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ARTICLE

Cobalt-catalyzed cyclization with the introduction of cyano, acyl and aminoalkyl groups

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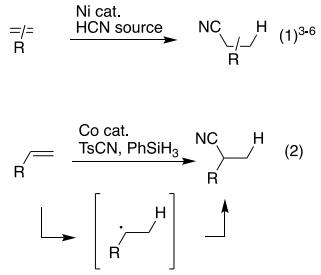
An efficient synthesis of carbo- and heterocycles using C=C, C=O and C=N bonds under cobalt catalysis is described. The substituents on olefins are key for controlling regio- and chemoselectivity in the initial hydrogen atom transfer step and quaternary carbons are efficiently constructed under mild conditions. Cyclopropane cleavage and tandem cyclization give highly functionalized bicyclic skeletons in a single operation.

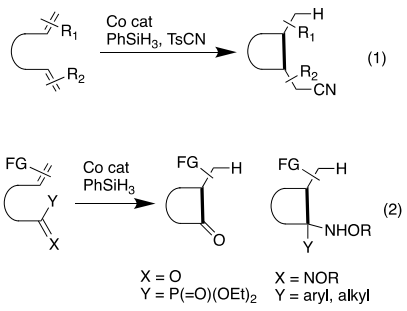
Introduction

A cyano group is a key functionality for determining the properties of organic molecules.[1] Therefore, its catalytic introduction to carbon-carbon unsaturated bonds has been a significant issue in synthetic chemistry.[2] Among various cyanation protocols, metal catalysis is a powerful tool for enhancing reaction efficiency and controlling selectivity. Particularly, nickel catalysis using simple and unactivated C-C multiple bonds has been an important hydrocyanation since its discovery (Scheme 1-1),[3] and styrene derivatives are representative substrates for achieving high regioselectivity.[4] Recent applications have successfully expanded the substrate diversity to the use of olefins,[5] terminal alkynes,[6] aryl allenes,[7] enynes,[8] and allene-ynes. [9]

Scheme 1. Metal-catalyzed hydrocyanation



Scheme 2. Hydrofunctionalizing cyclization (***This work***)



On the other hand, cobalt catalysis has been attractive synthetic tool,[10] and an alternative hydrocyanation mediated by radical species using simple olefins with TsCN and $PhSiH_3$ is reported (Scheme 1-2). [11] Carreira and a co-worker proved that it provided a predictable regiochemistry and functional group tolerance, and developed new reactions using TsN_3,[12] TsCl,[13] BocN=NBoc,[14] and oximes.[15] This radical strategy has great potential as a practical transformation because the reaction can proceed at room temperature and does not require the use of any toxic Sn reagents. These characteristics prompted us to establish new applications, and herein we report a new cyclization using olefins to connect C=C, C=O and C=N bonds under cobalt catalysis (Scheme 2).

Results and discussion

Aiming at the development of cobalt-catalyzed hydrocyanative cyclization and evaluation of its chemo-, regio- and stereoselectivity, we initially investigated **1a** with Co cat. (2 mol%) using TsCN (1.2 eq) and $PhSiH_3$ (1.2 eq). [11] The reaction proceeded smoothly to give a mixture of *cis*- and *trans*-**2a** without producing **3a** in 47% yield (*cis*:*trans* = 2.4:1) after 24 h (Table 1, entry 1). The reaction efficiency was enhanced when **1b** was used instead and the reaction completed in 6 h to give **2b** in 68% yield (*cis*:*trans* = 2.6:1) (entry 2). We propose that the catalytic cycle starts with regioselective hydrogen atom transfer of red olefin (Scheme 3). A hydride prefers to form a C-H bond at a terminal methylene. The release of Co(II) gives secondary radical (**A1**), [10b,c] which cyclizes to **A3**, and the resulting primary radical would be converted to **2** by trapping TsCN. [12] Since the conformational preference of **A2** would be favorable for *cis*-isomer formation, quaternary carbons in a tether such as in **1c** would be effective for stereoselectivity and cyclization. As expected, **1c** was transformed to *cis*-**2c** within 4 h in 82% yield, exclusively (entry 3). Chemoselectivity was observed

