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Ketone Synthesis by Direct, Orthogonal Chemoselective Hydroacylation of Alkenes with Amides: Use of Alkenes as Surrogates of Alkyl Carbanions

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Abstract Direct functionalization of alkenes and direct transformation of carboxamides are two exciting areas that have attracted considerable attention in recent years. We report herein that secondary amides, the least reactive derivatives of carboxylic acids, upon activated with triflic anhydride, can serve as effective hydroacylating reagents in partner with alkenes to yield ketones at ambient temperature. The method was applied to the one-step synthesis of racemic dihydro-*ar*-turmerone. In this method, alkenes serve as surrogates of organometallic reagents, which allows the orthogonal chemoselective reactions. The ready availability of many olefins such as camphene and norbornene permits one-step ketone synthesis that would require several steps by conventional methods.

Introduction

In organic chemistry, ketone is one of the most versatile functional groups for C–C bond formation. Numerous methods have been developed for the synthesis of ketones.[1] Among them, the conversion of carboxylic acid derivatives into ketones by addition of organometallic reagents occupy a central position. However, due to the well-known problem of over addition, indirect methods consisting of pre-conversion of carboxylic acids or esters into specially designed carboxylic derivatives such as thioesters[2] or chelating amides such as *N*-methyl-*N*-methoxy amides (Weinreb's amides),[3] followed by organometallic reagents addition, are employed routinely for the synthesis of ketones from carboxylic acids and esters (Scheme 1, a). Nevertheless, the above-mentioned methods cannot be used for the synthesis of ketones from common carboxamides (*N*-monoacylamines), the least reactive carbonyl compounds. Carboxamides are easily available[4] and bench stable compounds, and amide group is widely used as a directing group for both classical metalation – functionalization[5] and modern C–H functionalization.[6] Thus, the transformation of common carboxamides into ketones is in high demand.

In recent years, the direct transformations of amides have attracted considerable attention,[7] which cumulated in a number of chemoselective C–C bond forming methods.[8] However, the direct conversion of amides to ketones remains rare. In 2012, the Charette's group[9] and our group[10] reported independently the chemoselective syntheses of ketones by addition of organometallic reagents ($RMgX/R_2Zn$;[9] $RMgX/RLi\text{-}CeCl_3$[10]) to triflic anhydride (Tf_2O)/2-F-Pyr.-activated secondary amides (Scheme 1, b). In 2015, our group also developed a ketone synthesis by addition of Grignard reagents to Tf_2O/DTBMP-activated tertiary amides (Scheme 1, b).[11]

In all the above-mentioned methods, organometallic reagents are used as the alkylating reagents. In classical organic chemistry, reactive organometallic reagents such as organolithium and Grignard reagents represent the most versatile carbon nucleophiles for C–C bond formation. In the context of developing chemoselective and sustainable transformation, the major concern in contemporary organic synthesis,[12] the use of organometallic reagents as alkylating agents presents several drawbacks. For example, organometallic reagents need to be prepared from a stoichiometric amount of organic halides and a stoichiometric amount of metals in an anhydrous organic solvent. Moreover, the inherent high reactivity of organometallic reagents (highly nucleophilic, highly basic, and highly hygroscopic) make them of low functional group tolerance towards both electrophilic and nucleophilic partners.

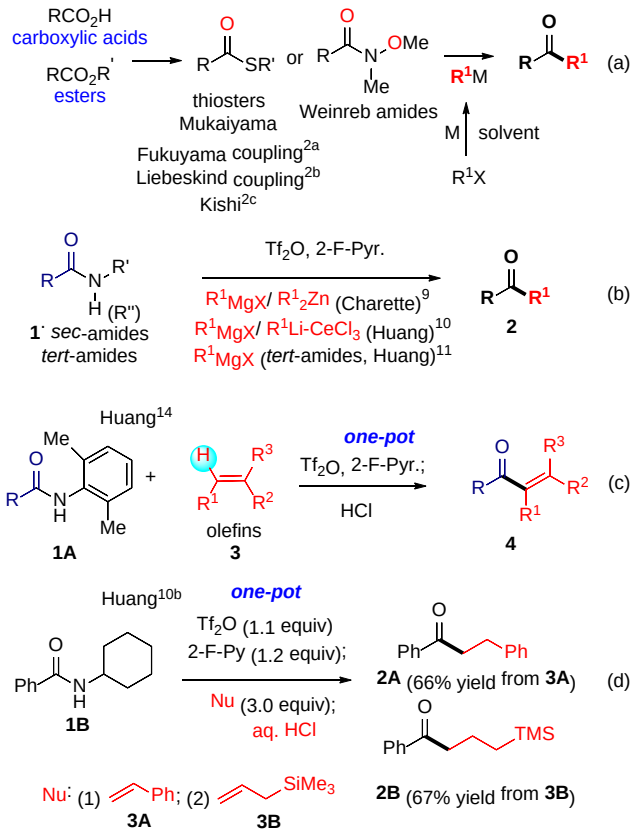
Olefins are a class of abundant chemical feedstocks. The functionalization of alkenes has attracted considerable attention in recent years.[1a,13] Recently, we have developed mild methods for the coupling of alkenes and arenes with *N*-(2,6-dimethyl) secondary amides **1A** to give α,β-unsaturated enones **4** and aromatic ketones, respectively (Scheme 1, c). In those reactions, alkenes/ arenes serve as mild alternates of alkenyl/aryl carbanions **A**.[14] During one of those investigations, we discovered that upon activating with triflic anhydride (Tf_2O), secondary amide **1B** can couple with styrene (**3A**) and allyltrimethylsilane (**3B**) to yield saturated ketones **2A** and **2B**, respectively (Scheme 1, d).[10b] Recognizing the importance and challenging of this reaction, a systematic investigation on this reaction was undertaken.[15] Very recently, Maulide and coworkers have reported a similar reaction.[16] This prompted us to report our own findings that is summarized in Scheme 1, e. Our results show that alkenes can be

used as surrogates of highly reactive alkyl metallic reagents (alkyl carbanions **B**) for the direct transformation of secondary amides **1** into aryl-alkyl ketones and alkyl-alkyl ketones **2**.

