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An Atom-Economical Access to β-Heteroarylated Ketones from Propargylic Alcohols via Tandem Ruthenium/Indium Catalysis

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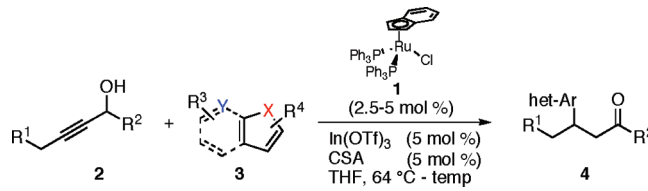
ABSTRACT



The direct and chemoselective synthesis of β-heteroarylated ketones from secondary propargyl alcohols through tandem Ru/In catalysis is reported. Both electron-rich and neutral heteroarenes, such as furans and indoles, efficiently undergo the redox isomerization/conjugate addition (RICA) sequence to provide the corresponding adducts in yields of up to 97%.

Heteroarenes are an integral motif of a multitude of naturally occurring and biologically active compounds.[1] Due in part to their relevance in the context of pharmaceutical applications, the preparation of functionalized heteroarenes has played a major role in numerous methodological and synthetic studies.[1,2] Among the most common methods for the synthesis of elaborate heteroaromatic compounds is the Friedel−Crafts alkylation.[3] However, a drawback of regular Friedel−Crafts procedures is the requirement for using electrophiles that have been prepared in a separate operation. Consequently, a significant synthetic and practical advantage is expected if the formation of the requisite electrophile and the subsequent S_EAr reaction would proceed under identical reaction conditions.[4] However, such a transformation is particularly difficult in the context of catalytic tandem processes, as the inherent reactivity of each of the reaction partners has to be efficiently governed by the same catalyst system. With such a concept in mind, we became interested in combining the Ru-catalyzed redox isomerization of propargyl alcohols to enones[5] with the Friedel−Crafts/conjugate addition reaction (Scheme 1).[2a,6] Such a strategy

(1) Dewick, P. M. *Medicinal Natural Products:A Biosynthetic Approach*, 3rd ed.; John Wiley & Sons Ltd: Chichester, 2009.

(2) (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem.* **2004**, *116*, 560–566. (b) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903–2915. (c) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances: Synthesis, Patents, Applications*, 4th ed.; Georg Thieme: Stuttgart, 2001.

(3) (a) Olah, G. A. *Friedel-Crafts and Related Reactions*, Vol. 2; Wiley Interscience: New York: 1964. (b) Manabe, K.; Aoyama, N.; Kobayashi, S. *Adv. Synth. Catal.* **2001**, *343*, 174–176. (c) Bandini, M.; Cozzi, P. G.; Giacomini,Melchiorre, M. P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700–3704. (d) Rueping, M.; Nachtsheim, B. J. *Beilstein J. Org. Chem.* **2010**, *6*, 1–24.

(4) For an example of deriving the electrophile from a styrene derivative, see: Niggemann, M.; Bisek, N. *Chem.—Eur. J.* **2010**, *16*, 11246–11249.

(5) (a) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130*, 11970–11978. (b) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **1995**, *117*, 9586–9587. For contributions by other researchers, see: (c) Ma, D.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1989**, 890–891. (d) For isomerization to a mixture of α,β- and β,γ-enones, see: (for Pd) Lu, X.; Ji, J.; Guo, C.; Shen, W. *J. Organomet. Chem.* **1992**, *428*, 259–266. (e) (for Ir) Ma, D.; Lu, X. *Tetrahedron Lett.* **1989**, *30*, 2109–2112. (f) Minn, K. *Synlett* **1991**, 115–116. (g) Hirai, K.; Suzuki, H.; Moro-Oka, Y.; Ikawa, T. *Tetrahedron Lett.* **1980**, *21*, 3413–3416.

(6) (a) Zhoua, W.; Xua, L.-W.; Yang, L.; Zhao, P.-Q.; Xia, C.-G. *J. Mol. Catal. A: Chem.* **2006**, *249*, 129–134. (b) Yamasaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739–743. (c) Scettri, A.; Villano, R.; Acocella, M. R. *Molecules* **2009**, *14*, 3030–3036.

