220; d) L. Wu, S. Qiu, G. Liu, *Org. Lett.* **2009**, *11*, 2707; e) H. Lu, H. Jian, Y. Hu, L. Wojtas, X. P. Zhangm, *Chem. Sci.* **2011**, *2*, 2361; f) S. M. Paradine, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 2036; g) S. M. Paradine, J. R. Griffin, J. Zhao, A. L. Petronico, S. M. Miller, M. C. White, *Nat. Chem.* **2015**, *7*, 987.
[14] A. Sharma, J. F. Hartwig, *J. Am. Chem. Soc.* **2013**, *135*, 17983.
[15] H. Bao, U. K. Tambar, *J. Am. Chem. Soc.* **2012**, *134*, 18495.
[16] Z. Wang, Z. He, L. Zhang, Y. Huang, *J. Am. Chem. Soc.* **2017**, *140*, 735.
[17] H. Lei, T. Rovis, *J. Am. Chem. Soc*. **2019**, *141*, 2268.
[18] X. Xiao, C. Hou, Z. Zhang, Z. Ke, J. Lan, H. Jiang, W. Zang, *Angew. Chem. Int. Ed.* **2016**, *55*, 11897; Angew. Chem. **2016**, *128*, 12076.

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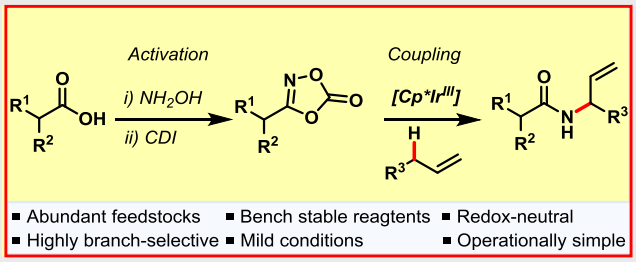

A new branch! A novel strategy for the mild, highly branch-selective and redox-neutral allylic C–H amidation is described. Naturally occurring and abundant carboxylic acids were activated to their corresponding dioxazolones and reliably coupled with the petrochemical feedstock of terminal and internal olefins. The synthetic value of this transformation was demonstrated in the coupling of complex and bioactive scaffolds.

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