Conia-Ene Reactions

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Catalytic Intramolecular Ketone Alkylation with Olefins by Dual Activation

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Abstract: *Two complementary methods for catalytic intramolecular ketone alkylation reactions with unactivated olefins, resulting in Conia-ene-type reactions, are reported. The transformations are enabled by dual activation of both the ketone and the olefin and are atom-economical as stoichiometric oxidants or reductants are not required. Assisted by Kool's aniline catalyst, the reaction conditions can be both pH- and redox-neutral. A broad range of functional groups are thus tolerated. Whereas the rhodium catalysts are effective for the formation of five-membered rings, a ruthenium-based system that affords the six-membered ring products was also developed.*

Intramolecular ketone–olefin/alkyne couplings, namely the Conia-ene reaction,[1] represent a powerful strategy for constructing ring systems through C–C bond formation, particularly owing to the orthogonal reactivity of carbonyl and alkenyl/alkynyl groups. With the advancement of π-acid catalysis, a number of elegant approaches have been developed for alkyne-mediated couplings, particularly those involving 1,3-dicarbonyl compounds.[2–5] In contrast, few cyclization reactions of an unactivated alkene and a regular ketone are known, which is likely due to the reduced coordination ability of olefins (compared to alkynes) and a poor enol/ketone ratio with normal ketones. The thermal Conia-ene reaction typically requires very high temperatures (300–400 °C), which limits the substrate scope and functional-group tolerance.[1] To the best of our knowledge, only two catalytic Conia-ene-type reactions involving simple ketone/olefin substrates have been reported to date (Figure 1 B). Widenhoefer[6] and co-workers first developed a palladium-catalyzed 6-*endo*-trig cyclization of γ,δ-enones for cyclohexanone synthesis; Che[7] et al. recently described a gold-catalyzed intramolecular hydroalkylation of ketones with aliphatic mono- and 1,1-disubstituted alkenes. While efficient, both methods require strong Brønsted or Lewis acids for ketone enolization, which potentially leads to incompatibility with acid-sensitive functional groups. Furthermore, Conia-ene-type cyclizations of aryl-substituted olefins have not been reported to date.

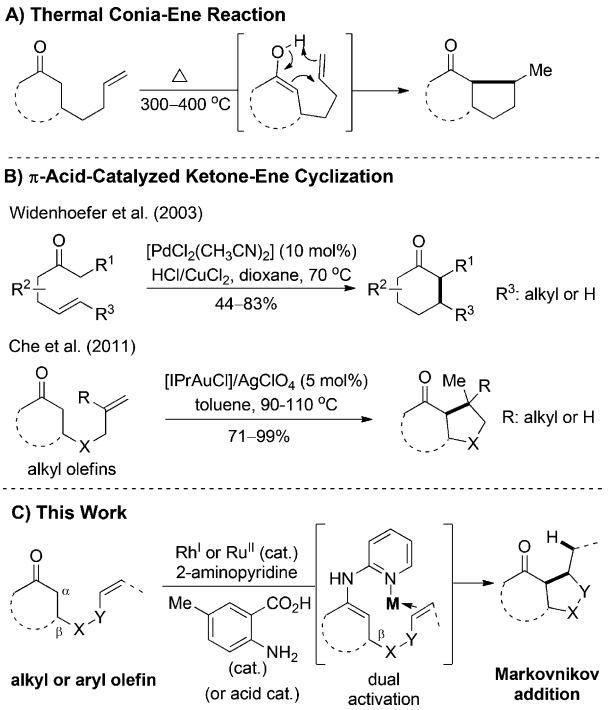

Figure 1. Intramolecular ketone alkylation with olefins. IPr = 1,3-bis(diisopropylphenyl)imidazolylidene.

To develop a broadly applicable intramolecular ketone–olefin coupling that avoids extreme temperatures or strongly acidic conditions, an alternative approach was sought without relying on ketone enolization. Herein, efforts toward developing a catalytic Conia-ene-type reaction by dual activation of the ketone and olefin are described. This approach is expected to operate under nearly pH-neutral conditions without stoichiometric oxidant or reductant, and should thus be applicable to a broad substrate scope and benefit from good functional-group compatibility.