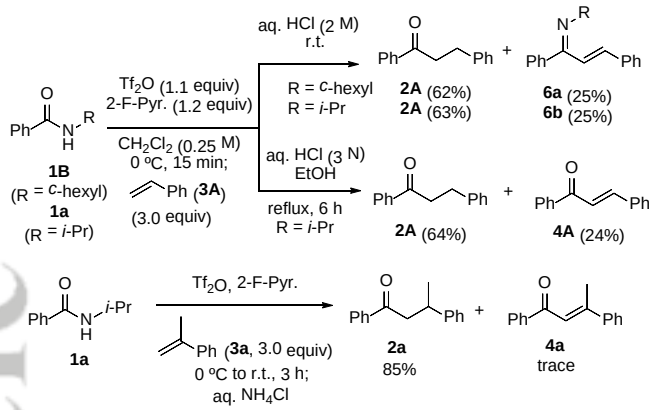
Results and Discussion

To start our investigation, the coupling of amide **1a** with styrene (**3A**) was reexamined (Scheme 2). According to our previous protocol,[10b] a 0.25 M solution of amide **1B** and 2-fluoropyridine (1.2 equiv) in CH_2Cl_2 was exposed to Tf_2O (1.1 equiv) at 0 °C for 15 min, and the resulted activated intermediated was treated with styrene (3.0 equiv) at rt for 3 h. After work-up with 2 M HCl, the desired ketone **2A**[10b] was isolated in 62% yield, along with α,β-enimine **6a**[14a,c] in 25% yield. Similarly, the reaction of amide **1a** produced ketone **2A** in 63% yield and α,β-enimine **6b** in 25% yield. For the later reaction, if acidic work-up was performed by refluxing the reaction mixture in 3 M HCl/ EtOH for 6 h, ketone **2A** and α,β-enone **4A**[14a,c] were obtained in 64% and 24% yield, respectively. To our delight, the reaction of α-methylstyrene (**3a**) with **1a** yielded, after work up with an aqueous NH_4Cl, ketone **2a** in 85% yield, and only trace of enone **4a** was observed.

Scheme 1 Reported methods for ketones synthesis from carboxylic acids and derivatives and our synthetic plan

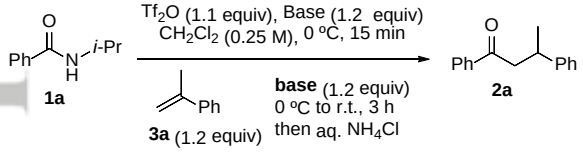


Scheme 2 Reinvestigation and preliminary investigation of the couplings of amides **1B** and **1a** with styrene



Next, we selected *N*-*i*-propylbenzamide (**1a**) as a prototype amide substrate, and α-methylstyrene (**3a**), a bulk chemical used in the polymer industry, as a nucleophile for our investigation. In view of the successful use of Tf_2O as a powerful amide activating agent in our previous investigations, we opted for this easily available reagent for amide activation, and the effect of base partner was first examined. It was encouraging to observe that treating a mixture of amide **1a** and Tf_2O with α-methylstyrene (**3a**) resulted in the clean formation of the desired ketone **2a** in 30% yield, along with the recovered starting amide in 59% yield (Table 1, entry 1). Whereas yield of **2a** was slightly improved with the use of triethylamine, pyridine is detrimental for the reaction. Encouragingly, good yields of **2a** were obtained by employing pyridine derivatives such as 2-chloropyridine (2-Cl-Pyr.), 2-fluoropyridine (2-F-Pyr.), 2,6-di-*tert*-butylpyridine (DTBP), and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), and 2-F-Pyr. turned out to be the most efficient base partner examined, affording the desired ketone **2a** in 88% yield (determined by NMR, 85% isolated yield). A survey of amount of nucleophile **3a** showed that 1.2 equiv. to be optimal, which produced ketone **2a** in 88% NMR yield (85% isolated yield) (see Table S1 in supporting information).

Table 1. Screening of base.

