Published in final edited form as:

Angew Chem Int Ed Engl. 2017 February 20; 56(9): 2376–2380. doi:10.1002/anie.201611642.

Distal-Bond-Selective C–C Activation of Ring-Fused Cyclopentanones: An Efficient Access to Spiroindanones

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Abstract

A site-selective rhodium-catalyzed C–C activation of ring-fused cyclopentanones was achieved to afford efficient access to a range of spiroindanones. The use of bulky 2-amino-6-picoline as a cocatalyst is key to the excellent selectivity of this C–C bond cleavage in cyclopentanones.

Keywords

C; C activation; cyclopentanones; homogeneous catalysis; rhodium; spirocycles

Carbon–carbon bond (C–C) activation, a process involving the conversion of relatively inert C–C bonds into more reactive M–C (M = transition metal) bonds, provides unusual bond disconnection strategies to access various versatile scaffolds.^[1] However, owing to the kinetic inertness of C–C *s* bonds, the applications of such strategies have been largely focused on ring-strained systems, including cyclopropane and cyclobutane derivatives, in which strain relief becomes a main driving force of the reaction.^[2,3] In contrast, despite the success of broadly useful methods involving C–CN bond cleavage,^[4] the C–C activation of

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Dedicated to Professor David Milstein on the occasion of his 70th birthday

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under <http://dx.doi.org/10.1002/anie.201611642>.

Conflict of interest: The authors declare no conflict of interest.

less- or non-strained systems,^[1d,e,5] particularly five- or six-membered rings, is rather challenging and underdeveloped.^[6,7]

Recently, our group developed a general approach for the catalytic activation of C–C bonds in simple 3-aryl-substituted cyclopentanones (Scheme 1a).^[8] Using $[\text{rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ as a precatalyst, IMes (1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene) as a ligand, and 2-aminopyridine as a cocatalyst, the proximal C1–C2 bond of cyclopentanones can be selectively activated through a temporary directing mode,^[9] followed by intramolecular C–H activation of the aryl group to ultimately provide functionalized α -tetralone products. Through a similar sequence, cleavage of the distal α -C–C bond (C1–C5 bond) would provide α -indanones. However, these have only been observed as minor products in some examples. An intriguing question thus arose: is it possible to steer the site selectivity of a C–C activation reaction with a complementary catalyst system? To the best of our knowledge, this has not been realized with less strained structures.^[10] Herein, we describe our efforts in developing a “distal-selective” C–C activation of 3-arylcyclopentanones with a new catalyst system for applications in α -indanone synthesis^[11,12]. While the focus is given to the activation of ring-fused cyclopentanones for the synthesis of diverse spiroindanone scaffolds (Scheme 1b), initial success with distal C–C activation of regular 3-arylcyclopentanones was also realized.

To overcome the challenge of activating the distal C1–C5 bond, our strategy is to destabilize the intermediate generated from the cleavage of the proximal C1–C2 bond of cyclopentanones. We hypothesized that, using a combination of a bulky NHC (N-heterocyclic carbene) ligand with a bulky aminopyridine cocatalyst, the steric repulsion between the aryl group and the ligands would disfavor Rh insertion into the proximal C1–C2 bond (intermediate **A1**, Figure 1). In addition, the buttressing effect in intermediate **A1** would restrict rotation of the aryl group, which in turn would hamper subsequent *ortho* C–H activation. As a result, activation and subsequent conversion of the distal C1–C5 bond is expected to be preferred.

To test this hypothesis, ring-fused cyclopentanone **1a**, which is conveniently prepared through a Pauson–Khand reaction and aryl conjugate addition sequence (for details, see the Supporting Information), was chosen as the initial model substrate (Table 1). Under the previous reaction conditions, the fused α -tetralone **1c** was found as the major product, together with spiroindanone **1b**, which was formed in only 28% yield, as an inseparable mixture (entry 1).^[8] Indeed, when employing a more sterically hindered 2-amino-6-picoline (**C1**) as a cocatalyst with IPr as a bulkier ligand, the site selectivity was completely switched to favoring the formation of the spiroindanone **1b**. After further optimization, the standard reaction conditions were secured (Table 1, entry 2). Under these conditions, the desired α -indanone product **1b** was afforded in excellent yield with >99:1 distal/proximal selectivity. The structure of α -indanone product **1b** was unambiguously confirmed by X-ray crystallography.^[13]

To gain further insight into this distal-selective C–C activation reaction, control experiments were performed (Table 1, entries 3–17). In the absence of pyridine or water or both, the reaction still gave excellent site selectivity, albeit with somewhat lower yields (entries 3–5).