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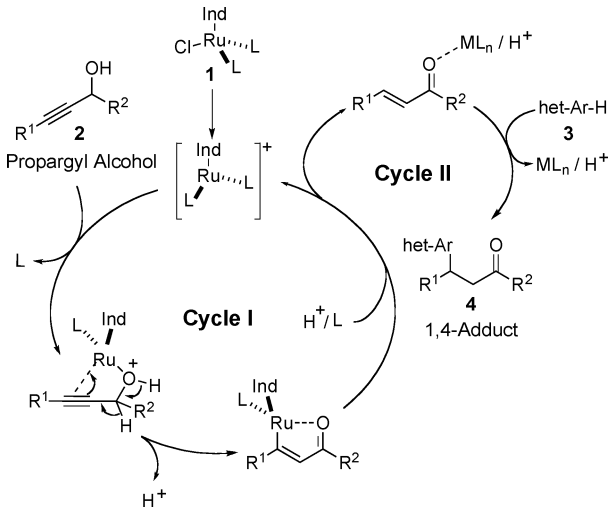
Scheme 1. Proposed Working Model for the Tandem Redox Isomerization/Conjugate Addition (RICA) Reaction[a]



[a] ML_n = $In(OTf)_3$ or $[IndRu(PPh_3)_2]^+$, Ind = indenide, het-Ar = heteroarene.

provides considerable advantages over traditional multistep approaches, in particular with respect to the principles of atom economy and minimal generation of hazardous waste.[7] The inherent atom-economic nature manifests itself in the fact that formation of propargyl alcohols of type **2**, which become the electrophiles for the Friedel−Crafts reaction, just involves the simple addition of terminal alkynes into aldehydes. Consequently, β-heteroaryl ketones **4** are rapidly derived from an addition sequence of three components: terminal alkynes, aldehydes, and heteroarenes. Simultaneously, this feature provides a profound advantage over common procedures for the synthesis of α,β-unsaturated carbonyl compounds, which generally rely on rather wasteful olefination chemistry involving phosphorus ylides.[8]

In the course of the reaction sequence, propargyl alcohols of type **2** are first chemoselectively isomerized to the desired electrophiles (Scheme 1, Cycle I). Subsequently, the latter undergo conjugate additions facilitated presumably by the same catalysts involved in the preceding step to give adducts **4** (Cycle II).[9] In previous work we demonstrated that oxygen- and nitrogen-based nucleophiles can undergo intramolecular conjugate addition reactions into α,β-unsaturated carbonyl compounds derived from propargyl alcohols through redox isomerization. The transiently formed Michael acceptors were shown to provide the corresponding oxa- and azacycles in good to excellent yields.[10] Driven by the high potential of these tandem reactions, we wanted to advance this method further by developing an intermolecular carbon−carbon bond-forming process, which, to the best of our knowledge, is unprecedented. Consequently, we report herein the first direct and regioselective synthesis of β-heteroarylated ketones from propargyl alcohols through a ruthenium/indium-catalyzed tandem redox isomerization/conjugate addition (RICA) sequence.

In initial experiments hex-3-yne-2-ol (**2a**) was exposed to ruthenium complex **1** (2.5 mol %),[11] indium triflate, and *R*-camphorsulfonic acid (CSA) (each 5 mol %) for 2 h at 64 °C in THF followed by the addition of 2-methylfuran (**3a**, 2.0 equiv) at room temperature (Table 1). After 16 h, adduct **4a** was isolated in a reasonable yield of 43% (entry 1). The amount of furan **3a** could be lowered from 2.0 to 1.3 equiv, if the reaction was conducted at 64 °C, which furnished the corresponding ketone **4a** in a significantly improved yield of 86% (entry 2).[12] These results merit additional comment, since reports on the Lewis or Brønsted acid catalyzed Friedel−Crafts alkylation of furans employing unactivated enones as electrophiles are rather scarce.[13] In a number of cases the employment of comparatively large excesses (4−5 equiv) of nucleophiles were reported to be operational.[13a,b] In that regard our method proved superior, as only 1.3 equiv of the furan derivatives were necessary to obtain conjugate addition products in high yields.

With a basic set of conditions in hand, investigations continued with exploring the scope of this method. Thus, various electron-rich, -neutral, and -deficient heteroarenes were tested (Table 1). While the electron-rich 2,3-dimethylfuran (**3b**) gave access to ketone **4b** in an excellent yield of 97%,[11] the use of its electron-deficient analog, methyl 2-methylfurancarboxylate (**3c**), resulted merely in the formation of hex-3-en-2-one and unreacted furan **3c** (entry 4).

Thus, under these operating conditions, simple enones are not activated sufficiently by the catalyst system to promote Friedel−Crafts/conjugate addition reactions with electron-poor furans.

We next focused on the employment of nitrogen-containing heteroarenes, such as indole derivatives. In general, the addition products were isolated in good to excellent yields ranging from 73% to 91% even with only 1.1 equiv of the indole nucleophiles (entries 5, 6, 9−11). The substrate 2-phenylindole (**3f**) furnished ketone **4f** in only 53% yield, presumably due to steric and electronic factors (entry 7). This hypothesis was supported by the observation that replacement of the phenyl ring for the smaller methyl group (entry 6, **3e**)

(7) Trost, B. M. *Science* **1991**, *254*, 1471–1477. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.