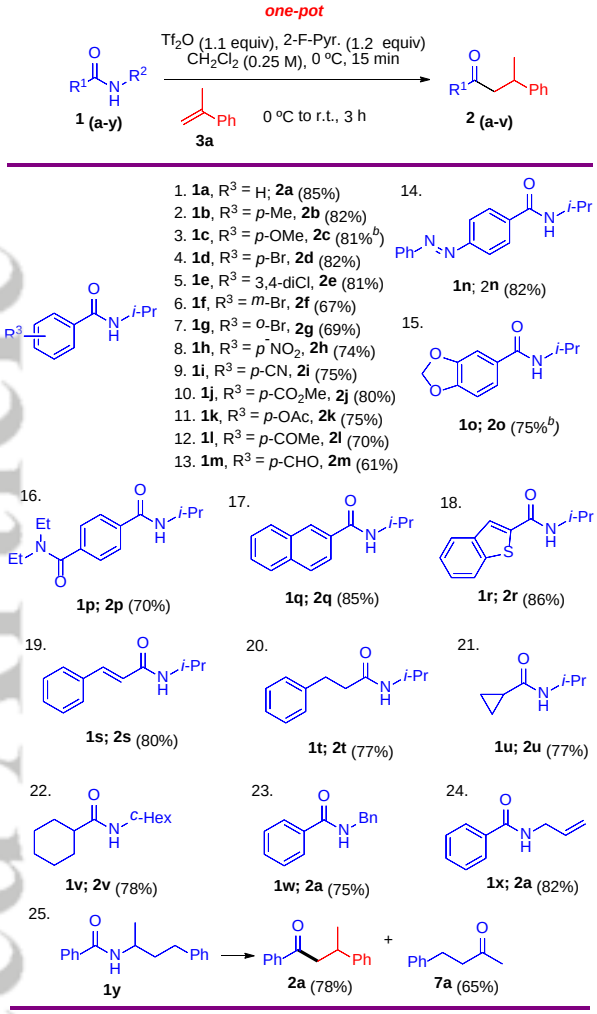


Entry	Base (1.2 equiv)	**2a** (% yield)[a]	**1a** (% yield)[a]
1	None	30	59
2	Et_3N	45	15
3	Pyr.	10	75
4	2-Cl-Pyr.	60	trace
5	**2-F-Pyr.**	**88 (85)[b]**	**trace**
6	DTBP	75	trace
7	DTBMP	82	trace

With the optimal reaction conditions in hand, the scope of amide substrate was surveyed, and the results are summarized in Table 2. The substituent effect on the phenyl ring was first examined. The reaction worked smoothly with benzamide derivatives bearing either an electron-donating group (Me, OMe, entries 2 and 3) or an electron-withdrawing group at *para*- and *meta*-positions (Br, 3,4-diCl, entries 4 and 5). Attenuate yields (67% and 69%) were obtained from *m*- and *o*-bromobenzamides (entries 6 and 7), which might due to steric hindrance for the latter case. Remarkably, the reaction demonstrated excellent functional group tolerance.[9] Benzamide derivatives bearing sensitive substituents: nitro, cyano, ester, acetate, ketone, and even aldehyde (formyl) groups reacted chemoselectively at the least reactive secondary amide group to give the corresponding functionalized ketones **2h** - **2m** in respectable 61% to 80% yields (entries 8 - 13). Similar chemoselectivity was observed for benzamides bearing a *p*-phenyldiazenyl and acetal groups (entries 14 and 15). Tertiary and secondary amide groups can also be distinguished with the latter being more reactive (entry 16). Good yields were obtained from *N*-isopropyl-2-naphthamide (**1q**) and electron-rich *N*-isopropylbenzo[*b*]thiophene-2-carboxamide (**1r**) (entries 17 and 18).

The reaction could be extended to both α,β–unsaturated (entry 19) and aliphatic amides (entries 20 and 21). Moreover, secondary amides bearing other *N*-substituents such as primary benzyl and allyl groups (entries 23 and 24) could be used as viable substrates. Interestingly, the reaction of amide bearing a secondary alkyl group **1y** yield, besides the desired ketone **2a** in 78% yield, another ketone **7a** in 65% yield (entry 25). The isolation of 4-phenylbutan-2-one (**7a**) is significant for understanding the mechanism of the reaction (*vide infra*).

Table 2. Amide scope[a]

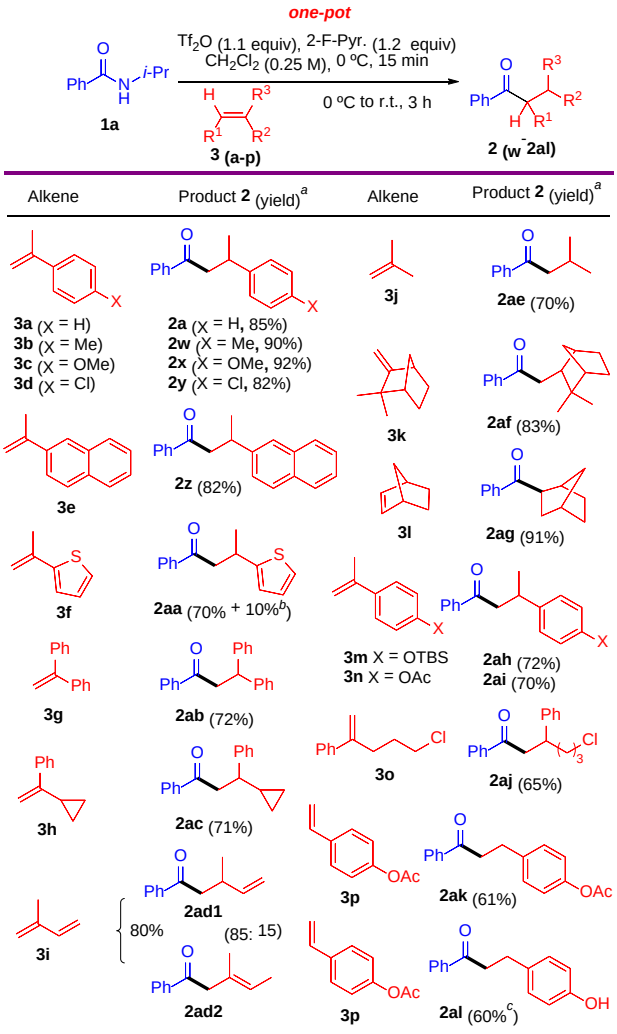


[a] Isolated yield; [b] The coupling step run at 40 °C.