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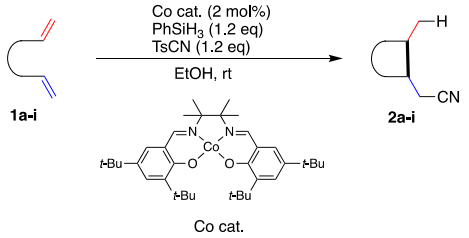
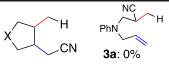
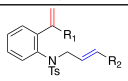
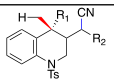
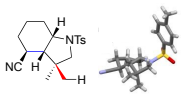
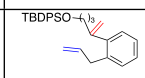
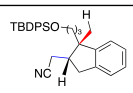
when non-symmetric dienes were used. For example, mono- and trisubstituted olefins in **1d** were effectively differentiated to give *cis*-**2d** in 62% yield as a sole product (entry 4). The former olefin is favored in the initial hydrogen atom transfer due to steric reasons. Mono- and disubstituted olefins in **1e** were also discriminable to cyclize to **2e** as a single product (entry 5). The tertiary carbon radical center from red olefin in **1e** would be favorably generated. Benzene-fused azacycles were synthesized from **1f-h**. All of the reactions completed within 2 h with high regioselectivity in the initial C-H bond formation at red olefins and the corresponding cyclized products were obtained in 58% to 90% yield (entries 6-8). In the case of indene formation, 1,1- and 1,2-disubstituted olefins in **1j** were also differentiable to give a sole bicyclic product (**2i**) while controlling three stereogenic centers, which was confirmed by X-ray crystallographic analysis (entry 9). The cyclization of **1j** proceeded slowly to give a mixture of *cis*- and *trans*-**2j** in respective yields of 55% and 25% (entry 10).

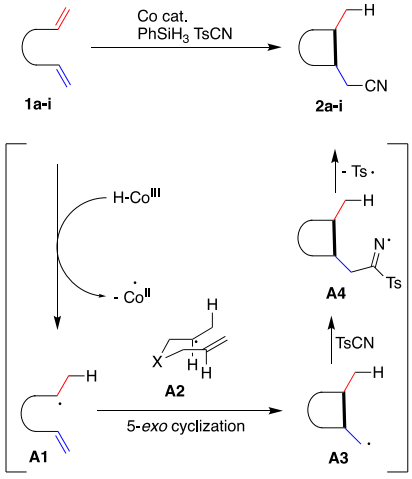
Table 1 Hydrocyanative cyclisation of **1**



Entry	Substrate		Time (h)	Products (%)	
1 2 3		**1a**: X = NPh **1b**: X = NTs **1c**: X = $C(CO_2Et)_2$	24 6 4	 **3a**: 0%	**2a**: 47 (*cis:trans* = 2.4:1) **2b**: 68 (*cis:trans* = 2.6:1) *cis*-**2c**: 82
4		**1d:** E = CO_2Et	9		*cis*-**2d**: 62
5		**1e:** E = CO_2Et	9		**2e**: 72
6 7 8		**1f**: R_1 = Me, R_2 = H **1g**: R_1 = R_2 = Me **1h**: R_1 = Et, R_2 = H	2 2 2		**2f**: 71 **2g**: 90 (dr = 1.9:1) **2h**: 58 (dr = 1.3:1)
9		**1i**	3		**2i**: 70 (single isomer)
10		**1j**	16		*cis*-**2j**: 55 with *trans*-**2j**: 25

