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Article

Palladium-Catalyzed Domino Aminocarbonylation of Alkynols: Direct and Selective Synthesis of Itaconimides

Yao Ge,[§] Fei Ye,[§] Ji Yang, Anke Spannenberg, Ralf Jackstell,* and Matthias Beller*

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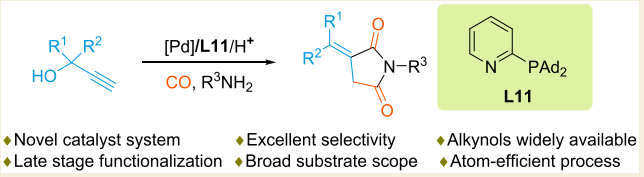
ABSTRACT: The first direct and selective synthesis of substituted itaconimdes by palladium-catalyzed aminocarbonylation of alkynols is reported. Key to the success of this transformation is the use of a novel catalyst system involving ligand **L11** and appropriate reaction conditions. In the protocol here presented, easily available propargylic alcohols react with *N*-nucleophiles including aryl- and alkylamines as well as aryl hydrazines to provide a broad variety of interesting heterocycles with high catalyst activity and excellent selectivity. The synthetic utility of the protocol is demonstrated in the synthesis of natural product **11** with aminocarbonylation as the key step. Mechanistic studies and control experiments reveal the crucial role of the hydroxyl group in the substrate for the control of selectivity.



KEYWORDS: *itaconimide, palladium, P ligand, aminocarbonylation, alkynol*

INTRODUCTION

Succinimides constitute an important class of organic molecules, which widely exist in a large number of five-membered natural products with diverse biological and pharmaceutical activities.[1−5] Among these compounds, itaconimide derivatives characterized by exocyclic C=C bonds are found in many natural products, and this structural motif is also present in current drug candidates (Scheme 1).[6−11] For example, longimide B **I** is known for its antitumor activity,[2,6] while compounds **II** and **III** showed potent GPR119 agonistic[7] and antagonist activity,[8] respectively. In addition, 3-arylmethylidene pyrrolidine-2,5-diones **IVa** and **IVb** were tested as type 2 5α-reductase (T2-5α-reductase) inhibitors.[9,10] As a final example, compound **V** is mentioned here displaying potent anti-Xa activity, whereby both the cyclic structure and the geometry provided by the double bond contribute to the pharmaceutical potential of **V**.[11] Interestingly, related fulgimides, e.g., **VI**, are also known to be molecular switches with many potential applications in optical materials.[12−14]

Moreover, itaconimides are recognized as useful synthons **VII** as they contain condensed functionalities for further scaffold diversification.[15−30] For example, they can be readily transformed into relevant pyrrolidines by reduction[15] and provide an easy access to the corresponding succinic acid derivatives by ring-opening reactions.[16−18] Furthermore, the fairly acidic methylene group shows nucleophilic ability,[19−25] which has been used in diazo-transfer reactions,[19] allylic additions,[20] and Michael addition reactions.[21−23] Finally, the activated exocyclic olefin can be further functionalized[26−32] through cycloadditions[26−29] and asymmetric hydrogenation reactions[30] and forms highly stable thio-Michael adducts that resist thiol-exchange-mediated breakdown under physiological conditions.[31,32]

Although the synthesis of itaconimides attracted significant interest in the area of drug development, relatively few synthetic methodologies to access this class of compounds in a general manner exist. Primarily, activated alkenes[33−44] such as α,β-unsaturated anhydrides,[33−35] the parent compound,[10] and maleimides[20,31,36−44] were used for their preparation (Scheme 2a−c). Thus, until today the most commonly used method involves conjugate-addition of triphenylphosphine to endocyclic olefinic maleimides followed by a Wittig reaction with aldehydes, resulting in the inevitable formation of (over)-stoichiometric amounts of phosphine oxides.[19,31,40−44] In addition, more specific three-component reactions of allenoates, isocyanides, and carboxylic acids and a cycloisomerization/rearrangement cascade of Ugi adducts have been also reported.[45,46]

Preferably, any new methodology in this area should be environmentally benign, atom-efficient, and straightforward. On the basis of our general expertise and recent works on carbonylations,[47−50] we had the idea that specifically such transformations can be also used to access itaconimides (Scheme 2d). Indeed, as one of the most important homogeneous catalytic processes, transition-metal-catalyzed carbonylation reactions allow for direct conversion of easily

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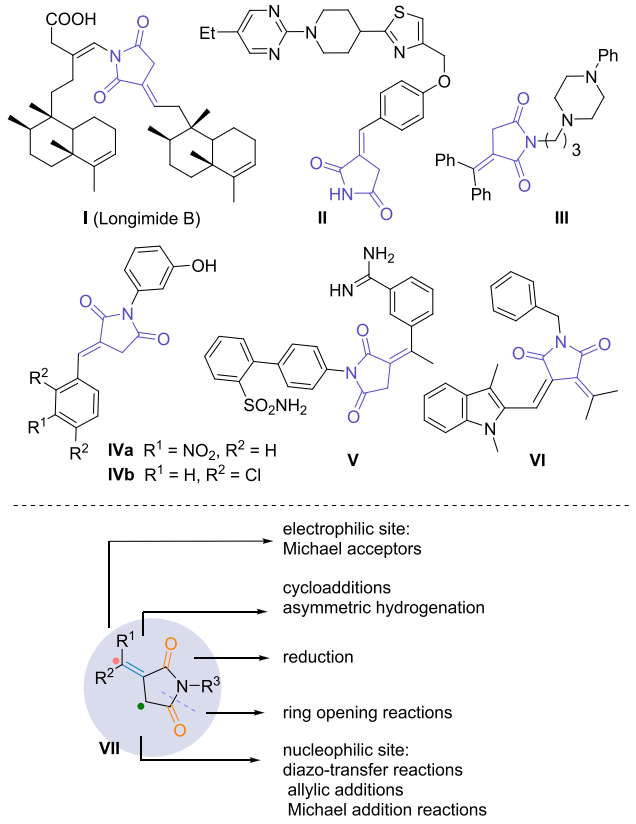
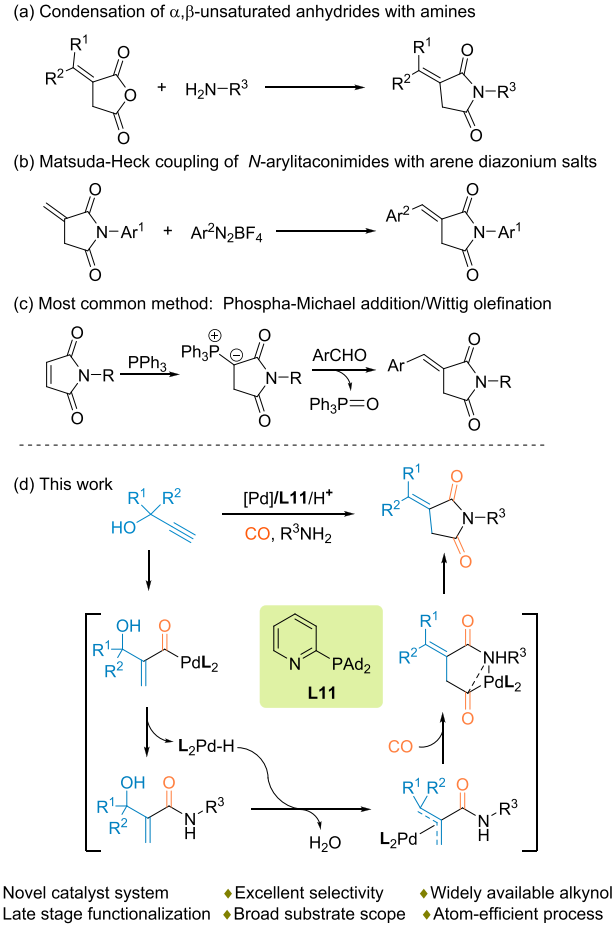
Scheme 1. Importance of Itaconimides: Selected Examples of Natural Compounds, Biologically Active Molecules, and Interesting Postfunctionalizations



Scheme 2. Summary of the Main Synthesis Methods of Itaconimides



available feedstocks into a variety of carbonylated compounds.[51−54] In this respect, the aminocarbonylation of propargyl alcohols which are commercially available or easily accessed is an ideal method. However, such methodologies are intrinsically challenging due to the problems associated with the acidity of the active metal hydride catalysts and the basicity of the amine reagent. Moreover, aminocarbonylations are prone to produce many side products such as esters (lactones), acids, and branched or linear *α,β*-unsaturated amides. Thus, it is not surprising that, to the best of our knowledge, no such process has been reported, and herein, we present the first example of a general and highly selective synthesis of itaconimide derivatives through Pd-catalyzed aminocarbonylation.