We next examined the scope of alkene (Table 3). Excellent yields were obtained from α-methylstyrenes bearing an electron-donating group (**3b**: Me, 90%; **3c**: OMe, 92%) at *para*-position of the prop-1-en-yl group, and an 82% yield was obtained from α-methyl-(*p*-chlorostyrene)(**3d**). Other prop-1-en-2-ylarenes such as 2-(prop-1-en-2-yl)naphthalene (**3e**) and 2-(prop-1-en-2-yl)thiophene (**3f**) reacted with similarly efficiency, but 10% of the eliminated side product (**4a**) was also yielded from **3f**. The yield (72%) from the reaction of ethene-1,1-diyldibenzene (**3g**) is lower than expected, whereas that (71%) from cyclopropylvinyl derivative (**4h**) is higher than expected considering a possible rearrangement. Apart from prop-1-en-2-ylarenes, alkenes can be extended to non-styrene derivatives such as 2,2-disubstituted terminal alkenes (**3i** and **3j**). Significantly, naturally occurring and commercially available terpenes camphene (**3k**) and norbornene (**3l**), a special 1,2-dialkylalkene, served as excellent alkene partners furnishing the corresponding ketones in excellent yields (**2af**: 83%; **2ag**: 91%) as single diastereomer. Although the stereochemistries of the products were not determined, in light of our recent results,[17] *exo*-substituted diastereomers were assume.

The advantages of using neutral alkenes as surrogates of reactive organometallic reagents (alkyl carbanions) is multiple. On one hand, not only it allows the use of amides bearing sensitive functional groups (e.g. **1h** - **1p**), but also it permits employing functionalized alkenes. The latter feature is showcased by alkenes **3m – 3p** bearing OTBS, OAc, and chloro substituents. On the other hand, the ready availability of many olefins such as commercially available terpenes camphene (**3k**) and norbornene (**3l**), as compared with the corresponding carbanions or organohalides represents another singular feature of the method. Interestingly, depending on the work-up conditions, phenol acetate in **3p** could either survival from the reaction or cleaved concomitantly to deliver directly free phenol group. Such features are not possible for the traditional addition reactions employing RM as nucleophiles.

Table 3. Alkene scope

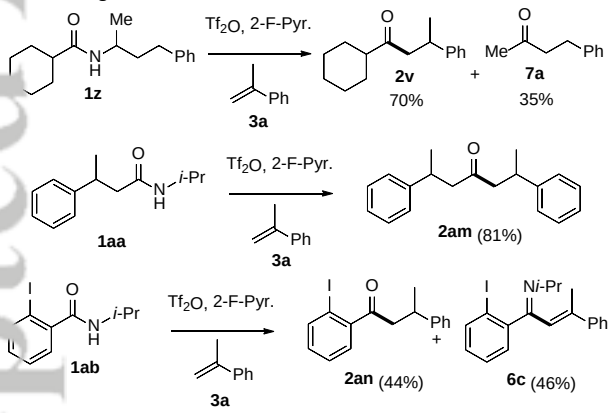


[a] Isolated yield, Work-up with sat. aq. NH_4Cl; [b] Yield of α,β-enone **4b**; [c] Work-up with 3 M HCl/ EtOH.

Because secondary amides are products of many synthetic methodologies,[4] the transformation of such products were envisioned (Scheme 3). In 2014, Fu reported a mild method for the synthesis of secondary amides featuring photoinduced, copper-catalyzed alkylation of amides with unactivated secondary alkyl halides at room temperature.[4a] The coupling of one of its product **1z** with α-methylstyrene (**3a**) yielded ketone **2v** in 70% yield, along with ketone **7a** in 35% yield. The hydroacylation of α-methylstyrene (**3a**) with amide **1aa**, a Beak's secondary amide directed methylation product,[5b] afforded ketone **2am** in 81% yield. The reaction of α-methylstyrene (**3a**) with *o*-iodobenzamide **1ab**, a secondary amide-directed C–H functionalization product described by Glorius,[6d] afforded ketone **2an** in 44% yield, along with enamine **6c** in 46% yield.

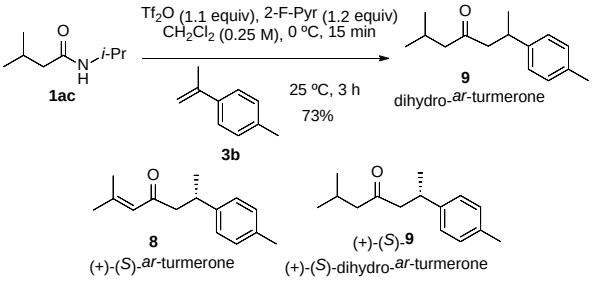
(+)-(*S*)-*ar*-turmerone (**8**) and (+)-(*S*)-dihydro-*ar*-turmerone (**9**) belong to bisabolane-type sesquiterpenoids.[18] These sesquiterpenoids possess a variety of biological activities including acetylcholinesterase inhibitory activity.[18b] To further demonstrate the synthetic potential of our method, the synthesis of dihydro-*ar*-turmerone (**9**) was undertaken. Simply by subjecting amide **1ac** to the standard hydroacylation with α-methylstyrene derivative (**3b**), the desired racemic dihydro-*ar*-turmerone (**9**) was synthesized in 73% yield.

