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Autotandem Catalysis with Ruthenium: Remote Hydroesterification of Allylic Amides

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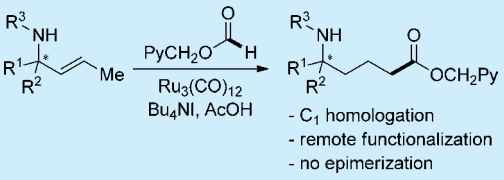
Supporting Information

ABSTRACT: A one-pot tandem sequence involving olefin isomerization and hydroesterification has been developed that enables the incorporation of a C_1-unit at the remote terminal position of allylic amides. Key observations suggest that generation of an active ruthenium hydride, formed by addition of acetic acid, allows both processes to take place under mild conditions in an autotandem catalytic, cascading fashion, which is characterized by the use of a single catalytic entity capable of promoting multiple distinct steps without operator intervention.



Numerous approaches are available for the ready synthesis of optically active allylic amines. These include diastereoselective reactions, most notably the additions that have been described using Ellman's auxiliary[1] and catalytic enantioselective methods.[2] Hydroacylation and the related hydroesterification reactions are recognized as powerful tools for synthetic chemistry and are increasingly gaining attention.[3,4] The processes provide direct means for C−C bond formation with olefins as starting materials in transformations characterized by high atom economy. Herein, we report a process employing $Ru_3(CO)_{12}$ for the conversion of allylic amides to δ-amido esters, a class of building blocks that are otherwise not easily accessed (Figure 1). The process is noteworthy, as it

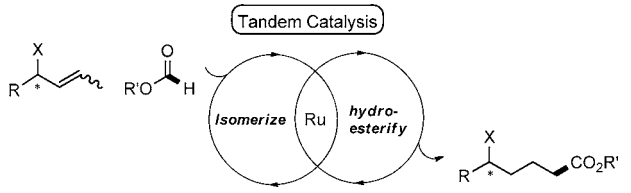


Figure 1. Autotandem catalytic cascading sequence involving olefin isomerization and hydroesterification.

involves a one-pot operation characterized as an autotandem catalytic process with a cascading sequence of transformations that includes olefin isomerization and hydroesterification by the same Ru catalyst.[5]

One-pot processes that involve cascading reactions provide attractive tools for organic synthesis.[6] They simplify operations and reduce the number of required isolations resulting in greater economy of the overall synthetic process. Of particular interest are autotandem catalytic reactions that are characterized by the use of a single catalytic entity capable of promoting multiple distinct steps without the need for operator intervention. There have been a notable number of intramolecular hydroacylation reactions that have been studied and developed.[3a] By contrast there are few examples of synthetically useful intermolecular counterparts.[3b] The paucity of these second variants results from decarbonylative decomposition pathways of the putative acyl- and formyl-metal species that compete with the bimolecular processes.[7] A recent approach to effect intermolecular hydroacylation[8] and hydroesterification[9] reactions has been to employ substrates or reagents incorporating directing groups with catalysts that can transiently form covalent intermediates. This effectively converts an intermolecular process into its intramolecular counterpart.

Since the seminal report of ruthenium catalyzed hydroesterification,[10] $Ru_3(CO)_{12}$ and its derivatives have been used for the homologative esterification of ethylene, cyclohexene, norbornene, and methyl acrylates.[11] Typically, the reactions require a large excess of olefins (2−8 equiv), high temperatures (170−230 °C), and elevated CO pressures (20−90 bar). One of the most convenient hydroesterification reagents, reported by Chang,[9a] is the formate ester derived from 2-pyridyl carbinol. With this reagent, simple terminal and cyclic olefins could be homologated when used in excess in the reaction (1.2−3 equiv).[9a,b] The method was later extended to simple allylic alcohols with modest success.[12] However, it is far from clear from this work whether hydroacylation could be relied upon as a preparatively useful transformation of optically active allylic and homoallylic alcohols, and whether the reaction could be extrapolated to include protected nonracemic allylic amines.