RESULTS AND DISCUSSION

Model Reaction and Catalyst Optimization

At the beginning of our studies, carbonylation of 1-ethynyl-1-cyclohexanol **1a** with 4-fluoroaniline **2a** was chosen as a benchmark reaction. As shown in Figure 1, via selective dicarbonylation of **1a**, it should be possible to obtain itaconimide **3aa** directly. However, a variety of other carbonylated products can be formed easily in this reaction. For example, the branched *α,β*-unsaturated amide **4**, linear *α,β,γ,δ*-unsaturated amide **5**, and linear *α,β*-unsaturated amide with an allylic hydroxyl group **6**.

In general, for palladium-catalyzed coupling processes, the choice of ligand is crucial and allows for controlling the selectivity and activity.[55−59] Thus, to achieve the desired target product **3aa**, we investigated the effect of different bidentate and monodentate phosphines (2 or 4 mol %, respectively) for the carbonylation of **1a** in the presence of 1 mol % $Pd(MeCN)_2Cl_2$, in dichloromethane at 40 bar CO, 120 °C. Using the classic ligand Xantphos **L1**, itaconimide **3aa** was obtained in only 7% yield; nevertheless, this demonstrated the feasibility of a double carbonylation process. Other bisphosphine ligands with different backbones and chelating units such as DBFphos **L2**, Naphos **L3**, 1,2-bis((di-*tert*-butylphosphan-yl)methyl)benzene **L4**, and bis(2-dicyclohexyl-phosphinophenyl) ether **L5** favored the formation of linear *α,β,γ,δ*-unsaturated amide **5**. No improvement of the chemoselectivity was achieved when monodentate phosphine ligand **L6** was tested.

Notably, the imidazole-based ligand **L7** showed high chemoselectivity for monoaminocarbonylation of **1a**, leading to amide **4** with 52% yield. Interestingly, when ligand **L8** was applied, the yield of unsaturated succinimide **3aa** was improved to 15%. Using ligands **L9** and **L10** which bear pyridyl substituents on the phosphorus atoms, ligand **L10** gave the best result (28% yield) in our preliminary ligand screening. To optimize the benchmark reaction further, we evaluated the influence of critical reaction parameters in the presence of **L10**. By variation of catalyst precursors, solvents, and other factors, the yield of **3aa** reached 80% with a selectivity of 8/1 (**3aa**/**5**) (see Supporting Information Tables S1−S4 for details). Gratifyingly, with ligand **L11** in which the phenyl groups are replaced with bulkier adamantyl substituents, the linear side product **5** was completely suppressed, giving **3aa** in 87% yield

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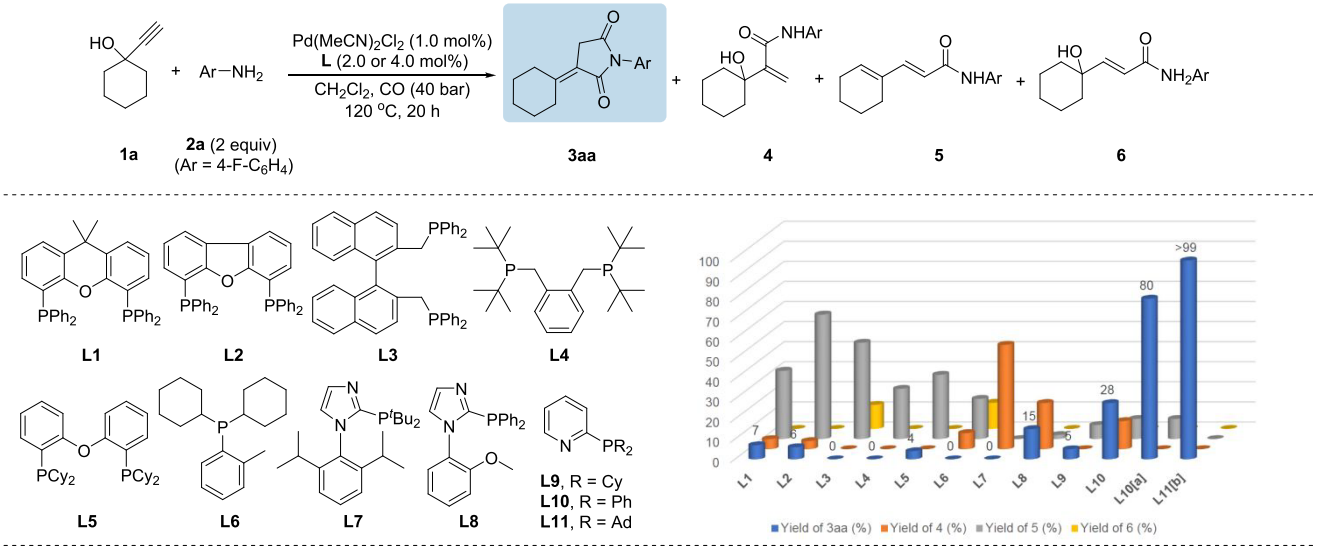

Figure 1. Pd-catalyzed aminocarbonylation of 1-ethynyl-1-cyclohexanol **1a**: influence of phosphine ligands. Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), $Pd(MeCN)_2Cl_2$ (1.0 mol %), bisphosphine ligand (2.0 mol %) or monophosphine ligand (4.0 mol %), CO (40 atm), CH_2Cl_2 (2.0 mL), 20 h at 120 °C. The yields of products were determined by GC analysis with mesitylene as an internal standard. [a] indicates the following conditions: $Pd(cod)Cl_2$ (1.0 mol %), **2a** (0.75 mmol), pentane (2.0 mL). [b] indicates the following conditions: $Pd(cod)Cl_2$ (1.0 mol %), **2a** (0.75 mmol), PTSA·H_2O (10 mol %), pentane (2.0 mL), 100 °C.

(see Supporting Information Table S4 for details). Lowering the reaction temperature (100 °C) resulted in an improved yield of **3aa** (94%), whereas a lower CO pressure (20 bar) had a negative effect on the desired product yield (82%) (see Supporting Information Table S5 for details), and finally, in the presence of 10 mol % PTSA, the yield of **3aa** reached >99% with excellent chemoselectivity.

Mechanistic Investigations and Catalytic Cycle

To gain insights into the reaction mechanism, several control experiments were conducted (Scheme 3). First, 1-ethynylcyclohexene **9** and cyclohexylacetylene **10** were examined under the standard conditions, showing the crucial role of the hydroxyl group in **1a** to accommodate the conversion of the propargylic alcohol. While **9** led to a complex mixture, cyclohexylacetylene **10** afforded monoaminocarbonylated products (see Supporting Information, Scheme S2).

Additionally, no conversion of **8** could be achieved when it was tested with amine **2a** under standard conditions, excluding the possibility of condensation of α,β-unsaturated anhydrides with the corresponding amines.