Scheme 3. The transformation of amides available by modern synthetic methodologies

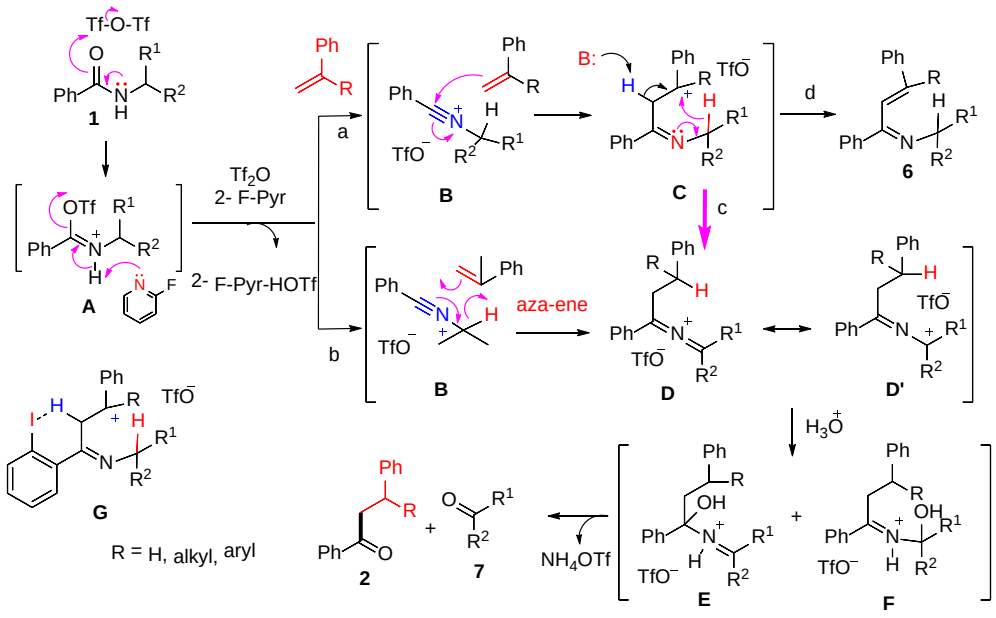


A plausible mechanism for the hydroacylation reaction is depicted in Scheme 5. Central to the mechanism is the generation of a highly reactive nitrilium intermediate **B** upon treatment of a secondary amide with Tf_2O, which has been detected in our previous work by both in situ IR and 2D NMR techniques.[14a,19] Another key point resides in the 1,5-hydride transfer that has been suggested when this reaction was discovered for the first time.[10b] The easy release of a ketone from the reaction just by work up with a sat. aqueous NH_4Cl is in support of the reactive intermediate **D**. The observation of the formation of **6** and **7** in some cases provides supports for the suggested mechanism. Moreover, the formation of enimine **6c** (Scheme 3) as the major product can be understood in terms of an intramolecular I···H interaction (cf. G in Scheme 5), which favors the β-elimination, and yields **6c** as the major product.

Scheme 4. One-step synthesis of racemic dihydro-*ar*-turmerone



Scheme 5. Plausible mechanism of the reaction



Conclusions

Starting from our recent finding, we have established an expedient and sustainable method for the synthesis of ketones from alkenes and amides. Running at room temperature, and employing neutral alkenes to replace conventionally used highly basic organometallic reagents as nucleophiles, the reactions conditions are quite mild. As a result, several sensitive functional groups on either nucleophilic partner (alkenes) or nucleophilic partner (amides) are tolerated. Moreover, the use of abundant and stable chemical feedstocks such as bulk chemicals α-methylstyrene, naturally occurring camphene and norbornene, permits one-step ketone synthesis that would require several steps by conventional methods. A detailed mechanism featuring a 1,5-hydride transfer is suggested, which is supported by the isolation of several side-products. Further exploration of this method is ongoing in our laboratories, and the results will be reported in due course.

Experimental

General procedure for the direct hydroacylation of alkenes with secondary amides to give ketones.

Tf_2O (185 μL, 1.1 mmol, 1.1 equiv) was added dropwise to a cooled (0 °C) solution of a secondary amide (1.0 mmol, 1.0 equiv) and 2-fluoropyridine (103 μL, 1.2 mmol, 1.2 equiv) in dichloromethane (4 mL, 0.25 M). The reaction was stirred for 15 min at 0 °C. To the resulting mixture, an alkene (1.2 mmol, 1.2 equiv) was added dropwise at 0 °C. The mixture was allowed to warm-up to room temperature (or 40 °C) and stirred for 3 h. The reaction was quenched with a saturated aqueous NH_4Cl solution (3 mL), and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium carbonate (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with ether/petroleum ether to afford the desired ketone.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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References

[1] For a perspective, see: (a) Raviola, C.; Protti, S.; Ravelli, D.; Maurizio F. Photogenerated Acyl/Alkoxycarbonyl/Carbamoyl Radicals for Sustainable Synthesis. *Green Chem.* **2019**, *21*, 748-764. For a leading

[a] *Department, Institution, Address 1*
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[b] *Department, Institution, Address 2*
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[c] *Department, Institution, Address 3*
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reference, see: (b) Moon, S.-Y.; Jung, S.-H.; Kim, U. B.; Kim, W. S. Synthesis of Ketones via Organolithium Addition to Acid Chlorides Using Continuous Flow Chemistry. *RSC Adv.* **2015**, *5*, 79385-79390.