(8) (a) Gosney, I.; Rowley, A. G. *Org. Synth.* **1979**, *1*, 5–153. Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863.

(9) When hex-3-en-2-one, derived from alcohol **2a**, was separately reacted with indole **3h** in the presence of either Ru-catalyst **1**, $In(OTf)_3$, or CSA, both the In- and the CSA-catalyst provided adduct **4h** in similar yields and reaction time when compared to the mixture of catalysts. Ru-complex **1**, however, did not provide any of adduct **4h**.

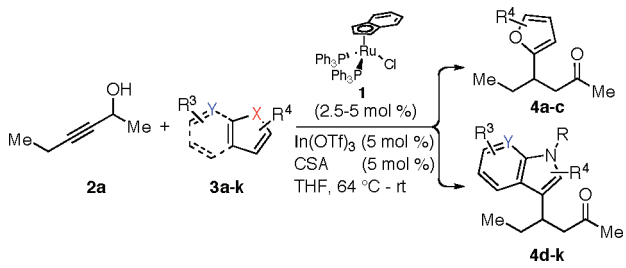
(10) (a) Trost, B. M.; Maulide, N.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130*, 16502–16503. (b) Trost, B. M.; Gutierrez, A. C.; Livingston, R. C. *Org. Lett.* **2009**, *11*, 2539–2542.

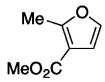
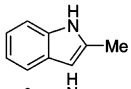
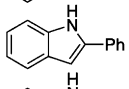
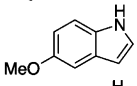
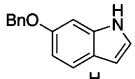
(11) In the course of experiments 5 mol % of ruthenium catalyst **1** were found to provide the most reliable results for the RICA reactions.

(12) Due to the high volatility of adducts **4a** and **4b** the yields were determined by ^1H NMR using 4-methoxyacetophenone as an internal standard.

(13) (a) For an example of an asymmetric addition, see: Adachi, S.; Tanaka, F.; Watanabe, K.; Harada, T. *Org. Lett.* **2009**, *11*, 5206–5209. For nonasymmetric examples, see: (b) Soriente, A.; Arienzo, R.; De Rosa, M.; Palombi, L.; Spinella, A.; Scettri, A. *Green Chem.* **1999**, *1*, 157–162. (c) Poirier, J.-M.; Dujardin, G. *Heterocycles* **1987**, *25*, 399–407. In these reported experiments 2-methylfuran was used in large excess (4−5 equiv).

Table 1. Redox Isomerization/Conjugate Addition of Propargyl Alcohol **2a** with Heteroarenes **3a−k**



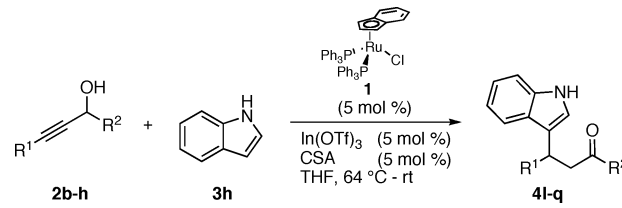
entry	heteroarene		conditions[a]	yield [%]
1		**3a**	2.0 equiv, rt, 18 h[b]	43
2		**3a**	1.3 equiv, 64 °C, 18 h[b]	86[c]
3		**3b**	1.3 equiv, 64 °C, 17 h[b]	97[c]
4		**3c**	1.3 equiv, 64 °C, 24 h[d]	n.a.
5		**3d**	1.1 equiv, rt, 18 h	87
6		**3e**	1.1 equiv, 64 °C, 18 h	91
7		**3f**	1.1 equiv, rt, 16 h	53
8		**3g**	1.1 equiv, 64 °C, 48 h	n.a.
9		**3h**	1.1 equiv, 64 °C, 16 h	80
10		**3i**	1.1 equiv, rt,18 h[b]	73
11		**3j**	1.1 equiv, rt, 18 h	79
12		**3k**	1.1 equiv, 64 °C, 18 h	n.a.

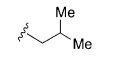
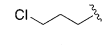
[a] General procedure: hex-3-yn-2-ol (1.00 equiv), $IndRu(PPh_3)_2Cl$ (5 mol %), $In(OTf)_3$ (5 mol %), *R*-CSA (5 mol %), THF (0.2 M), 64 °C, 60−120 min, then 64 °C or cooling to rt and addition of heteroarene (1.10−2.0 equiv). [b] 2.5 mol % of Ru-catalyst were used. [c] Yield was determined by ^{1}H NMR using 4-methoxyacetophenone as an internal standard. [d] 3 mol % of Ru-catalyst were used. n.a. = no addition observed.