To determine the key intermediate which itaconimide **3aa** was generated from, amides **4**, **5**, **6**, and **7** were isolated and reacted with CO under standard conditions, separately. No conversion was noted using linear $\alpha,\beta,\gamma,\delta$-unsaturated amide **5** as the starting material. Furthermore, **6** and **7** could not be transformed to **3aa** either. However, testing the branched amide **4** with an allylic hydroxyl group in the carbonylation reaction provided **3aa** in 32% yield. The observed lower yield of **3aa** may result from different concentrations of **4** in the control experiment compared to the catalytic process (Scheme 3a, see Supporting Information Schemes S2 and S3 for details).

Next, the kinetic progress of the reaction between alkynol **1a** and 4-fluoroaniline **2a** was examined under the optimal conditions. As shown in Scheme 3b, **1a** is initially converted into the monoaminocarbonylation product **4**. Then, **3aa** is generated along with the consumption of the reaction intermediate **4**. Starting material **1a** is fully converted, and the formation of the branched amide **4** achieves a maximum yield of 48% after 40 min. In the following 60 min, the yield of desired product **3aa** increases quickly and reaches >99% yield after 100 min. Over the course of the reaction, formation of **7** is observed only in small amounts (maximum 10% yield), which could be explained by the equilibrium with **4**.

On the basis of these findings and previous mechanistic studies of Pd-catalyzed aminocarbonylations,[55−59] we propose the following main reaction pathway (Scheme 3c). Initially, the stable Pd^{II} salt is in situ reduced to give Pd^0 phosphine complexes **A** in the presence of an excess amount of ligand.[60−63] After protonation, active complex **B** is afforded. Then, the carbon−carbon triple bond of alkynol **1a** coordinates to Pd to form complex **C**, and subsequent triple bond insertion affords regioselectively the branched alkenyl-Pd intermediate **D**. Pd complex **D** directly undergoes a facile CO insertion process to give the corresponding acyl Pd species **E**. Next, aminolysis of intermediate **E** leads to the monoaminocarbonylation product **4** and regenerates the palladium hydride species **B**. Compound **4** is also prone to dehydration to form **7**, which can be a reversible process. After cycle I, complex **B** reacts with **4**, forming the π-allyl-palladium intermediate **F**. This intermediate undergoes a fast equilibrium with the corresponding σ-palladium complexes **G**. Finally, CO insertion and aminolysis lead to the desired product **3aa**.

Substrate Scope

With optimized reaction conditions established, we examined the scope of this three-component process with respect to alkynols. As shown in Table 1a, diverse propargylic alcohols can be applied in the carbonylation transformation, demonstrating a practical strategy utilizing abundant alkynol feedstocks directly as robust surrogates for the construction of itaconimides. Different substituents (*tert*-butyl, phenyl) at the 4-position of cyclohexyl group were compatible with the reaction conditions, giving rise to **3ba** and **3ca** in high yield (77% and 88%, respectively). This transformation also displayed good functional group tolerance. Hence, the

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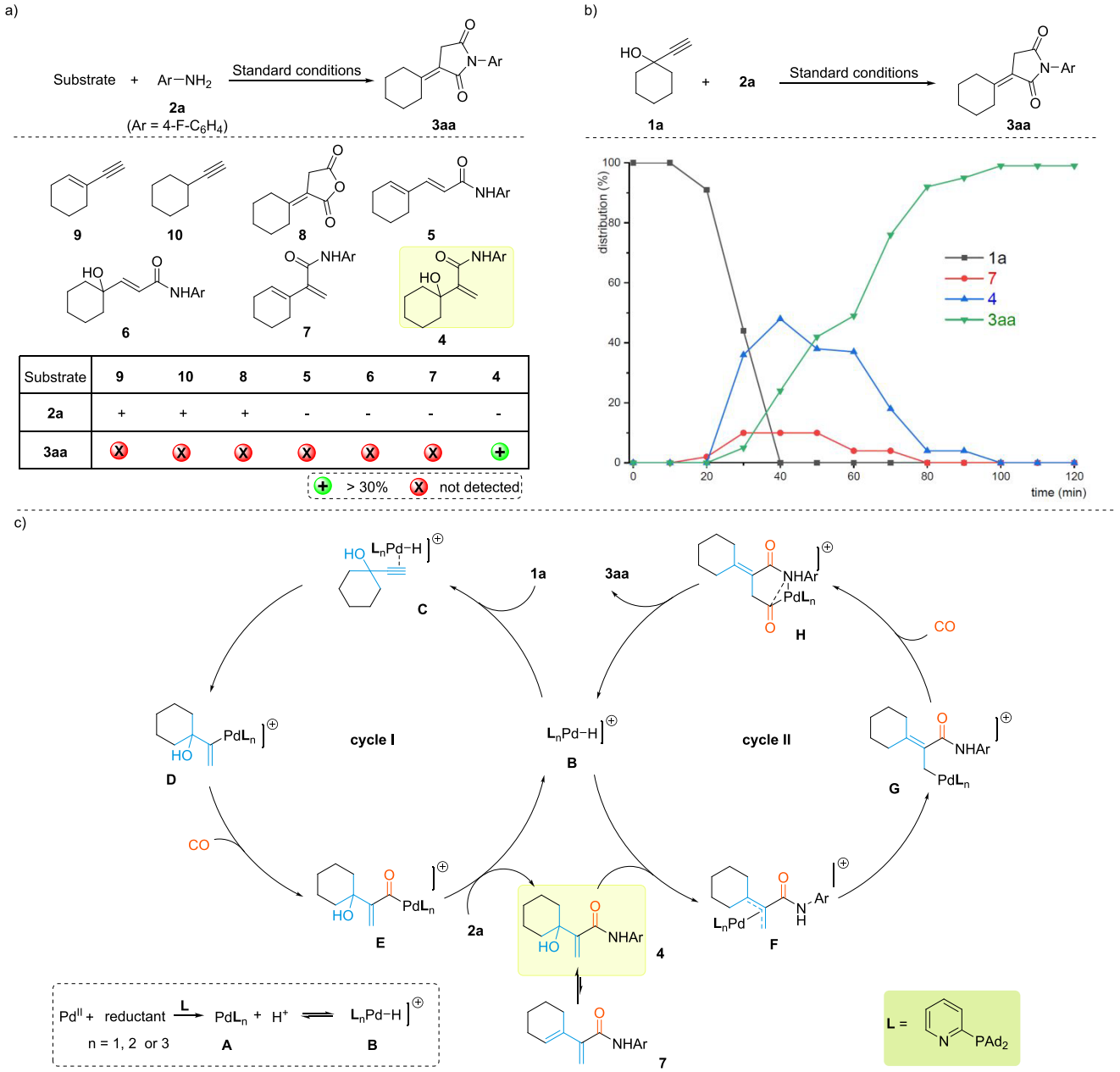
Scheme 3. (a) Control Experiments, (b) Kinetic Monitoring of Intermediates over Time, and (c) Proposed Catalytic Cycle[a]



[a]Standard conditions: Pd(cod)Cl_2 (1.0 mol %), **L11** (4.0 mol %), PTSA·H_2O (10 mol %), pentane (2.0 mL), CO (40 atm), 100 °C, 20 h, **1a** or **4**−**10** (0.5 mmol), 4-fluoroaniline (0.75 mmol). The yields of products were determined by crude ^{1}H NMR analysis using dibromomethane as the internal standard.