Recently, we reported an intermolecular ketone α-alkylation reaction by coupling with simple olefins using a bifunctional ligand (7-azaindoline) that is capable of forming an enamine with the ketone and then directs Rh insertion into the vinyl C–H bond.[8] The alkylation shows complete regioselectivity for unsymmetric ketones, occurring solely at the less hindered site. Furthermore, only the anti-Markovnikov (linear) alkylation products were obtained with both alkyl and aryl olefins. We hypothesized that this cooperative activation mode[9] could be adopted for an intramolecular C–H/olefin cyclization,[10] enabling a chemoselective Conia-ene-type transformation (Figure 1 C). However, four obsta-

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cles need to be overcome: 1) The reaction at the more hindered site of the ketone, as required by the intramolecular reaction, is difficult owing to an unfavorable steric interaction between the metal and the β-substituent (opposite selectivity to the intermolecular version); 2) the reactivity of non-ethylene olefins could be an issue as they have shown low reactivity in intermolecular settings; 3) the control of the linear/branched regioselectivity is another concern; and 4) finding a mild way to form enamines with ketones that is compatible with the alkylation conditions is nontrivial. Hence, an efficient catalytic system had to be developed for the intramolecular cyclization.

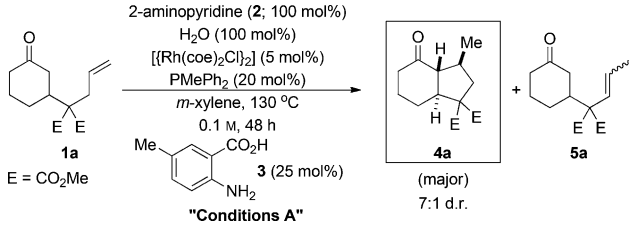
Cyclic ketone **1a** was employed as the model substrate. Initially, under the conditions that worked best for the intermolecular reaction[8] (with IMes and 7-azaindoline as the ligands), only 20% of the cyclized product (**4a**) was obtained with approximately 35% of the olefin-migration side product **5a**. Interestingly, after carefully evaluating several cocatalysts, the less hindered simple 2-aminopyridine (**2**) was found to be more effective for this intramolecular alkylation (Table 1).[11] Inspired by Kool's aniline-based catalysts for hydrazone or oxime formation,[12] 5-methyl-2-aminobenzoic acid (**3**) was used as the cocatalyst to facilitate condensation of 2-aminopyridine with the ketone substrate. After a survey of rhodium precatalysts, ligands, solvents, and additives, fused ring **4a** was obtained in 74% yield (7:1 d.r.; conditions A).[13] One key feature is that the reaction conditions are both pH- and redox-neutral. In contrast to the intermolecular reaction, complete selectivity for the branched (Markovnikov addition) product was observed. Moreover, no competitive activation of the ketone α-C–C bond was observed.[14]

To gain a better understanding of the reaction conditions, a set of control experiments were carried out. Formation of the bicyclic product was not observed without the Rh catalyst or 2-aminopyridine (Table 1, entries 2 and 3). In the absence of 5-methyl-2-aminobenzoic acid (**3**), **4a** was formed in only 8% yield (entry 4). The product yield was slightly reduced under anhydrous conditions or when $[\{Rh(coe)_2Cl\}_2]$ and $PMePh_2$ were substituted by Wilkinson's catalyst (entries 5 and 6), although the exact reason is unclear. *meta*-Xylene proved to be a better solvent than toluene and 1,4-dioxane (entries 7 and 8). Interestingly, replacement of 2-aminopyridine (**2**) with aniline alone or both aniline and pyridine only provided a small amount of the cyclization product, confirming the important role of 2-aminopyridine in this transformation (entries 9 and 10). Gratifyingly, the cyclization also proceeds at lower temperature, for example, 110°C, but it then requires a longer reaction time (entry 11). The use of a catalytic amount of **2** or 2.5 mol% of the rhodium dimer proved less efficient (entries 12 and 13). During these studies, a complementary set of reaction conditions (conditions B) was also discovered; it involves the use of **2** (25 mol%), $TsOH{\cdot}H_2O$ (10 mol%), and Wilkinson's catalyst (10 mol%) at 150°C and provided **4a** as a single diastereomer in a comparable yield (entry 14). Substrate **1a** could also be cyclized in a cationic gold catalyzed process,[7] but a different diastereomer was obtained as the major product.