[2] (a) Fukuyama, T.; Tokuyama, H. Palladium-mediated synthesis of aldehydes and ketones from thiol esters. *Aldrichimica Acta* **2004**, *37*, 87–96. (b) Yang, H.; Li, H.; Wittenberg, R.; Egi, M.; Huang, W.; Liebeskind, L. S. Ambient Temperature Synthesis of High Enantiopurity *N*-Protected Peptidyl Ketones by Peptidyl Thiol Ester-Boronic Acid Cross-Coupling. *J. Am. Chem. Soc.* **2007**, *129*, 1132–1140. (c) Lee, J. H.; Kishi, Y. One-Pot Ketone Synthesis with Alkylzinc Halides Prepared from Alkyl Halides via a Single Electron Transfer Process: New Extension of Fukuyama Ketone Synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 7178–7186.

[3] Nahm, S.; Weinreb, S. M. *N*-Methoxy-*N*-Methylamides as Effective Acylating Agents. *Tetrahedron Lett.* **1981**, *22*, 3815–3818.

[4] For a recent review, see: (a) Lanigan, R. M.; Sheppard, T. D. *Eur. J. Org. Chem.* **2013**, 7453–7465. For selected examples, see: (b) Tian, D.-S.; Li, C.-X.; Gu, G.-X.; Peng, H.-N.; Zhang, X.-M.; Tang, W.-J. Stereospecific Nucleophilic Substitution with Arylboronic Acids as Nucleophiles in the Presence of a CONH Group *Angew. Chem. Int. Ed*. **2018**, *57*, 7176-7180. (c) Wang, Z.-B.; Yin, H.-L.; Fu, G. C. Catalytic Enantioconvergent Coupling of Secondary and Tertiary Electrophiles with Olefins. *Nature* **2018**, *563*, 379-383. (d) Li, X. W. ; Lin, F. G.; Huang, K. M.; Wei, J. L.; Li, X. Y.; Wang, X. Y.; Geng, X. Y.; Jiao, N. Selective α-Oxyamination and Hydroxylation of Aliphatic Amides. *Angew. Chem., Int. Ed.* **2017**, *56*, 12307–12311. (e) Do, H. Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. Photoinduced, copper-catalyzed alkylation of amides with unactivated secondary alkyl halides at room temperature. *J. Am. Chem. Soc.* **2014**, *136*, 2162-2167.

[5] For a review, see: Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933. For an example, see: (b) Lutz, G. P.; Du, H.; Gallagher, D. J.; Beak, P. Synthetic Applications of the β-Lithiation of β-Aryl Secondary Amides: Diastereoselective and Enantioselective Substitutions. *J. Org. Chem.* **1996**, *61*, 4542-4554.

[6] For reviews, see: (a) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. A Simple and Versatile Amide Directing Group for C–H Functionalizations. *Angew. Chem. Int. Ed*. **2016**, *55*, 10578–10599. (b) Zhu, C.; Wang, R.; Falck, J. R. Amide-Directed Tandem C–C/C–N Bond Formation through C–H Activation. *Chem. -Asian J.* **2012**, *7*, 502-1514. For selected references, see: (c) Yan, S.-Y.; Han, Y.-Q.; Yao, Q.-J.; Nie, X.-L.; Liu, L.; Shi, B.-F. Palladium(II)–Catalyzed Enantioselective Arylation of Unbiased Methylene C(sp^3)–H Bonds Enabled by a 2–Pyridinylisopropyl Auxiliary and Chiral Phosphoric Acids. *Angew. Chem. Int. Ed*. **2018**, *57*, 9093-9097. (d) Choi, G. J.; Zhu, Q.-L.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Amide-Directed Photoredox-Catalysed C–C Bond Formation at Unactivated sp^3 C–H bonds. *Nature* **2016**, *539*, 268-271. (e) Yu, D.-G.; Gensch, T.; de Azambuja, F.; Vásquez-Céspedes, S.; Glorius, F. Co(III)-Catalyzed C–H Activation/Formal S_N-Type Reactions: Selective and Efficient Cyanation, Halogenation, and Allylation. *J. Am. Chem. Soc.* **2014**, *136*, 17722-17725.

[7] For reviews, see: (a) Huang, P.-Q. Direct Transformations of Amides: Tactics and Recent Progress. *Acta Chim. Sinica* **2018**, *76*, 357-365. (b) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide Activation: An Emerging Tool for Chemoselective Synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899-7925. (c) Sato, T.; Yoritate, M.; Tajima, H.; Chida, N. Total Synthesis of Complex Alkaloids by Nucleophilic Addition to Amides. *Org. Biomol. Chem.* **2018**, *16*, 3864-3875. (d) Kaiser, D.; Maulide, N. Making the Least Reactive Electrophile the First in Class: Domino Electrophilic Activation of Amides. *J. Org. Chem.* **2016**, *81*, 4421-4428. (e) Pace, V.; Holzer, W.; Olofsson, B. Increasing the Reactivity of Amides towards Organometallic Reagents: An Overview. *Adv. Synth. Catal.* **2014**, *356*, 3697-3736.