carbonylations of substrates **1d** and **1e** containing heteroatoms (sulfur, nitrogen) were successful, providing **3da** and **3ea** in good yields (67% and 87%). Moreover, a wide array of carbocyclic ring systems (4-, 5-, and 12-membered) were amenable to this approach, delivering the corresponding unsaturated succinimides **3fa**−**3ha** in 76−98% yields. Notably, sterically crowded alkynol **1i** also reacted smoothly, giving **3ia** in 84% yield. Noncyclic alkynols **1j**−**1n** bearing different alkyl and benzyl groups furnished the corresponding desired products **3ja**−**3na** with 35−98% yields. When α-monoalkyl-substituted propargyl alcohols **1o**−**1q** and the α-monoaryl-substituted alkynol **1r** were subjected to the optimized conditions, this catalytic system exhibited good activities (53−76% yields) and >20/1 E/Z selectivities. In addition, the diaryl-substituted propargyl alcohol **1s** was well-tolerated by the catalyst to afford **3sa** in 79% yield. The effectiveness of this methodology is showcased by the late-stage modification of biorelevant derivatives, which provides easy access to diverse itaconimide derivatives, highlighting the substrate scope of this protocol and its utility in organic synthesis. More specifically, tropinone-derived propargylic alcohol **1t** could be applied to afford the desired product **3ta** in decent yield. Pentoxifyllin, a drug with anti-inflammatory properties, can be transformed to the corresponding product **3ua** in 73% yield (E/Z = 1/1).

Next, we evaluated the scope of this aminocarbonylation process with respect to amines. As shown in Table 1b, a variety of aromatic amines with electron-neutral, electron-deficient, and electron-rich substituents led to the corresponding

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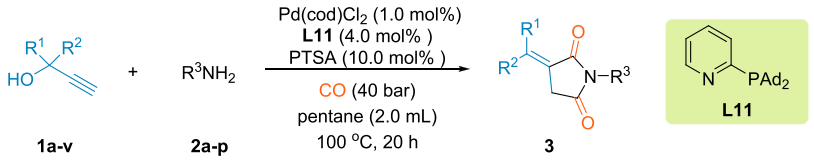
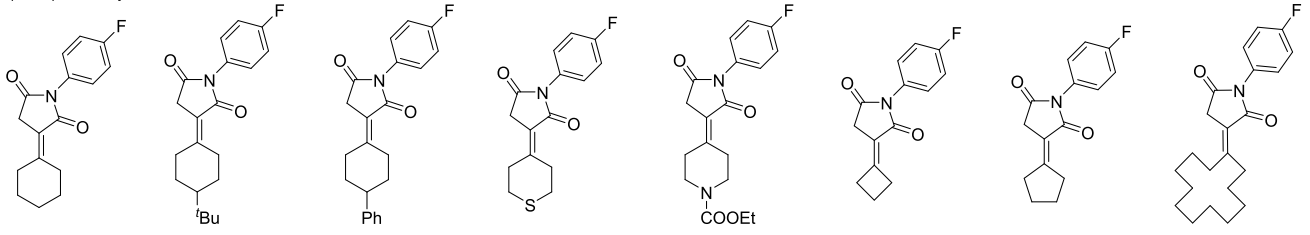
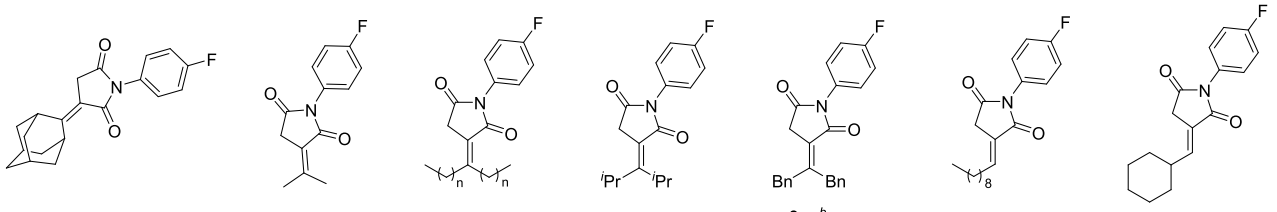
Table 1. Pd-Catalyzed Aminocarbonylation of Alkynols 1a−v with Amines 2a−p[a]



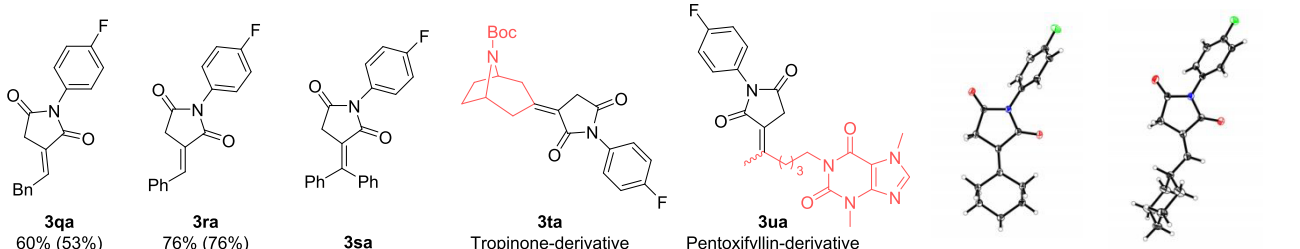
a) Scope of alkynols



3aa >99% (98%) | **3ba** 84% (77%) | **3ca** 94% (88%) | **3da** 71% (67%) | **3ea** 92% (87%) | **3fa** 80% (76%) | **3ga** 99% (98%) | **3ha** 98% (95%)

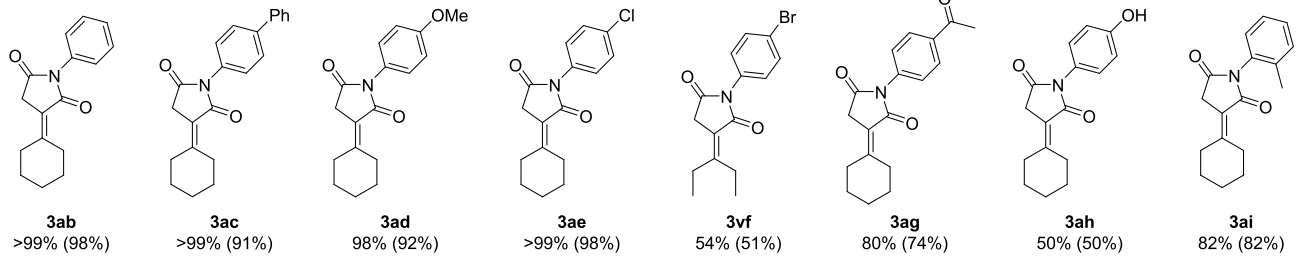


3ia >99% (84%) | **3ja** >99% (98%) | n = 3, **3ka** 94% (88%) n = 4, **3la** 82% (80%) | **3ma** 61% (58%) | **3na**[b] 35% (35%) | **3oa** 77% (74%), E/Z> 20/1 | **3pa** 72% (72%), E/Z> 20/1

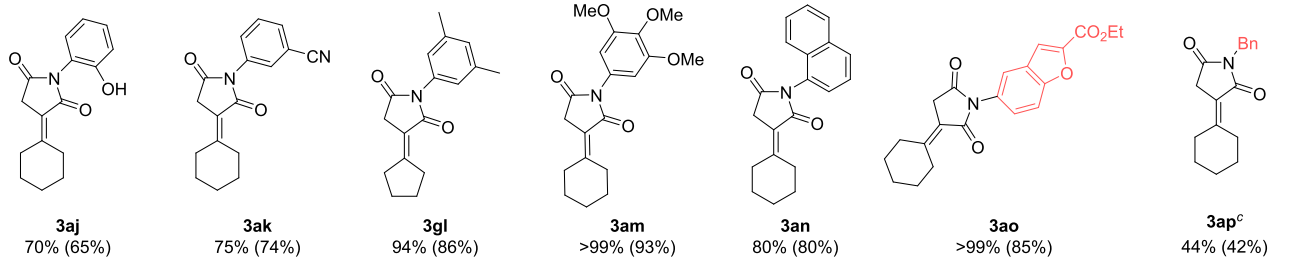


3qa 60% (53%) E/Z> 20/1 | **3ra** 76% (76%) E/Z> 20/1 | **3sa** 82% (79%) | **3ta** Tropinone-derivative 53% (53%) | **3ua** Pentoxifyllin-derivative 81% (73%), E/Z = 1/1 | Crystal structure of **3aa**[d] | Crytal structure of **3pa**[d]

b) Scope of amines



3ab >99% (98%) | **3ac** >99% (91%) | **3ad** 98% (92%) | **3ae** >99% (98%) | **3vf** 54% (51%) | **3ag** 80% (74%) | **3ah** 50% (50%) | **3ai** 82% (82%)