The substrate scope was initially explored with different ketones (Table 2). Whereas the reaction of cyclopentanone **1b** under conditions A gave the corresponding product in only 41% yield, surprisingly, the use of bulkier 3-methyl-2-aminopyridine provided **4b** in 71% yield as a single diastereomer (*S*,*S*,*S*), but the exact reason is unclear. Generally, for ketones that are known to be less prone to enamine formation, for example, linear, aryl, or medium-sized cyclic ketones,[15] the conditions with $TsOH{\cdot}H_2O$ (conditions B) led to higher reactivity than conditions A. For example, whereas cycloheptanone **1c** gave product **4c** in only 43% yield under conditions A (even at 150°C), conditions B afforded the product in 82% yield. Moreover, low conversion (<20%) was observed for acyclic and aryl ketone substrates under conditions A; however, under modified conditions B, the desired cyclization products (**4d** and **4e**) could be isolated in synthetically useful yields. Cyclooctanone **1f**, a much more challenging substrate, gave considerable olefin isomerization with low conversion into the desired product even under conditions B. Gratifyingly, the use of an electron-deficient ligand, tris(3,5-di(trifluoromethyl)phenyl)phosphine (30 mol%), along with $[\{Rh(coe)_2Cl\}_2]$ (5 mol%) and $AgPF_6$ (10 mol%), suppressed the olefin isomerization, and provided the desired 8,5-fused bicycle (**4f**).[16]

The functional-group compatibility was first examined with cyclohexanone-based substrates (Table 3). As expected, owing to the pH/redox neutrality, a remarkable range of functional groups, including benzyl ethers, esters, acetals, and

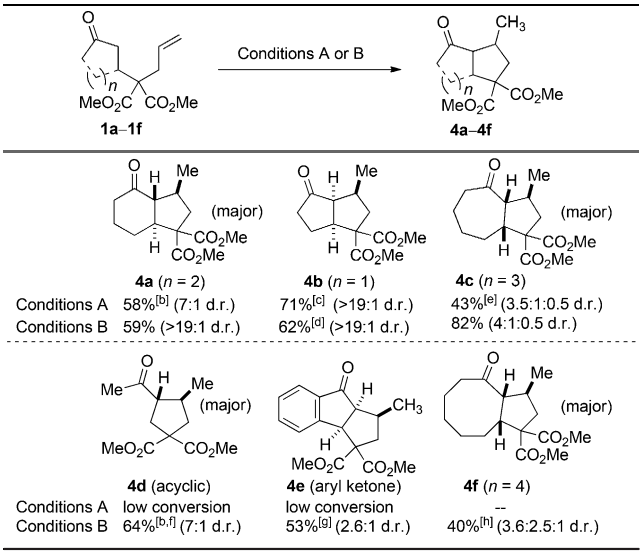
Table 1: Selected optimization studies.[a]



Entry	Variations from "conditions A"	**4a** [%][b]	d.r. (**4**)	**5a** [%][b]
1	–	74 (58)[c]	7:1	2
2	without $[\{Rh(coe)_2Cl\}_2]$	–	–	–
3	without **2**	–	–	12
4	without **3**	8	3:1	–
5	without H_2O	61	6:1	–
6	$[RhCl(PPh_3)_3]$ instead of $[\{Rh(coe)_2Cl\}_2]$ and $PMePh_2$	56	6:1	7
7	toluene instead of *m*-xylene	56	6:1	7
8	1,4-dioxane instead of *m*-xylene	21	2.4:1	–
9	aniline instead of **2**	10	1:1.4	–
10	aniline and pyridine instead of **2**	6	2:1	–
11	110°C for 5 days instead of 130°C	64 (56)[c]	7:1	3
12	**2** (25 mol%) and **3** (7 mol%)	38	3.3:1	3
13	$[\{Rh(coe)_2Cl\}_2]$ (2.5 mol%)	26	5:1	–
14	$[RhCl(PPh_3)_3]$ (10 mol%), $TsOH{\cdot}H_2O$ (10 mol%), **2** (25 mol%), *m*-xylene, 150°C, 0.1 M (conditions B)	66 (59)	–[d]	–