It is reasonable to propose that pyridine helps to stabilize the Rh^I catalyst when it is off the cycle,^[14] and water enhances the turnover frequency through promoting imine hydrolysis to release the **C1** cocatalyst. When using a combination of the IMes ligand with 2-aminopyridine (**C2**), although the proportion of the α -indanone product **1b** slightly increased compared to the original conditions (entry 1), there was nearly no selectivity between the two products (entry 6). In addition, changing the NHC ligand from IPr to IMes resulted in much lower efficiency and reduced site selectivity (entry 7). The C6 substitution on the amine cocatalyst was found to be crucial for the site selectivity (entries 8–13 vs. entry 2). In contrast, employing cocatalysts **C3–C5**, which are substituted at other positions, resulted in poor site-selectivity (entries 9–11). Variation of the methyl group in the cocatalyst to an ethyl group gave lower yield but with no influence on the site selectivity (entry 12); however, the use of 6-phenyl substituted cocatalyst **C7** completely shut down the reaction (entry 13). THF was found to be less efficient as a solvent than 1,4-dioxane (entry 14). High reaction concentration (1.0M) proved beneficial to the conversion (entry 15). 80% yield was still obtained at 130 °C (entry 16). The use of PPTS instead of a combination of TsOH·H₂O and pyridine gave a comparable yield and equally excellent selectivity (entry 17).

With the optimized reaction conditions in hand, the substrate scope was then tested (Table 2). Nitrogen-tethered ring-fused cyclopentanones were first explored (Table 2, entries 1–6). Electron-rich or electron-neutral aryl-substituted substrates afforded the desired spirocycles in comparable yields (oxygen atoms in entries 1, 2 and 4), while an electron-deficient one resulted in a decreased yield and reduced site selectivity (entry 3). This trend proved to be general for substrates with other linkers as well. The oxygen-linked substrates showed equal or slightly higher reactivity than the corresponding nitrogen-linked ones (entries 7–15). A broad range of functional groups, including methyl or benzyl ether, aryl chloride, furan, terminal olefin, ester, and silyl ethers, are tolerated. *Meta*- and *ortho*-substituted substrates also worked smoothly to afford the corresponding products with no decrease in site selectivity (entries 12 and 13). The naphthyl-substituted ring-fused cyclopentanones are compatible substrates, affording naphthyl-fused spiroindanones in good yields (entries 14 and 15). It should be noted that C–H activation occurred at the less hindered position when *meta*- or 2-naphthyl-substituted substrates were employed (entries 12 and 14). Besides forming heterocycle-based products, the use of carbon tethers is also effective to provide all-carbon spirocycles (entries 16 and 17). In addition, the six-membered ring-fused cyclopentanone (**18a**) was found to be a suitable substrate, albeit giving lower reactivity and selectivity (entry 18). The ring-fused cyclohexanone substrate **19a** showed low reactivity under the current reaction conditions, although the spiroindanone product **19b** was isolated in 21 % yield in our previous work^[8] (entry 19).^[15]

The feasibility of promoting distal-selective C–C activation of other types of 3-aryl cyclopentanones was next investigated (Table 3). To our delight, when employing the IPr/**C1** catalyst system, the site selectivity for the 3-methyl-3-phenyl cyclopentanone (**20a**) was completely switched from 21:79 to 78:22 favoring indanone formation.^[16] In addition, while far from being satisfactory, significant improvements in the distal/proximal (d/p) ratio were observed for simple *o*-tolyl and phenyl-substituted cyclopentanones (**21a** and **22a**).

In summary, we have realized the distal-selective C–C activation of ring-fused 3-aryl cyclopentanones, which provides a distinct method for the synthesis of spiroindanones. The key to the site selectivity is the use of a bulky 2-amino-6-picoline cocatalyst. Preliminary success with distal-selective C–C activation of other 3-aryl cyclopentanones was also achieved. While it is clear that the substitution pattern on the cyclopentanone ring significantly affects the site selectivity of the reaction, a more detailed understanding of this system remains to be disclosed. Future work will focus on improvement of the site selectivity for non-ring-fused substrates and the development of a general distal-selective C–C activation of cyclopentanones through in-depth mechanistic studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was supported by NIGMS (R01GM109054). G.D. is a Searle Scholar and Sloan fellow. Y.X. acknowledges the International Postdoctoral Exchange Fellowship Program 2015 from the Office of China Postdoctoral Council (OCPC, document 38, 2015). Johnson Matthey is acknowledged for a generous donation of Rh salts. Prof. Dr. M. C. Young, and Mr. K.-Y. Yoon are thanked for the X-ray structure.