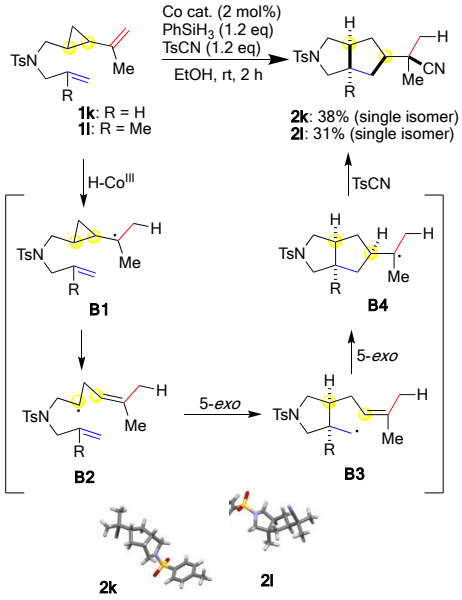
The discrimination of olefins and sp^2 carbons observed above was next used as a radical clock (Scheme 4). If the initial hydrogen atom transfer occurs on red olefins regioselectively, a [3+2] cycloaddition sequence[16] through cyclopropane-cleavage (**B2**) followed by 5-*exo* cyclization (**B3**, **B4**) should be expected. Actually, **1k** and **1l** were suitable for this cycloaddition and the single products (**2k**,**l**) were exclusively obtained in respective yields of 38% and 31%.

Scheme 3. Plausible reaction pathway



Since *cis*-**2j** can be a useful precursor for a tricyclic system by controlling three contiguous stereogenic centers, we next investigated its transformation (Scheme 5). Treatment of *cis*-**2j** by desilylation-bromination gave **3b**, which was a precursor for double alkylation. The first intramolecular alkylation using LDA gave **3c** as an inseparable diastereomixture (1.2:1), which was then transformed to a single diastereomer (**3d**) by stereoselective methylation in 90% yield (2 steps). This strategy could be used for the synthesis of a key intermediate of Taiwaniaquinone H[17] using modified substrates.

Scheme 4. [3+2] Cycloaddition via cyclopropane cleavage



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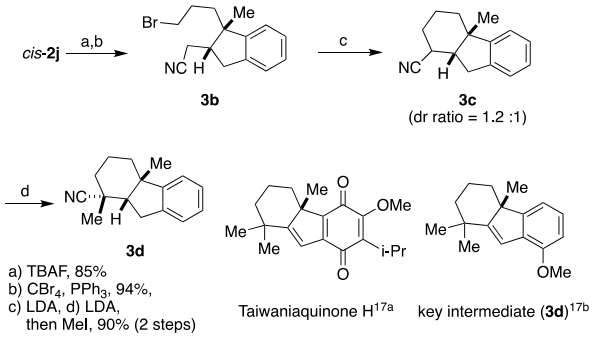
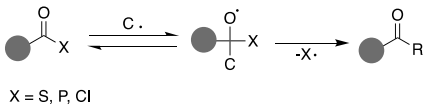
Scheme 5. Transformation of *cis*-**2j** to tricyclic skeletone



To clarify the synthetic utility of the above cyclization under cobalt catalysis, we next examined the use of activated C=O bonds as electrophiles for hydroacylation.[18,19] Despite the broad generality of metal-mediated carbonylation, many challenges still remain in radical carbonylation because radical addition to C=O is a reversible process. Therefore, the choice of nucleophilic carbon radicals and cleavable C-X bonds is a key issue for promoting this transformation (Scheme 6).[20] However, previous studies used harsh conditions and toxic Sn reagents, which are unsuitable for practical synthesis and prevented the use of various electrophilic C-X bonds. To solve these problems, a new acylation protocol was next examined using simple olefins and acylphosphates[21] as alternative radical precursors (Scheme 7).