3aj 70% (65%) | **3ak** 75% (74%) | **3gl** 94% (86%) | **3am** >99% (93%) | **3an** 80% (80%) | **3ao** >99% (85%) | **3ap**[c] 44% (42%)

[a]Standard reaction conditions: **1** (0.5 mmol), $Pd(cod)Cl_2$ (1.0 mol %), **L11** (4.0 mol %), $PTSA{\cdot}H_2O$ (10.0 mol %), **2** (0.75 mmol), CO (40 atm), pentane (2.0 mL), 20 h at 100 °C. Isolated yields were given within the parentheses. The NMR yields (values before the parentheses) were determined by crude ^1H NMR analysis using dibromomethane as the internal standard. [b]**1n** (0.1 mmol), **2a** (0.15 mmol), $Pd(cod)Cl_2$ (5.0 mol %), **L11** (20.0 mol %), $PTSA{\cdot}H_2O$ (0.1 mmol). [c]**1a** (0.5 mmol), $BnNH_2$**2p** (1 mmol), $PdBr_2$ (1.0 mol %), **L10** (4.0 mol %), TFA (10.0 mol %), CO (40 atm), CH_2Cl_2 (2.0 mL), 20 h at 120 °C. [d]Displacement ellipsoids correspond to 30% probability. See Supporting Information Section 2.5 for details.

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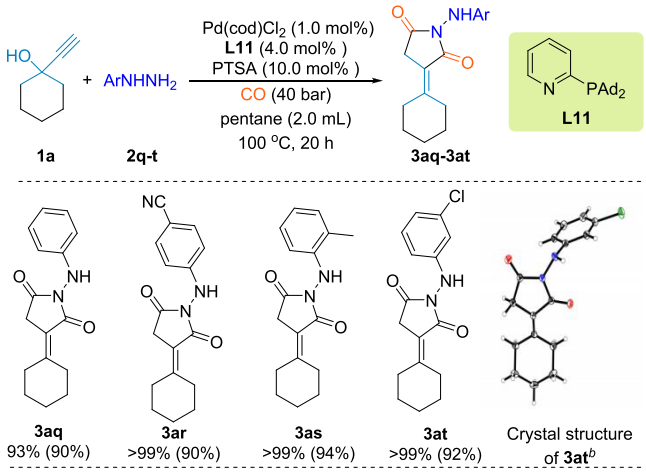
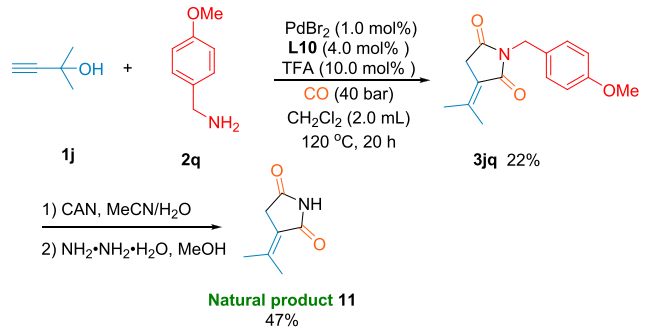
Table 2. Pd-Catalyzed Aminocarbonylation of 1a with Aryl Hydrazines 2q−t[a]



[a]Standard reaction conditions: **1a** (0.5 mmol), $Pd(cod)Cl_2$ (1.0 mol %), **L11** (4.0 mol %), $PTSA{\cdot}H_2O$ (10.0 mol %), **2** (0.75 mmol), CO (40 atm), pentane (2.0 mL), 20 h at 100 °C. Isolated yields were given within the parentheses. The NMR yields (values before the parentheses) were determined by crude ^1H NMR analysis using dibromomethane as the internal standard. [b]Displacement ellipsoids correspond to 30% probability. See Supporting Information Section 2.5 for details.

Scheme 4. Synthesis of Natural Product 11 with Aminocarbonylation as Key Step



carbonylative products in good yields (51−98%). The substituents on the arylamines had no real impact on the catalysis. Specifically, the reactions of arylamines bearing phenyl, methoxy, and chlorine substituents proceeded smoothly, providing the corresponding products **3ab−3ae** in 91−98% isolated yields. Notably, bromine-substituted arylamines, which are known to be sensitive to palladium catalysis, also worked well and afforded **3vf** in 51% yield. Interestingly, the 4-aminoacetophenone **2g** and 4-aminophenol (**2h**) which contain functional groups reacted well to give **3ag** and **3ah** in 74% and 50% yield, respectively. The position of substituents on the phenyl ring has no influence on the reaction outcome. Hence, arylamines **2i−2k** afforded **3ai−3ak** in 65−82% yields. Moreover, arylamines **2l−2n** containing multiple substituents proved to be efficient coupling partners and gave the corresponding products in 80−93% yields. To be noted, heteroaromatic amine **2o** with an easily functionalized ester group led to **3ao** in quantitative conversion with excellent chemoselectivity.

The carbonylation in the presence of aliphatic amines continues to be a highly challenging goal due to their stronger basicity compared with arylamines.[64] Nevertheless, using benzyl amine **2p** as a representative example gave the desired **3ap** as the major product (44% yield; see Supporting Information Tables S6−S8 for details).

Finally, we became interested in the use of other *N*-nucleophiles instead of amines. In this respect, specifically aryl hydrazines attracted our interest; these constitute important synthons in the synthesis of many biologically active and industrially important organic compounds.[65,66] Indeed, when phenylhydrazine **2q** was reacted with **1a** under the previously optimized conditions, the corresponding unsaturated succinimide **3aq** was isolated as the sole product in excellent yield (90%). Apart from phenylhydrazine, 4-hydrazinylbenzonitrile **2r**, *o*-tolylhydrazine **2s**, and 3-chlorophenylhydrazine **2t** were employed as efficient *N*-nucleophiles (Table 2). In all cases, >99% NMR yields were obtained, and the chemoselectivities for double carbonylative products **3ar−3as** were excellent. Notably, these novel hydrazine derivatives offer interesting possibilities for the straightforward synthesis of other heterocycles.[67−71]

The synthetic utility of our protocol is further demonstrated in the straightforward synthesis of natural product **11**, which was isolated from an endophytic fungus.[72] Itaconimide **3jq** was obtained without additional optimization by aminocarbonylation of 2-methyl-3-butyn-2-ol **1j** and benzylic amine **2q**. Subsequent removal of the *N*-*p*-methoxybenzyl protecting group with CAN gave natural product **11** (Scheme 4).

CONCLUSION

In summary, we report a new catalytic domino transformation which allows an efficient synthesis of itaconimides from easily available propargylic alcohols. Key to this effective methodology is a straightforward aminocarbonylation reaction in the presence of a novel palladium catalystinvolving ligand **L11**. This protocol complements the currently known methods for carbonylation reactions in organic synthesis, allowing access to this so far overlooked class of compounds. In fact, 40 out of 41 molecules prepared here have not been described before to the best of our knowledge.