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 16. For non-fused 3-aryl cyclopentanone substrates, the addition of pyridine resulted in decreased yields. For example, the yield for substrate **20a** dropped from 92% to 68% with no effect on the site selectivity when 10 mol% of pyridine was used as the additive.

Figure 1.
Proposed model for the distal-bond selectivity.

Scheme 1.

Catalytic C–C bond activation in 3-aryl cyclopentanones. IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene.

Table 1

Selected optimization studies of C–C bond activation with ring-fused cyclopentanone **1a**.^[a]

Entry	Variation from standard conditions	Total yield [%] ^[b]	Ratio 1b/1c ^[b]
1	original conditions ^[c]	78	36:64
2	None	90 (84)	>99:1
3	without pyridine	75	60:1
4	without H_2O	78	70:1
5	without pyridine and H_2O	71	42:1
6	IMes/ C2 instead of IPr/ C1	61	53:47
7	IMes instead of IPr	59	38:1
8	C2 instead of C1	63	65:35
9	C3 instead of C1	41	53:47
10	C4 instead of C1	76	48:52
11	C5 instead of C1	80	56:44
12	C6 instead of C1	74	>99:1
13	C7 instead of C1	<1	–
14	THF instead of 1,4-dioxane	43	>99:1
15	0.5 M	70	>99:1
16	130 °C instead of 140 °C	80	>99:1
17	PPTS instead of pyridine and $\text{TsOH}\cdot\text{H}_2\text{O}$	85	>99:1

^[a] Run on a 0.2 mmol scale in a 4 mL vial.

^[b] Determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

^[c] Reported in our previous work (Ref. [8]). Conditions: 5 mol % $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$, 10 mol % IMes, 10 mol % $\text{TsOH}\cdot\text{H}_2\text{O}$, 25 mol % 2-aminopyridine (**C2**) and 50 mol % H_2O in 1,4-dioxane (0.5 M) at 140 °C for 48 h. PPTS=pyridinium *p*-toluenesulfonate.

Table 2Substrate scope of the C–C bond activation with ring-fused cyclopentanones.^[a]

Entry	Substrate	Major product/Yield
1		1b , 84%
2		2b , 74%
3		3b , 57% ^[c]
4		4b , 88%
5		5b , 53%
6		6b , 62%
7		7b , 92%

Entry	Substrate	Major product/Yield
8	8a	8b , 89%
9	9a	9b , 84%
10	10a	10b , 62%
11	11a	11b , 41%
12	12a	12b , 82%
13	13a	13b , 55%
14	14a	14b , 86%
15	15a	15b , 61%

Entry	Substrate	Major product/Yield
16	16a	16b , 70%
17	17a	17b , 50% (85% ^[d])
18	18a (X-ray obtained) ^[13]	18b , 34% ^[e]
19	19a	19b , 6% (21% ^[d])

^[a] Run on a 0.2 mmol scale in a 4 mL vial.

^[b] Total yields of isolated product were provided and the distal/proximal (d/p) ratio is >40:1 unless otherwise noted.

^[c] d/p = 13:1.

^[d] 5 mol % [Rh(C₂H₄)₂Cl]₂, 15 mol % IPr, 20 mol % MeSO₃H, 100 mol % **C1**, 20 mg 4 Å molecular sieves in 1,4-dioxane (1 M) at 150 °C for 48 h.^[8]

^[e] d/p = 4.8:1.

Table 3Switching the site-selectivity of C–C bond activation in cyclopentanones.^[a]

Substrate	“Distal” Product	“Proximal” Product	Total Yield (d/p ratio) ^[b]
IMes/C2: 78% (36:64) ^[c] IPr/C1: 71% (98:2)
IMes/C2: 95% (21:79) ^[c] IPr/C1: 92% (78:22)
IMes/C2: 94% (22:78) ^[c] IPr/C1: 80% (53:47)
IMes/C2: 86% (8:92) ^[c] IPr/C1: 67% (25:75)

^[a] Run on a 0.2 mmol scale in a 4 mL vial. IMes/C2 conditions: 5 mol% [Rh(C₂H₄)₂Cl]₂, 10 mol% IMes, 10 mol% TsOH·H₂O, 25 mol% 2-aminopyridine (C2) and 50 mol% H₂O in 1,4-dioxane (0.5 M) at 140°C for 48 h; The IPr/C1 conditions: 5 mol% [Rh(C₂H₄)₂Cl]₂, 10 mol% IPr, 10 mol% TsOH·H₂O, 50 mol% 2-amino-6-picoline (C1) in 1,4-dioxane (1.0 M) at 140°C for 48 h.

^[b] Determined by ¹H NMR using 1,1,2,2-tetrachloroethane as the internal standard.

^[c] See Ref. [8].