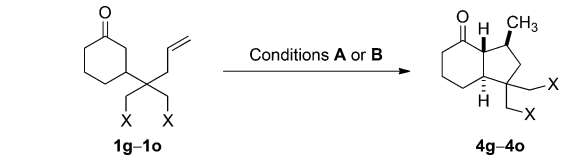
[a] All reactions were run on 0.1 mmol scale with 1.0 mL of the indicated solvent. [b] Determined by 1H NMR spectroscopy using 1,2-tetrachloroethane as the internal standard. [c] Yield of the isolated major diastereomer. [d] Single diastereomer. coe = cyclooctene.

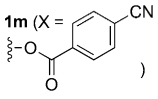
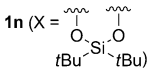
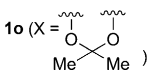
Table 2: Ketone scope.[a]



[a] Yields of isolated products are given. [b] Yield of the major isomer. [c] 2-Amino-3-methylpyridine (100 mol%) was used instead of **2**. [d] 2-Amino-3-methylpyridine (25 mol%) was used instead of **2**. [e] 150°C. [f] 2-Aminopyridine (100 mol%) and $AgPF_6$ (10 mol%) were used. [g] **2** (100 mol%) was used. [h] $[\{Rh(coe)_2Cl\}_2]$ (5 mol%), tris(3,5-di(trifluoromethyl)phenyl)phosphine (30 mol%), and $AgPF_6$ (10 mol%) were used.

Table 3: Substrates with various functional groups.[a]

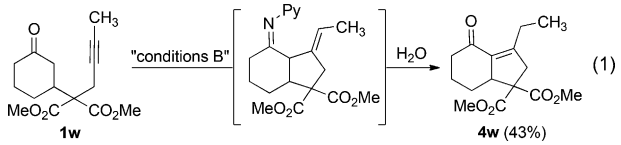


Substrate	Conditions A	Conditions B
1g (X = OBn)	47%	69%[b]
1h (X = OAc)	55%[c]	59%
1i (X = OTBS)	69%[d]	64%
1j (X = OMOM)	67%[c]	59%
1k (X = OBoc)	45%[e]	decomp.
1l (X = OPMB)	53%[c]	decomp.
1m (X = )	55%	68%
1n (X = )	73%	71%[f]
1o (X = )	71% (6.5:1 d.r.)	12%

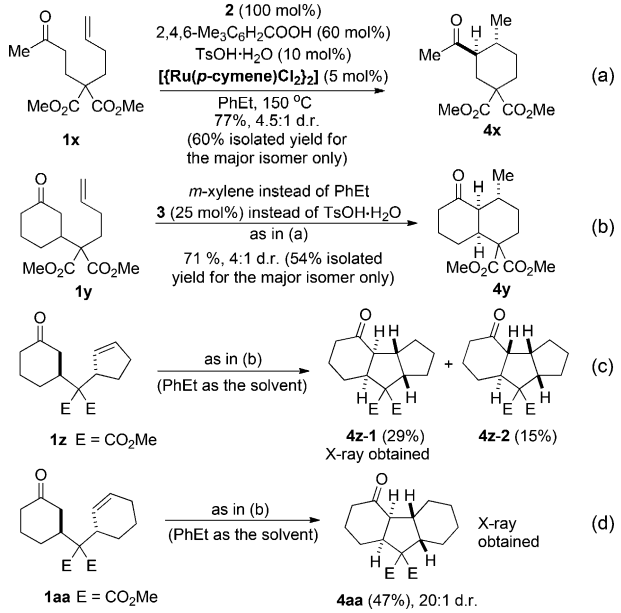
[a] Unless otherwise mentioned, all yields refer to the isolated major isomer, and the reactions gave >10:1 d.r. [b] $[\{Rh(coe)_2Cl\}_2]$ (5 mol%) and tris(3,5-di(trifluoromethyl)phenyl)phosphine (30 mol%) instead of $[RhCl(PPh_3)_3]$. [c] 3 days. [d] 4 days. [e] 110°C, 5 days. [f] Isolated after hydrogenation of the reaction mixture using Pd/C and H_2. MOM = methoxymethyl.