The general applicability of this highly selective protocol is demonstrated by reacting more than 20 versatile alkynols including structurally complex and biologically active molecules. Furthermore, diverse *N*-nucleophiles including arylamines, alkylamines, and aryl hydrazines can be easily employed. Control experiments reveal the presence of the hydroxyl group to be essential for the selective synthesis of the desired products. Mechanistic studies further suggest a novel sequential double carbonylation process with the branched amide **4** as a key intermediate.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.1c00221.

Additional experimental results and procedures and characterization data (PDF)

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AUTHOR INFORMATION

Corresponding Authors

Ralf Jackstell − *Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Rostock 18059, Germany*; Email: ralf.jackstell@catalysis.de

Matthias Beller − *Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Rostock 18059, Germany*; orcid.org/0000-0001-5709-0965; Email: Matthias.Beller@catalysis.de

Authors

Yao Ge − *Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Rostock 18059, Germany*

Fei Ye − *Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Rostock 18059, Germany; Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Key Laboratory of Organosilicon Material Technology of Zhejiang Province, Hangzhou Normal University, 311121 Hangzhou, P. R. China*

Ji Yang − *Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Rostock 18059, Germany*

Anke Spannenberg − *Leibniz-Institut für Katalyse e.V. an der Universität Rostock, Rostock 18059, Germany*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacsau.1c00221

Author Contributions

§Y.G. and F.Y. contributed equally.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

PTSA·H_2O, *p*-toluenesulfonic acid monohydrate

REFERENCES

(1) Miller, C. A.; Long, L. M. Anticonvulsants. I. An Investigation of N-R-α-R1-α-Phenylsuccinimides. *J. Am. Chem. Soc.* **1951**, *73*, 4895−4898.

(2) Sashidhara, K. V.; Singh, S. P.; Kant, R.; Maulik, P. R.; Sarkar, J.; Kanojiya, S.; Ravi Kumar, K. Cytotoxic cycloartane triterpene and rare isomeric bisclerodane diterpenes from the leaves of *Polyalthia longifoliavar. pendula*. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5767−5771.

(3) Rybka, S.; Obniska, J.; Rapacz, A.; Filipek, B.; Zmudzki, P. Synthesis and evaluation of anticonvulsant properties of new *N*-Mannich bases derived from pyrrolidine-2,5-dione and its 3-methyl-, 3-isopropyl, and 3-benzhydryl analogs. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 1412−1415.

(4) Kaminski, K.; Obniska, J.; Chlebek, I.; Liana, P.; Pekala, E. Synthesis and biological properties of new *N*-Mannich bases derived from 3-methyl-3-phenyl- and 3,3-dimethyl-succinimides. Part V. *Eur. J. Med. Chem.* **2013**, *66*, 12−21.

(5) Socała, K.; Mogilski, S.; Pieróg, M.; Nieoczym, D.; Abram, M.; Szulczyk, B.; Lubelska, A.; Latacz, G.; Doboszewska, U.; Wlaź, P.; Kamiński, K. KA-11, a Novel Pyrrolidine-2,5-dione Derived Broad-Spectrum Anticonvulsant: Its Antiepileptogenic, Antinociceptive Properties and in Vitro Characterization. *ACS Chem. Neurosci.* **2019**, *10*, 636−648.

(6) Luo, K.; Bao, Y.; Liu, F.; Xiao, C.; Li, K.; Zhang, C.; Huang, R.; Lin, J.; Zhang, J.; Jin, Y. Synthesis and biological evaluation of novel benzylidene-succinimide derivatives as noncytotoxic antiangiogenic inhibitors with anticolorectal cancer activity *in vivo*. *Eur. J. Med. Chem.* **2019**, *179*, 805−827.

(7) Kim, H.; Cho, S. J.; Yoo, M.; Kang, S. K.; Kim, K. R.; Lee, H. H.; Song, J. S.; Rhee, S. D.; Jung, W. H.; Ahn, J. H.; Jung, J.-K.; Jung, K.-Y. Synthesis and biological evaluation of thiazole derivatives as GPR119 agonists. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 5213−5220.

(8) López-Rodríguez, M. L.; Morcillo, M. J.; Rovat, T. K.; Fernández, E.; Vicente, B.; Sanz, A. M.; Hernández, M.; Orensanz, L. Synthesis and Structure-Activity Relationships of a New Model of Arylpiperazines. 4.[1] 1-[ω-(4-Arylpiperazin-1-yl)alkyl]-3-(diphenylmethylene)-2,5-pyrrolidinediones and −3-(9H-fluoren-9-ylidene)-2,5pyrrolidinediones: Study of the Steric Requirements of the Terminal Amide Fragment on 5-HT_{1A} Affinity/Selectivity. *J. Med. Chem.* **1999**, *42*, 36−49.

(9) Nolan, C. J.; Evans, B. A. J.; Smith, H. J.; Ahmadi, M.; Nicholls, P. J.; Hewlins, M. J. E. Inhibitors of Type 2 5α-Reductase from Human Genital Skin Fibroblasts Based on 3-Phenylmethylene Pyrrolidine-2, 5-dione. *Pharm. Sci.* **1997**, *3*, 249−257.

(10) Riemer, N.; Shipman, M.; Wessig, P.; Schmidt, B. Iterative Arylation of Itaconimides with Diazonium Salts through Electrophilic Palladium Catalysis: Divergent β-H-Elimination Pathways in Repetitive Matsuda-Heck Reactions. *J. Org. Chem.* **2019**, *84*, 5732−5746.

(11) Song, Y.; Clizbe, L.; Bhakta, C.; Teng, W.; Wong, P.; Huang, B.; Tran, K.; Sinha, U.; Park, G.; Reed, A.; Scarborough, R. M.; Zhu, B.-Y. Design and synthesis of factor Xa inhibitors and their prodrugs. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 297−300.

(12) Pal, B.; Chang, C.-H.; Zeng, C.-J.; Lin, C.-H. Template-Assisted Benzannulation Route to Pentacene and Tetracene Derivatives and its Application to Construct Amphiphilic Acenes That Self-Assemble into Helical Wires. *Chem. - Eur. J.* **2017**, *23*, 17542−17548.

(13) Remón, P.; Bälter, M.; Li, S.; Andréasson, J.; Pischel, U. An All-Photonic Molecule-Based D Flip-Flop. *J. Am. Chem. Soc.* **2011**, *133*, 20742−20745.

(14) Andréasson, J.; Straight, S. D.; Moore, T. A.; Moore, A. L.; Gust, D. Molecular All-Photonic Encoder-Decoder. *J. Am. Chem. Soc.* **2008**, *130*, 11122−11128.

(15) Ohki, S.; Ozawa, N.; Yabe, Y.; Matsuda, H. Anticholinergic Agents. Synthesis of 1, 1, 4-Trimethyl- and 1, 1, 5-Trimethyl-3-diphenylmethyl-enepyrrolidinium Halides. *Chem. Pharm. Bull.* **1976**, *24*, 1362−1370.

(16) Mangaleswaran, S.; Argade, N. P. An Easy Access to (*E*)-Alkylidenesuccinic Acids. *Synthesis* **2003**, *2003*, 343−345.

(17) Haval, K. P.; Argade, N. P. Haval-Argade contrathermodynamic rearrangement of alkylidenesuccinimides to alkylmaleimides via the corresponding isoimides: a general approach to alkyl and dialkyl substituted maleimides. *Tetrahedron* **2006**, *62*, 3557−3563.

(18) Haval, K. P.; Argade, N. P. Synthesis of Natural Fimbrolides. *Synthesis* **2007**, *2007*, 2198−2202.