led to heteroarylated ketone **4e** in 91% yield. Placement of the methyl group at the 1-position was found to be inconsequential and furnished addition product **4d** in an isolated yield of 87% (entry 5). However, when 3-methylindole (**3g**) was subjected to the standard reaction conditions, no reactivity beyond enone formation was observed. Even at elevated reaction temperatures (64 °C) we could not isolate any of the addition product. It should be noted that both the *N*-alkyl and *N*-H indoles give good yields of only C-alkylations (entries 5 and 9). This finding underscores the high degree of chemoselectivity inherent to this method for C-3 functionalization of the indole core. Remarkably, sensitive substrates, such as 5-methoxy- (**3i**) and 6-benzyloxyindole (**3j**), gave rise to the corresponding heteroarylated ketones in very good isolated yields of 73% and 79%, respectively (entries 10, 11). These results demonstrate that functional groups, such as ethers as well as unprotected indole nitrogen atoms (Table 1, entry 6, 7, 9−11), are compatible with the reaction protocol. As in the case of furan **3c**, electron-deficient 7-azaindole (**3k**) turned out to be an unreactive substrate for the conjugate addition (entry 12). We also briefly looked at electron-rich aromatic hydrocarbons, such as 2,6-dimethoxytoluene. Under the tested reaction conditions, however, we did not observe the desired Friedel−Crafts product. The inert behavior of electron-deficient heteroarenes (Table 1, entries 4, 8, and 12) and aromatic hydrocarbons further highlights the chemoselectivity of the catalyst system.

To demonstrate the potential of the RICA reaction further, investigations continued with a series of functionalized propargyl alcohols (Table 2). Substrates containing a halide

Table 2. Redox Isomerization/Conjugate Addition of Propargyl Alcohols **2b−h** with Indole **3h**[a]



entry	alcohol	R^1	R^2	yield [%]
1	**2b**			72
2	**2c**			97
3	**2d**			88
4	**2e**			79[b]
5	**2f**			83
6	**2g**			82[c]

[a] General procedure: propargyl alcohol **2b−h** (1.00 equiv), $IndRu(PPh_3)_2Cl$ (5 mol %), $In(OTf)_3$ (5 mol %), *R*-CSA (5 mol %), THF (0.2 M), 64 °C, 60−120 min, then addition of indole **3h** and stirring for 18 h, rt. [b] dr = 2.6:1. [c] dr = 3.3:1.

substituent or a nonconjugated C−C double bond (Table 2, entries 3 and 5) were well tolerated under the reaction conditions, providing the 1,4-adducts in 83% and 88% yield, respectively. A highly strained cyclopropyl unit, incorporated in alcohol **2d**, remained intact (Table 2, entry 3). No isomerization of the transiently formed vinyl cyclopropyl entity was detected. In previous work we have already demonstrated that other functional groups, such as ketones,

silyl ethers, esters, and nonpropargylic alkynes, or common nitrogen protecting groups like ^{t}Boc and sulfonamides were all compatible with the RICA reaction conditions.[8] This broad functional group tolerance emphasizes the synthetic utility of this process, especially with regard to polyfunctionalized substrates. Another important observation was the fact that steric encumbrance in proximity to the carbinol (**2b**, **2e**) and alkyne (**2g**) portion of the propargyl unit had no deleterious effect on the reaction outcome (entries 1, 4, and 6, 72%, 79%, and 82%). In order to briefly study the influence of γ- and α'-stereogenic centers (R^1, R^2 = 1-phenylethyl) on the diastereoselectivity in the Friedel−Crafts/conjugate addition, propargyl alcohols **2e** and **2g** were synthesized. As expected for alcohol **2e**, the more distal α'-stereogenic center had only a moderate influence on the diastereoselectivity, resulting in a dr of 2.6:1. However, placement of the 1-phenylethyl group vicinal to the alkyne led to a somewhat increased dr of 3.3:1.

In summary, we have described the first direct synthesis of a wide range of β-heteroarylated ketones from propargyl alcohols using the Ru/In-catalyzed tandem redox isomerization/conjugate addition reaction. Both electron-rich and -neutral heteroarenes were shown to undergo the RICA reaction efficiently in good to excellent yields. A key aspect of this method is the recognition of the catalyst system as being capable of both the redox isomerization of propargyl alcohols and promotion of the 1,4-addition of heteroarenes into simple enones under very mild conditions. Due to the latter aspect in combination with the high chemoselectivity, this method offers an excellent functional group tolerance. The atom-economic nature of this strategy results from the fact that such adducts are derived from a simple addition sequence of terminal alkynes, aldehydes, and heteroarenes. Conceptually, our approach is distinct from traditional procedures for the synthesis of the requisite electrophiles, as many of these depend on highly dissipative olefination chemistry.[8] Currently, we are looking at the development of an asymmetric variant of this operation, which will be discussed in due course.

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Supporting Information Available: Experimental procedures, spectrocopic data, and spectra of ^{1}H NMR and ^{13}C NMR for the addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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