nitriles, are tolerated under conditions A. Acid-sensitive but synthetically important functional groups, such as *tert*-butyldimethylsilyl (TBS) ether (**1i**), *tert*-butylcarbonate (OBoc) (**1k**), *para*-methoxybenzyl (PMB) ether (**1l**), and acetonide (**1o**) moieties, survived reactions under these conditions, which represents a significant advantage over π-acid-catalyzed reactions.[6,7]

Aside from aliphatic α-alkenes, aryl olefins (**1p**–**1t**), known to be unstable under strongly acidic conditions,[17] can also be used as the coupling partners in this dual-activation approach (Table 4). Latent nucleophiles, such as anisole and unprotected phenol substrates (**1q** and **1r**), are well tolerated under both reaction conditions. It is not surprising that driven by strain relief, C–C activation of cyclobutanone **1u** occurred and provided bridged bicycle **4u** in 56% yield.[18] Furthermore, the Thorpe–Ingold effect was found to be important for the success of the cyclization. Cyclization with an alkyne moiety also proved to be successful with this catalytic system, and the resulting β,γ-unsaturated imine underwent olefin migration to give conjugated ketone **4w** upon hydrolysis [Eq. (1)].[19]



Whereas the current conditions can only be applied for the formation of five-membered rings, after extensive investigation, a ruthenium-based system was discovered that enables 6-*exo*-trig cyclizations with both cyclic and acyclic ketones (Scheme 1 a, b).[20] Remarkably, internal alkenes (e.g., **1z** and **1aa**), unreactive in the presence of the Rh

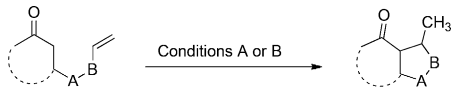


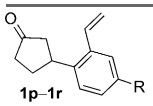
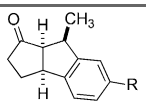
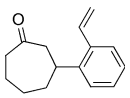
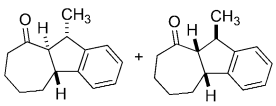
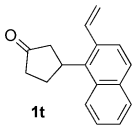
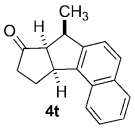
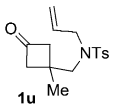
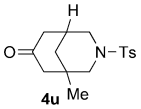
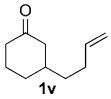
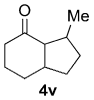
Scheme 1. Ruthenium-catalyzed synthesis of six-membered rings. TsOH = *para*-toluenesulfonic acid.

catalysts, cyclized to give tricyclic rings in the presence of the ruthenium catalyst (Scheme 1 c, d). Nevertheless, the standard substrate (**1a**) showed much higher reactivity with the Rh than with the Ru system.

In conclusion, a catalytic intramolecular ketone–olefin coupling has been developed by taking advantage of a unique dual-activation mode. This approach is expected to be complementary to previously developed processes, and provides a broad implication for developing related transformations beyond this work. Detailed mechanistic studies and studies to further extend the applicability of the ruthenium system are ongoing.

Table 4: Further substrate scope.[a]



Substrate	Product		Cond. A	Cond. B
 **1p–1r**		**4p** (R = H) **4q** (R = OMe) **4r** (R = OH)	84 %[b] 86 %[b] 69 %[b]	76 %[c] 79 %[c] 63 %[c]
 **1s**	 **4s-1** + **4s-2**		48 %[e] (1.7:1 d.r.)	54 % (2:1 d.r.)
 **1t**	 **4t**		68 %	72 %[f]
 **1u**	 **4u**		49 %	56 %
 **1v**	 **4v**		–[g]	–

[a] Unless otherwise mentioned, a single diastereomer was observed. [b] 2-Amino-3-methylpyridine (100 mol%) instead of **2**. [c] 2-Amino-3-methylpyridine (25 mol%) instead of **2**. [d] 2-Amino-3-methylpyridine (50 mol%), $[RhCl(PPh_3)_3]$ (15 mol%), 24 h. [e] 150 °C. [f] BHT (20 mol%) was added. [g] The desired product was not observed.

Acknowledgements

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