In separate unrelated work, ruthenium(II) complexes, such as $[HRuCl(PPh_3)_3]$, as well as $Ru_3(CO)_{12}$ have been shown to promote olefin isomerization *via* hydrometalation driven by the stability of the resulting product.[13,14] We hypothesized that the putative [Ru−H] species proposed as an intermediate in hydroesterification reactions might be competent in olefin transposition, potentially enabling isomerization−hydroesterification cascade sequences (Figure 2). Prior work with metal-

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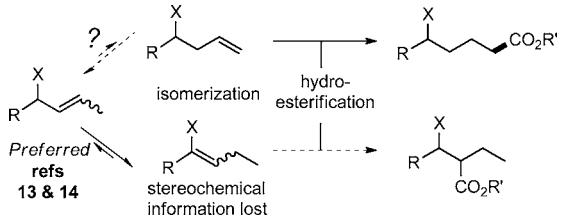


Figure 2. Strategic combination of ruthenium catalyzed isomerization and hydroesterification.

catalyzed olefin isomerization would suggest that uncontrolled isomerization could be problematic, as it would lead to a potential loss of stereochemical information by formation of achiral intermediates (e.g., an enamine, for X = nitrogen in Figure 2). Nonetheless, the successful coupling of these two reactions that otherwise have been only studied separately would lead to a process furnishing remotely functionalized ester building blocks.

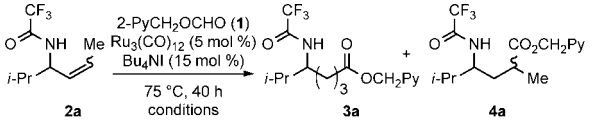
In the initial investigations (Table 1), trifluoroacetamide **2a** was used as limiting substrate with a 2-fold excess of pyridin-2-

Table 1. Effect of Solvent and Acetic Acid Additive[a]

entry	conditions	conv (%)	ratio **3a**:**4a**
1	DMF	15	5:1
2	THF	40	10:1
3	THF, AcOH (5 mol %)	90	3:1
4	THF, AcOH (10 mol %)	>95	3:1
5	THF, Bu_4NOAc (10 mol %)	35	3:1

[a]**2a** (0.15 mmol), **1** (0.30 mmol), $Ru_3(CO)_{12}$ (5 mol %), and Bu_4NI (15 mol %) were stirred in a sealed vial with the given amount of AcOH in the appropriate solvent (0.23 mL) for 40 h at 75 °C. Conversion and ratios (**3a**:**4a**) were determined by integration of the crude ^{19}F NMR against a $PhCF_3$ standard.

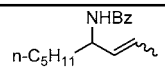
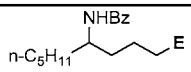
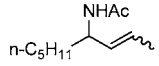
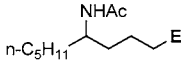
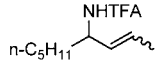
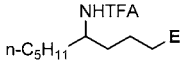
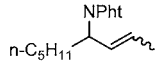
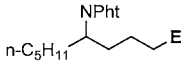
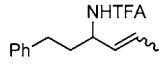
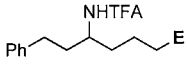
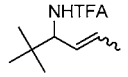
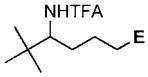
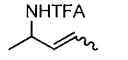
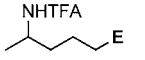
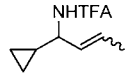
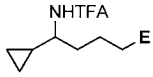
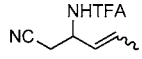
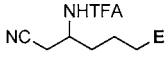
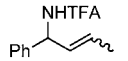
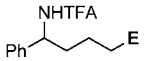
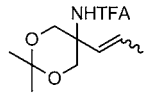
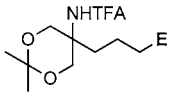
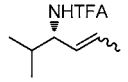
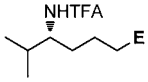
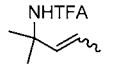
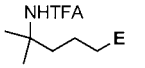
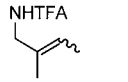
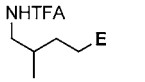
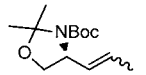
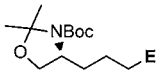
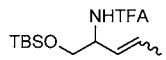
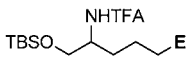
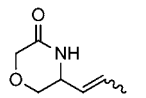
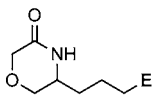
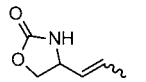
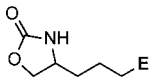
ylmethyl formate (**1**) in DMF. Under these conditions, formation of the terminal products δ- (**3a**) and γ- (**4a**) amino esters occurred with a preference for the unbranched product **3a**, while no β-amido ester was observed. Further investigation revealed that the use of THF as solvent resulted improved conversion (entry 2). In our efforts to optimize the process, we found that the addition of substoichiometric quantities of acetic acid (5−10 mol %) to the reaction mixture resulted in a dramatic enhancement in activity (entries 3, 4).[15] This effect was not observed when using Bu_4NOAc as an additive in lieu of acetic acid, underscoring the significance of proton cocatalysis (entry 5). The use of Bu_4NI was necessary, even in the presence of acetic acid, and a control reaction where this was omitted resulted in no observed conversion.[16]