[8] For pioneering work, see: (a) Falmagne, J. B.; Escudero, J.; Taleb-Saharaoui, S.; Ghosez, L. Cyclobutanone and Cyclobutenone Derivatives by Reaction of Tertiary Amides with Alkenes or Alkynes. *Angew. Chem., Int. Ed.* **1981**, *20*, 879-880. For selected examples, see: (b) Movassaghi, M.; Hill, M.; Ahmad, O. K. Direct Synthesis of Pyridine Derivatives. *J. Am. Chem. Soc.* **2007**, *129*, 10096-10097. (c) Cui, S. L.; Wang, J.; Wang, Y. G. Synthesis of Indoles via Domino Reaction of *N*-Aryl Amides and Ethyl Diazoacetate *J. Am. Chem. Soc.* **2008**, *130*, 13526-13527. (d) Xiao, K.-J.; Luo, J.-M.; Ye, K.-Y.; Wang, Y.; Huang, P.-Q. Direct, One-pot Sequential Reductive Alkylation of Lactams/Amides with Grignard and Organolithium Reagents through Lactam/Amide Activation. *Angew. Chem., Int. Ed.* **2010**, *49*, 3037-3040. (e) Shirokane, K.; Kurosaki, Y.; Sato, T.; Chida, N. A Direct Entry to Substituted *N*-Methoxyamines from *N*-Methoxyamides via *N*-Oxyiminium Ions. *Angew. Chem., Int. Ed.* **2010**, *49*, 6369-6372. (f) Xiao, K.-J.; Wang, A.-E; Huang, P.-Q. Direct Transformation of Secondary Amides into Secondary Amines: Triflic Anhydride Activated Reductive Alkylation. *Angew. Chem., Int. Ed.* **2012**, *51*, 8314-8317. (g) Shirokane, K.; Wada, T.; Yoritate, M.; Minamikawa, R.; Takayama, N.; Sato, T.; Chida, N. Total Synthesis of (±)-Gephyrotoxin by Amide-Selective Reductive Nucleophilic Addition. *Angew. Chem., Int. Ed.* **2014**, *53*, 512-516. (h) Peng, B.; Geerdink, D.; Farès, C.; Maulide, N. Chemoselective Intermolecular α-Arylation of Amides. *Angew. Chem., Int. Ed*. **2014**, *53*, 5462–5466. (i) White, K. L.; Mewald, M.; Movassaghi, M. Direct Observation of Intermediates Involved in the Interruption of the Bischler−Napieralski Reaction. *J. Org. Chem.* **2015**, *80*, 7403-7411. (j) Romanens, A.; Bélanger, G. Preparation of Conformationally Restricted $\beta^{2,2}$- and $\beta^{2,2,3}$-Amino Esters and Derivatives Containing an All-Carbon Quaternary Center. *Org. Lett.* **2015**, *17*, 322-325. (k) Katahara, S.; Kobayashi, S.; Fujita, K.; Matsumoto, T.; Sato, T.; Chida, N. An Iridium-Catalyzed Reductive Approach to Nitrones from *N*-Hydroxyamides. *J. Am. Chem. Soc.* **2016**, *138*, 5246-5249. (l) Fuentes de Arriba, A. L.; Lenci, E.; Sonawane, M.; Formery, O.; Dixon, D. J. Iridium-Catalyzed Reductive Strecker Reaction for Late-Stage Amide and Lactam Cyanation. *Angew. Chem., Int. Ed*. **2017**, *56*, 3655-3659. (m) Fan, T.; Wang, A.; Li, J.-Q.; Ye, J.-L.; Zheng, X.; Huang, P.-Q. Versatile One-Pot Synthesis of Polysubstituted Cyclopent-2-enimines from α,β-Unsaturated Amides: Imino-Nazarov Reaction. *Angew. Chem., Int. Ed.* **2018**, *57*, 10352-10356. (n) Trillo, P.; Slagbrand, T.; Adolfsson, H. Straightforward α-Amino Nitrile Synthesis Through $Mo(CO)_6$-Catalyzed Reductive Functionalization of Carboxamides. *Angew. Chem., Int. Ed*. **2018**, *57*, 12347-12351. (o) Ou, W.; Han, F.; Hu, X.-N.; Chen, H.; Huang, P.-Q. Iridium-Catalyzed Reductive Alkylations of Secondary Amides. *Angew. Chem., Int. Ed.* **2018**, *57*, 11354-11358. (p) Xie, L.-G.; Dixon, D. J. Iridium-Catalyzed Reductive Ugi-Type Reactions of Tertiary Amides. *Nat. Commun.* **2018**, *9*, 2841. (q) Hiraoka, S.; Matsumoto, T.; Matsuzaka, K.; Sato, T.; Chida, N.

Approach to Fully Substituted Cyclic Nitrones from *N*-Hydroxylactam Derivatives: Development and Application to the Total Synthesis of Cylindricine C. *Angew. Chem., Int. Ed.* **2019**, *58*, 4381-4385.

[9] Bechara, W. S.; Pelletier, G.; Charette, A. B. Chemoselective Synthesis of Ketones and Ketimines by Addition of Organometallic Reagents to Secondary Amides. *Nat. Chem.* **2012**, *4*, 228-234.

[10] (a) Xiao, K.-J.; Wang, A.-E; Huang, Y.-H.; Huang, P.-Q. Versatile and Direct Transformation of Secondary Amides into Ketones via Organocerium Reagents-Based Deaminative Alkylation. *Asian J. Org. Chem*. **2012**, *1*, 130–132. (b) Xiao, K.-J.; Huang, Y.-H.; Huang, P.-Q. General Direct Transformation of Secondary Amides to Ketones via Amide Activation. *Acta Chim. Sinica* **2012**, *70*, 1917–1922.

[11] Huang, P.-Q.; Wang, Y.; Xiao, K.-J.; Huang, Y.-H. A General Method for the Direct Transformation of Common Tertiary Amides into Ketones and Amines by Addition of Grignard Reagents. *Tetrahedron* **2015**, *71*, 4248-4254.