(19) Chupakhin, E.; Gecht, M.; Ivanov, A.; Kantin, G.; Dar'in, D.; Krasavin, M. (*E*)-3-Arylidene-4-diazopyrrolidine-2,5-diones: Preparation and Use in Rh^{II}-Catalyzed X-H Insertion Reactions towards Novel, Medicinally Important Michael Acceptors. *Synthesis* **2021**, *53*, 1292−1300.

(20) Wang, J.; Liu, H.; Fan, Y.; Yang, Y.; Jiang, Z.; Tan, C.-H. Bicyclic Guanidine-Catalyzed Direct Asymmetric Allylic Addition of *N*-Aryl Alkylidene-Succinimides. *Chem. - Eur. J.* **2010**, *16*, 12534−12537.

(21) Zhao, B.-L.; Du, D.-M. Organocatalytic cascade Michael/Michael reaction for the asymmetric synthesis of spirooxindoles containing five contiguous stereocenters. *Chem. Commun.* **2016**, *52*, 6162−6165.

(22) Zhao, B.-L.; Zhang, D.; Liu, L.; Du, D.-M. Organocatalytic asymmetric Michael addition of α-alkylidene succinimides to nitrostyrenes. *Org. Biomol. Chem.* **2016**, *14*, 6337−6345.
(23) Tehri, P.; Peddinti, R. K. DBU-catalyzed [3 + 2] cycloaddition and Michael addition reactions of 3-benzylidene succinimides with 3-ylidene oxindoles and chalcones. *Org. Biomol. Chem.* **2019**, *17*, 3964−3970.
(24) Song, T.; Li, L.; Zhou, W.; Zheng, Z.-J.; Deng, Y.; Xu, Z.; Xu, L.-W. Enantioselective Copper-Catalyzed Azide-Alkyne Click Cycloaddition to Desymmetrization of Maleimide-Based Bis(alkynes). *Chem. - Eur. J.* **2015**, *21*, 554−558.
(25) Chen, M.-Y.; Xu, Z.; Chen, L.; Song, T.; Zheng, Z.-J.; Cao, J.; Cui, Y.-M.; Xu, L.-W. Catalytic Asymmetric Huisgen Alkyne-Azide Cycloaddition of Bisalkynes by Copper(I) Nanoparticles. *ChemCatChem* **2018**, *10*, 280−286.
(26) Luo, W.; Hu, H.; Nian, S.; Qi, L.; Ling, F.; Zhong, W. Phosphine-catalyzed [3 + 2] annulation reaction: highly regio- and diastereoselective synthesis of 2-azaspiro[4.4]nonene-1,3-diones. *Org. Biomol. Chem.* **2017**, *15*, 7523−7526.
(27) Yang, W.-L.; Liu, Y.-Z.; Luo, S.; Yu, X.; Fossey, J. S.; Deng, W.-P. The copper-catalyzed asymmetric construction of a dispiropyrrolidine skeleton via 1,3-dipolar cycloaddition of azomethine ylides to α-alkylidene succinimides. *Chem. Commun.* **2015**, *51*, 9212−9215.
(28) Kaur, A.; Kaur, M.; Singh, B. One-pot Regioselective Synthesis of Novel 1-*N*-Methyl-spiro[2,3′]oxindole-spiro[3,3″]-1″-*N*-arylpyrrolidine-2″,5″-dione-4-arylpyrrolidines through Multicomponent 1,3-Dipolar Cycloaddition Reaction of Azomethine Ylide. *J. Heterocyclic Chem.* **2015**, *52*, 827−833.
(29) Haddad, S.; Boudriga, S.; Porzio, F.; Soldera, A.; Askri, M.; Knorr, M.; Rousselin, Y.; Kubicki, M. M.; Golz, C.; Strohmann, C. Regio- and Stereoselective Synthesis of Spiropyrrolizidines and Piperazines through Azomethine Ylide Cycloaddition Reaction. *J. Org. Chem.* **2015**, *80*, 9064−9075.
(30) Liu, Y.; Zhang, W. Iridium-catalyzed asymmetric hydrogenation of α-alkylidene succinimides. *Angew. Chem., Int. Ed.* **2013**, *52*, 2203−2206.
(31) Kalia, D.; Malekar, P. V.; Parthasarathy, M. Exocyclic Olefinic Maleimides: Synthesis and Application for Stable and Thiol-Selective Bioconjugation. *Angew. Chem., Int. Ed.* **2016**, *55*, 1432−1435.
(32) Kim, H. Y.; Wiles, J. A.; Wang, Q.; Pais, G. C. G.; Lucien, E.; Hashimoto, A.; Nelson, D. M.; Thanassi, J. A.; Podos, S. D.; Deshpande, M.; Pucci, M. J.; Bradbury, B. J. Exploration of the Activity of 7-Pyrrolidino-8-methoxyisothiazoloquinolones against Methicillin-Resistant *Staphylococcus aureus* (MRSA). *J. Med. Chem.* **2011**, *54*, 3268−3282.
(33) Abdallah, S. M.; Hefny, H. A. Microwave synthesis of some new antimicrobial and antiproliferative butenamides and pyrrolidine-2,5-diones. *Turk. J. Chem.* **2011**, *35*, 463−474.
(34) Martynov, A. V. New Approach to the Synthesis of *trans*-Aconitic Acid Imides. *Russ. J. Org. Chem.* **2005**, *41*, 723−726.
(35) Abass, E. M. Synthesis of Arylmethylene-Butanimides and Butenamides and Evaluation of their Biological Activity. *J. Chem. Bio. Phys. Sci. Sec. A* **2015**, *5* (1), 10−18.
(36) Ballini, R.; Bosica, G. A direct method for the synthesis of polyfunctionalized unsaturated carbonyl derivatives by Michael addition of nitroalkanes to enediones with the help of DBU. *Tetrahedron* **1995**, *51*, 4213−4222.
(37) Morita, T.; Akita, M.; Satoh, T.; Kakiuchi, F.; Miura, M. Ruthenium-Catalyzed Cross-Coupling of Maleimides with Alkenes. *Org. Lett.* **2016**, *18*, 4598−4601.
(38) Sharma, S.; Han, S. H.; Oh, Y.; Mishra, N. K.; Lee, S. H.; Oh, J. S.; Kim, I. S. Cross-Coupling of Acrylamides and Maleimides under Rhodium Catalysis: Controlled Olefin Migration. *Org. Lett.* **2016**, *18*, 2568−2571.
(39) Keerthana, M. S.; Manoharan, R.; Jeganmohan, M. Cobalt(III)-Catalyzed Redox-Neutral Coupling of Acrylamides with Activated Alkenes via C-H Bond Activation. *Synthesis* **2020**, *52*, 1625−1633.
(40) Schirmer, M.-L.; Adomeit, S.; Spannenberg, A.; Werner, T. Novel Base-Free Catalytic Wittig Reaction for the Synthesis of Highly Functionalized Alkenes. *Chem. - Eur. J.* **2016**, *22*, 2458−2465.
(41) Hedaya, E.; Theodoropulos, S. The preparation and reactions of stable phosphorus ylides derived from maleic anhydrides, maleimides or isomaleimides. *Tetrahedron* **1968**, *24*, 2241−2254.
(42) Haval, K. P.; Argade, N. P. General Strategy for the Synthesis of Natural and Unnatural Dialkylmaleic Anhydrides. *J. Org. Chem.* **2008**, *73*, 6936−6938.
(43) Yan, L.; Yang, W.; Shen, Y.; Li, L.; Jiang, Z. A One-pot Green Synthesis of Alkylidenesuccinimides. *Chin. J. Chem.* **2011**, *29*, 1906−1910.
(44) Bayat, M.; Hosseini, S. R.; Asmari, E. Simple synthesis of (*E*) and (*Z*)-2-(arylmethylidene)-*N*-phenyl succinimides via Wittig olefination by using *PS-TPP* resin. *Phosphorus, Sulfur Silicon Relat. Elem.* **2017**, *192*, 98−102.
(45) Huang, X.; Sha, F. A Novel Three-Component Reaction of Allenoates, Isocyanides, and Carboxylic Acids: Facile Synthesis of Highly Substituted Acryl Imide Derivatives. *J. Org. Chem.* **2008**, *73*, 1173−1175.
(46) Ramanivas, T.; Parameshwar, M.; Gayatri, G.; Nanubolu, J. B.; Srivastava, A. K. Asymmetric Synthesis of Functionalized 2,5-Pyrrolidinediones and β-Lactams through Diastereospecific Cycloisomerization/Rearrangement of Chiral Ethanolamine-Derived Ugi Adducts. *Eur. J. Org. Chem.* **2017**, *2017*, 2245−2257.
(47) Driller, K. M.; Klein, H.; Jackstell, R.; Beller, M. Iron-Catalyzed Carbonylation: Selective and Efficient Synthesis of Succinimides. *Angew. Chem., Int. Ed.* **2009**, *48*, 6041−6044.
(48) Prateeptongkum, S.; Driller, K. M.; Jackstell, R.; Spannenberg, A.; Beller, M. Efficient Synthesis of Biologically Interesting 3,4-Diaryl-Substituted Succinimides and Maleimides: Application of Iron-Catalyzed Carbonylations. *Chem. - Eur. J.* **2010**, *16*, 9606−9615.
(49) Liu, H.; Lau, G. P. S.; Dyson, P. J. Palladium-Catalyzed Aminocarbonylation of Alkynes to Succinimides. *J. Org. Chem.* **2015**, *80*, 386−391.
(50) Sha, F.; Alper, H. Ligand- and Additive-Controlled Pd-Catalyzed Aminocarbonylation of Alkynes with Aminophenols: Highly Chemo- and Regioselective Synthesis of α,β-Unsaturated Amides. *ACS Catal.* **2017**, *7*, 2220−2229.
(51) van Leeuwen, P. W. N. M.; Claver, C. *Rhodium Catalyzed Hydroformylation*; Springer: Netherlands, 2002; Vol. *22*.
(52) Breit, B. In *Metal Catalyzed Reductive C@C Bond Formation: A Departure from Preformed Organometallic Reagents*; Krische, M. J., Ed.; Springer: Berlin, 2007; pp 139−172.
(53) Franke, R.; Selent, D.; Börner, A. Applied Hydroformylation. *Chem. Rev.* **2012**, *112*, 5675−5732.
(54) Friis, S. D.; Lindhardt, A. T.; Skrydstrup, T. The Development and Application of Two-Chamber Reactors and Carbon Monoxide Precursors for Safe Carbonylation Reactions. *Acc. Chem. Res.* **2016**, *49*, 594−605.
(55) Liu, J.; Han, Z.; Wang, X.; Wang, Z.; Ding, K. Highly Regio- and Enantioselective Alkoxycarbonylative Amination of Terminal Allenes Catalyzed by a Spiroketal-Based Diphosphine/Pd(II) Complex. *J. Am. Chem. Soc.* **2015**, *137*, 15346−15349.
(56) Fang, X.; Jackstell, R.; Beller, M. Selective Palladium-Catalyzed Aminocarbonylation of Olefins with Aromatic Amines and Nitroarenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 14089−14093.
(57) Fang, X.; Li, H.; Jackstell, R.; Beller, M. Selective Palladium-Catalyzed Aminocarbonylation of 1,3-Dienes: Atom-Efficient Synthesis of β,γ-Unsaturated Amides. *J. Am. Chem. Soc.* **2014**, *136*, 16039−16043.
(58) Liu, J.; Schneider, C.; Yang, J.; Wei, Z.; Jiao, H.; Franke, R.; Jackstell, R.; Beller, M. A General and Highly Selective Palladium-Catalyzed Hydroamidation of 1,3-Diynes. *Angew. Chem., Int. Ed.* **2021**, *60*, 371−379.
(59) Liu, J.; Li, H.; Spannenberg, A.; Franke, R.; Jackstell, R.; Beller, M. Selective Palladium-Catalyzed Aminocarbonylation of Olefins to Branched Amides. *Angew. Chem., Int. Ed.* **2016**, *55*, 13544−13548.