(1)

Under the optimized conditions, a wide variety of substrates bearing both alkyl and aryl groups could be used (Table 2). Both *E* and *Z* olefins could be employed as substrates and exhibited indistinguishable reactivity. In addition to the *N*-trifluoroacetamides, other amine protecting groups could be employed such as benzamides, acetamides, phthalimides (entries 1−3), and *N*-Boc amines (entry 15). It is noteworthy

Table 2. Isomerization−Hydroesterification of Allylic Amines (Eq 1)[a]

entry	substrate	product(major)	yield[b]
1			82% (11%)
2			66% (28%)
3			81% (15%)
4[c]			82%[d] (4:1)
5			71% (16%)
6			75%
7			73% (21%)
8			68% (21%)
9			82% (15%)
10			81% (19%)
11[c]			81%
12[e]			76% (18%)
13			89%
14			53%
15[e]			76%
16			78% (11%)
17			81%
18			85%

[a]Conditions: Substrate **2** (1 equiv), **1** (2 equiv), $Ru_3(CO)_{12}$ (5 mol %), Bu_4NI (15 mol %), and AcOH (10 mol %) in THF (0.67 M) for 48 h at 75 °C. [b]Isolated yield of the major product (**3**) after chromatography and of minor product in parentheses. [c]In DMF (0.67 M) at 135 °C for 18 h. [d]Combined yield of inseparable mixture of major and minor products in 4:1 ratio. [e]No racemization was observed.

that more sterically hindered substrates required higher temperatures (135 °C) for effective conversion to product. (entries 4 and 11). At lower temperatures, the formation of products was slower than the unproductive decarbonylation of reagent **1**, and 2-pyridyl methanol was the only observed

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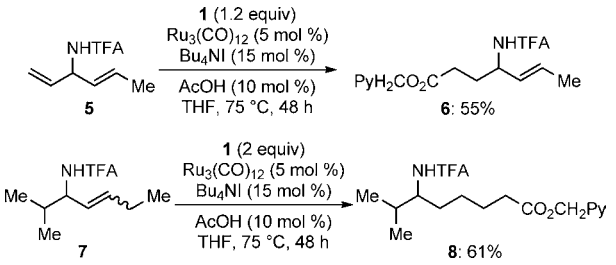
reaction product. In those cases, a switch to higher boiling DMF as solvent was necessary. A wide variety of functional groups were tolerated under the reaction conditions including cyclopropanes (entry 8), nitriles (entry 9), acetals (entry 11), silyl ethers (entry 16), ethers (entry 17), and cyclic carbamates (entry 18). Trisubstituted olefins were also competent substrates (entry 14) and lead to exclusive formation of the isomerized, unbranched product. Notably, no erosion of stereochemical information was observed (entries 12, 15) and optically active products could ultimately be isolated in enantiopure form when the reaction was conducted with optically pure allylic amines. This observation is particularly interesting given that, in most cases, ruthenium has been shown to effect the isomerization of olefins toward conjugation with heteroatoms,[13] which in the cases presented would result in loss of stereochemical information as shown in Figure 2. In the present case, however, we hypothesize that the steric bulk of the allylic amides is sufficient to inhibit unproductive isomerization.

When an allylic amide was used as a substrate incorporating both internal and terminal olefins (**5**), the hydroacylation reaction occurred preferentially on the latter (Scheme 1). This

Scheme 1. Selective Hydroesterification of a Terminal Olefin (5) and Remote Hydroesterification of 7



resulted in selective formation of the γ-amino ester product **6**. Multiple isomerizations could also be used to functionalize a more remote terminal position of the substrate . Thus exposure of **7** to the reaction conditions yielded ε-amino ester **8** by double alkene isomerization, followed by selective homologation of the terminal position.