[12] (a) Kümmerer, K. Sustainable Chemistry: A Future Guiding Principle. *Angew. Chem. Int. Ed.* **2017**, *56*, 16420–16421. (b) Li, C.-J.; Trost, B. M. Green Chemistry for Chemical Synthesis. *Proc. Natl. Acad. Sci*. U.S.A. **2008**, *105*, 13197-13202.

[13] For two reviews, see: (a) Liu, Y.; Bandini, M. Nickel Catalyzed Functionalization of Allenes. *Chinese J. Chem.* **2019***, 37,* 431-441. (b) Wu, X.; Wu, S.; Zhu, C. Radical-mediated Difunctionalization of Unactivated Alkenes through Distal Migration of Functional Groups. *Tetrahedron Lett. 2018, 59,* 1328-1336. For a recent example, see: (c) Zhang, Z.-Z.; Zhu, L.; Li, C.-Z. Copper-Catalyzed Carbotrifluoromethylation of Unactivated Alkenes Driven by Trifluoromethylation of Alkyl Radicals. *Chinese J. Chem.* **2019***, 37,* 452-456.

[14] (a) Huang, P.-Q.; Huang, Y.-H.; Geng, H.; Ye, J.-L. Metal-Free C–H Alkyliminylation and Acylation of Alkenes with Secondary Amides. *Sci. Rep.* **2016**, *6*, 28801. (b) Huang, P.-Q.; Huang, Y.-H.; Xiao, K.-J. Metal-free Intermolecular Coupling of Arenes with Secondary Amides: Chemoselective Synthesis of Aromatic Ketimines and Ketones, and *N*-Deacylation of Secondary Amides. *J. Org. Chem.* **2016**, *81*, 9020-9027. (c) Huang, P.-Q.; Huang, Y.-H. Further Studies on The Direct Synthesis of α,β-Unsaturated Ketimines and α,β-Enones by Chemoselective Dehydrative Addition of Functionalized Alkenes to Secondary Amides. *Chin. J. Chem.* **2017**, *35*, 613-620. (d) Wu, D.-P.; He, Q.; Chen, D.-H.; Ye, J.-L.; Huang, P.-Q. A Stepwise Annulation for the Transformation of Cyclic Ketones to Fused 6 and 7-Membered Cyclic Enimines and Enones. *Chin. J. Chem.* **2019**, *37*, 315-322. See also: (e) Huang, P.-Q.; Huang, Y.-H.; Wang, S.-R. One-pot Synthesis of *N*-Heterocycles and Enimino Carbocycles by Tandem Dehydrative Coupling–Reductive Cyclization of Halo-*sec*-Amides and Dehydrative Cyclization of Olefinic *sec*-Amides. *Org. Chem. Front.* **2017**, *4*, 431-444.

[15] Taken in part from: Geng, H. Studies on the Direct Transformation Methodologies of Secondary Amides Based on Amide Activation and Ni-Catalyzed Alcoholysis of *N*-Acyloxazolidinones. PhD dissertation of Xiamen University, 2018.

[16] Li, J.; Oost, R.; Maryasin, B.; Gonzalez, Leticia; Maulide, N. A Redox-Neutral Synthesis of Ketones by Coupling of Alkenes and Amides. *Nat. Commun*. **2019**, *10*, 2327.

[17] Huang, Y.-H.; Wang, S.-R.; Wu, D.-P.; Huang, P.-Q. Intermolecular Dehydrative [4 + 2] Aza-Annulation of *N*‑Arylamides with Alkenes: A Direct and Divergent Entrance to Aza-Heterocycles. *Org. Lett.* **2019**, *21*, 1681−1685.

[18] (a) Fujiwara, M.; Yagi, N.; Miyazawa, M. Acetylcholinesterase Inhibitory Activity Of Volatile Oil From Peltophorum Dasyrachis Kurz ex Bakar (Yellow Batai) and Bisabolane-Type Sesquiterpenoids. *J. Agric. Food Chem.* **2010**, *58*, 2824-2829. (b) Fujiwara, M.; Marumoto, S.; Yagi, N.; Miyazawa, M. Biotransformation of Turmerones by *Aspergillus niger*. *J. Nat. Prod.* **2011**, *74*, 86-89.

[19] Ye, J.-L.; Zhu, Y.-N.; Geng, H.; Huang, P.-Q. Metal-Free Synthesis of Quinolines by Direct Condensation of Amides with Alkynes: Revelation of *N*-Arylnitrilium Intermediates by 2D NMR Techniques. *Sci. China: Chem.* **2018**, *61*, 687-694.

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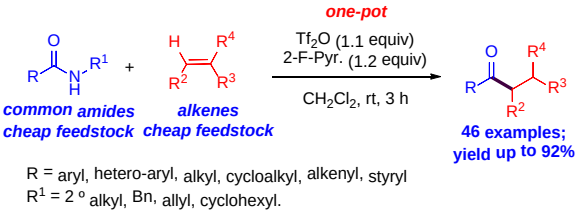
Ketone Synthesis by Direct, Orthogonal Chemoselective Hydroacylation of Alkenes with Amides: Use of Alkenes as Surrogates of Alkyl Carbanions



We report the Tf_2O-mediated hydroacylation of alkenes with secondary amides, which constitutes a mild and versatile method for ketone synthesis. The use of cheap feedstock alkenes as surrogates of organometallic reagents for selective addition to secondary amides, the least reactive carboxylic acid derivatives, presents several advantages.

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