https://doi.org/10.1021/jacsau.1c00221
JACS Au 2021, 1, 1257−1265

(60) Goldbach, V.; Falivene, L.; Caporaso, L.; Cavallo, L.; Mecking, S. Single-Step Access to Long-Chain α,ω-Dicarboxylic Acids by Isomerizing Hydroxycarbonylation of Unsaturated Fatty Acids. *ACS Catal.* **2016**, *6*, 8229−8238.
(61) Dong, K.; Sang, R.; Wei, Z.; Liu, J.; Dühren, R.; Spannenberg, A.; Jiao, H.; Neumann, H.; Jackstell, R.; Franke, R.; Beller, M. Cooperative catalytic methoxycarbonylation of alkenes: uncovering the role of palladium complexes with hemilabile ligands. *Chem. Sci.* **2018**, *9*, 2510−2516.
(62) Amatore, C.; Jutand, A.; M'Barki, M. A. Evidence of the formation of zerovalent palladium from $Pd(OAc)_2$ and triphenylphosphine. *Organometallics* **1992**, *11*, 3009−3013.
(63) Amatore, C.; Carre, E.; Jutand, A.; M'Barki, M. A. Rates and Mechanism of the Formation of Zerovalent Palladium Complexes from Mixtures of $Pd(OAc)_2$ and Tertiary Phosphines and Their Reactivity in Oxidative Additions. *Organometallics* **1995**, *14*, 1818−1826.
(64) Hunter, E. P. L.; Lias, S. G. Evaluated Gas Phase Basicities and Proton Affinities of Molecules: An Update. *J. Phys. Chem. Ref. Data* **1998**, *27*, 413−656.
(65) Balgotra, S.; Verma, P. K.; Vishwakarma, R. A.; Sawant, S. D. Catalytic advances in direct functionalizations using arylated hydrazines as the building blocks. *Catal. Rev.: Sci. Eng.* **2020**, *62*, 406−479 and references therein.
(66) Huang, Y.; Choy, P. Y.; Wang, J.; Tse, M.-K; Sun, R. W.-Y.; Chan, A. S.-C.; Kwong, F. Y. Palladium-Catalyzed Monoarylation of Arylhydrazines with Aryl Tosylates. *J. Org. Chem.* **2020**, *85*, 14664−14673 and references therein.
(67) Abdou, W. M.; Khidre, R. E.; Barghash, R. F. Regioselective Condensation of Alkylidenephosphoranes to *N*-Methoxy- and *N*-Anilino-1*H* isoindole-1,3-(2*H*)-diones. *Synth. Commun.* **2012**, *42*, 1967−1978.
(68) King, F. D. Synthesis and thermal reactions of 1,2-dihydro-1,2,4-benzotriazines. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3381−3385.
(69) Cumming, J. G.; Lin, X.; Liu, H.; Najera, I.; Qiu, Z.; Sandrin, V.; Tang, G.; Wu, G. Patent WO 2018001948 A1, 2018.
(70) Sako, M. Product class 18: pyridopyridazines. *Science of Synthesis* **2004**, *16*, 1109−1153.
(71) Goldstein, D. M.; Rueth, M. Patent US 20070219195 A1, 2007.
(72) Ye, K.; Ai, H.-L.; Liu, J.-K. Identification and bioactivities of secondary metabolites derived from endophytic fungi isolated from ethnomedicinal plants of Tujia in Hubei province: a review. *Nat. Prod. Bioprospect.* **2021**, *11*, 185−205.

https://doi.org/10.1021/jacsau.1c00221
JACS Au 2021, 1, 1257−1265