Intrigued by the dramatic benefits of added acetic acid, we have conducted some mechanistic studies in order to gain insight into the process. Accordingly, reaction of the catalyst mixture ($Ru_3(CO)_{12}$/Bu_4NI 1:3) with acetic acid and reagent **1** in d_8-THF at 70 °C was monitored by ^{1}H NMR spectroscopy (Figure 3). Upon addition of acetic acid (2 equiv relative to $Ru_3(CO)_{12}$) to the catalyst mixture, resonances corresponding to singlets at δ = −10.1 and δ = −12.5 ppm are formed, and

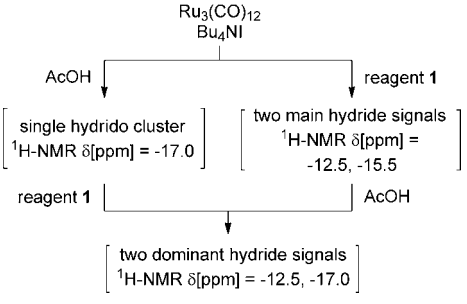


Figure 3. Ruthenium hydride species observed by ^{1}H NMR.

these are replaced over 12 h by a single dominant singlet resonance at δ = −17.0 ppm. The observed signals are in good accordance with hydrides of ruthenium carbonyl clusters and are likely formed by metal cluster protonation. In contrast, addition of reagent **1** to the catalyst mixture (in the absence of acetic acid) at 70 °C results in only the very slow formation of two main hydride signals over the course of several hours: δ = −12.5, δ = −15.5. The appearance of these resonances can be accelerated by the addition of acetic acid to the mixture, which results in the formation of two dominant singlets at δ = −12.5 and δ = −17.0 ppm. The formation of ruthenium cluster hydrides by protonation has been shown to benefit from coordination of electron rich and particularly anionic ligands,[17] including halides.[18] Indeed, it is not surprising that in control experiments no hydride signals were observed when Bu_4NI was not used. The dramatic improvement in reactivity observed with the combination of Bu_4NI and AcOH suggests that formation of an active metal hydride promotes olefin isomerization, and ultimately allows it to be coupled with hydroesterification in an efficient tandem process.

In summary we have developed an operationally simple, generally applicable, and efficient method for the generation of remotely functionalized δ-amido esters commencing with allylic amines. The reaction process benefits from a broad selection of routes for the preparation of optically active allylic amines, and the transformation enables ready access to enantioenriched building blocks. The reactions can be carried out at high concentrations, use inexpensive ruthenium as the catalyst, and do not require a pressurized CO atmosphere. More broadly, the process constitutes an example of autotandem catalysis, which is characterized by the use of a single catalytic entity capable of promoting multiple distinct steps without operator intervention. Ongoing efforts in our group are now aimed at unraveling other ruthenium-cluster catalyzed cascades as well as understanding the exact nature of the catalytic species. In this respect, the observation concerning the benefits of added acetic acid may prove useful in other Ru-cluster catalyzed isomerization processes.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Examples: (a) Cogan, D. A.; Liu, G.; Ellman, J. A. *Tetrahedron* **1999**, *55*, 8883. (b) Brak, K.; Ellman, J. A. *J. Am. Chem. Soc.* **2009**, *131*, 3850. (c) Brak, K.; Ellman, J. A. *J. Org. Chem.* **2010**, *75*, 3147.

(2) Reviews: (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.

(3) (a) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (b) Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869.

(4) Recent synthetic uses of hydroesterification reactions: (a) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 569. (b) Murray, T. J.; Forsyth, C. J. *Org. Lett.* **2008**, *10*, 3429.

(5) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365.

(6) Bruggink, A.; Schoevaart, R.; Kieboom, T. *Org. Process Res. Dev.* **2003**, *7*, 622.

(7) For selected methods that exploit aldehyde decarbonylation, see: (a) Tsuji, J.; Ohno, K. *Tetrahedron Lett.* **1965**, *6*, 3969. (b) Beck, C. M.; Rathmill, S. E.; Park, Y. J.; Crabtree, R. H. *Organometallics* **1999**, *18*, 5311. (c) Kreis, M.; Palmelund, A.; Bunch, L.; Madsen, R. *Adv. Synth. Catal.* **2006**, *348*, 2148. (d) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331. (e) Guo, X.; Wang, J.; Li, C.-J. *J. Am. Chem. Soc.* **2009**, *131*, 15092.

(8) Selected examples: (a) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070. (b) Jun, C.-H.; Lee, H.; Hong, J.-B.; Kwon, B.-I. *Angew. Chem., Int. Ed.* **2002**, *41*, 2146. (c) Willis, M. C.; McNally, S. J.; Beswick, P. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 340. (d) Moxham, G. L.; Randell-Sly, H. E.; Brayshaw, S. K.; Woodward, R. L.; Weller, A. S.; Willis, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7618. (e) Osborne, J. D.; Randell-Sly, H. E.; Currie, G. S.; Cowley, A. R.; Willis, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 17232. (f) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330. (g) Delius, M.; Le, C. M.; Dong, V. M. *J. Am. Chem. Soc.* **2012**, *134*, 15022. (h) Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354. (i) Murphy, S. K.; Petrone, D. A.; Coulter, M. M.; Dong, V. M. *Org. Lett.* **2011**, *13*, 6216.

(9) (a) Ko, S.; Na, Y.; Chang, S. *J. Am. Chem. Soc.* **2002**, *124*, 750. (b) Na, Y.; Ko, S.; L. K. Hwang, S.; Chang, S. *Tetrahedron Lett.* **2003**, *44*, 4475. (c) Yokota, K.; Tatamidani, H.; Fukumoto, Y.; Chatani, N. *Org. Lett.* **2003**, *5*, 4329. For the related hydroamidation reaction, see: (d) Ko, S.; Han, H.; Chang, S. *Org. Lett.* **2003**, *5*, 2687.

(10) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* **1983**, *256*, 135.

(11) For selected examples, see: (a) Keim, W.; Becker, J. *J. Mol. Catal.* **1989**, *54*, 95. (b) Suzuki, Y.; Katoh, H.; Ishii, Y.; Hidai, M. *J. Mol. Catal. A: Chemical* **1995**, *95*, 129. (c) Kondo, T.; Yoshii, S.; Tsuji, Y.; Watanabe, Y. *J. Mol. Catal.* **1989**, *50*, 31. (d) Kondo, T.; Okada, T.; Mitsudo, T. *Organometallics* **1999**, *18*, 4123.

(12) Wang, L.; Floreancig, P. E. *Org. Lett.* **2004**, *6*, 4207.

(13) Reviews: (a) Naota, T.; Takaya, H.; Murahashi, S.-I. *Chem. Rev.* **1998**, *98*, 2599. (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. Examples with Ru(II): (c) Zoran, A.; Sasson, Y.; Blum, J. *J. Org. Chem.* **1981**, *46*, 255. (d) Suzuki, H.; Koyama, Y.; Moro-Oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1979**, *20*, 1415. (e) Stille, J. K.; Becker, Y. *J. Org. Chem.* **1980**, *45*, 2139. (f) Reuter, J. M.; Salomon, R. G. *J. Org. Chem.* **1977**, *42*, 3360.

(14) Selected ruthenium cluster catalyzed isomerization: (a) Caulton, K. G.; Thomas, M. G.; Sosinsky, B. A.; Muetterties, E. L. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4274. (b) Kaspar, J.; Graziani, M.; Dolcetti, G.; Trovarelli, A.; Ganzerla, R. *J. Mol. Catal.* **1988**, *48*, 29. (c) Gafney, H. D.; Xu, S.-P. *Inorg. Chim. Acta* **1995**, *240*, 645. Applications in tandem processes: (d) Beller, M.; Zimmermann, B.; Geissler, H. *Chem.—Eur. J.* **1999**, *5*, 1301. (e) Jun, C.-H.; Lee, H.; Park, J.-B.; Lee, D.-Y. *Org. Lett.* **1999**, *1*, 2161.

(15) Acetic acid has been shown to accelerate the isomerization of 1-pentene to *cis*/*trans*-2-pentene catalyzed by $Ru_3(CO)_{12}$. See: Castiglioni, M.; Milone, L.; Osella, D.; Vaglio, G. A.; Valle, M. *Inorg. Chem.* **1976**, *15*, 394.

(16) For the reported effect of Bu_4NI, see: (a) Park, E. J.; Lee, J. M.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 4355. For studies on halide ion additives for hydroesterification, see: (b) Lavigne, G.; Lugan, N.; Kalck, P.; Soulie, J. M.; Lerouge, O.; Saillard, J. Y.; Halet, J. F. *J. Am. Chem. Soc.* **1992**, *114*, 10669. (c) Lugan, N.; Lavigne, G.; Soulie, J. M.; Fabre, S.; Kalck, P.; Saillard, J. Y.; Halet, J. F. *Organometallics* **1995**, *14*, 1712.

(17) (a) Andreu, P. L.; Cabeza, J. A.; del Río, I.; Riera, V.; C. Bois, C. *Organometallics* **1996**, *15*, 3004. (b) Mayr, A.; Lin, Y. C.; Boag, N. M.; Kaesz, H. D. *Inorg. Chem.* **1982**, *21*, 1704.

(18) (a) Kampe, C. E.; Boag, N. M.; Knobler, C. B.; Kaesz, H. D. *Inorg. Chem.* **1984**, *23*, 1390. (b) Lavigne, G.; Kaesz, H. D. *J. Am. Chem. Soc.* **1984**, *106*, 4647.