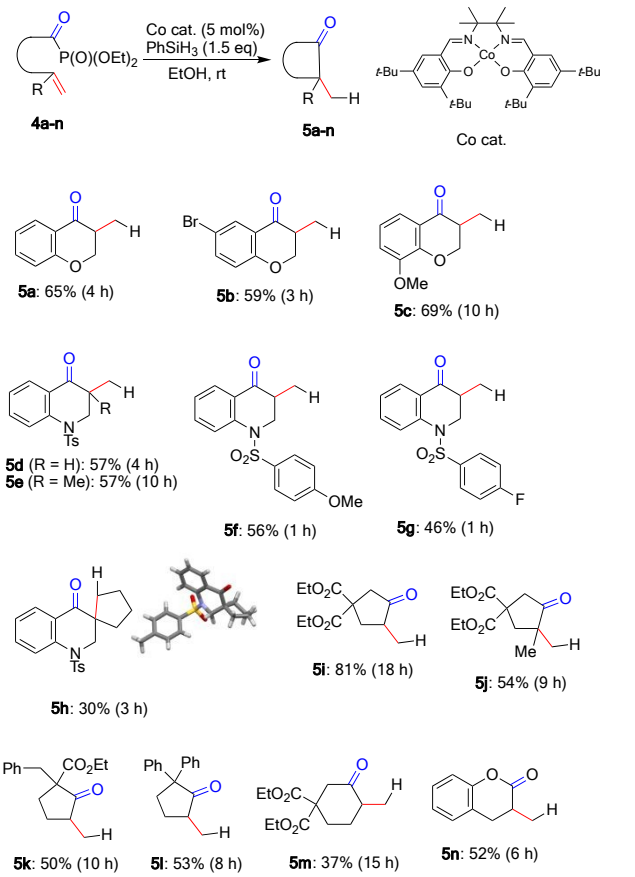
Scheme 6. Radical addition to carbonyls



previous work: C-X, Sn reagents and heat
This work: olefin, silane, RC(=O)P at rt

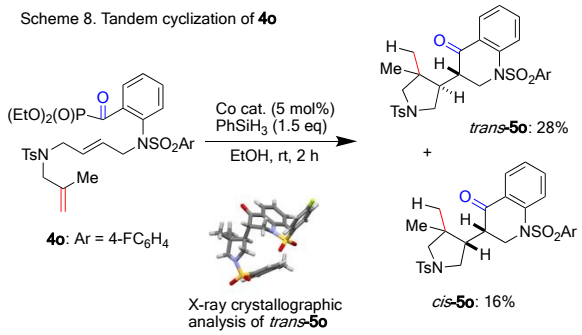
Initially, benzene-fused substrates (**4a-h**) with Co cat. (5 mol%) were used for hydroacylative cyclization to construct a 6-membered ring with oxygen and nitrogen atoms (**5a-h**). The olefinic carbons in **4a** were effectively differentiated to cyclize at the more-substituted sp^2 carbon and the corresponding adduct (**5a**) was obtained as a sole isomer in 65% yield. A bromo substituent on the benzene ring was inert under this radical cyclization and gave **5b** in 59% yield. A methoxy group as well as various sulfonamides instead of oxygen showed similar reactivity to give the cyclized products (**5c-g**) in 46% to 57% yield, and a spiro ring-system in **5h** could also be used for its construction. In the formation of cyclopentenones using linear aliphatic substrates, quaternary carbons in precursors increased the cyclization efficiency. For example, malonate derivative (**5i**) was obtained in 81% yield and other cyclopentenones (**5j-l**) were obtained in moderate yield. However, formation of a 6-membered ring decreased the yield of **5m** to 37% even after 15 h. In lactone formation, a similar hydroacylative cyclization proceeded to give **5n** as a single product in 52% yield.

Scheme 7. Hydroacylative cyclization of acylphosphates



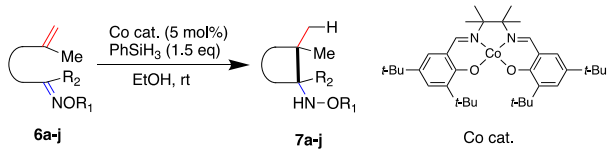
Since 1,1- and 1,2-disubstituted olefins were discriminable in the reaction of **1g,i**, carboacylative cyclization was examined next. Red olefin in **4o** was more favorable for initial and regioselective hydrogen atom transfer,[10b] and the subsequent cyclization sequence on *trans*-olefin gave tricyclic products (**5o**) (Scheme 8). The structure of the major diastereomer was established to be *trans*-**5o** by X-ray crystallographic analysis.

Scheme 8. Tandem cyclization of **4o**

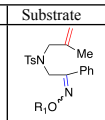
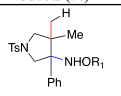
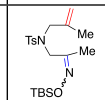
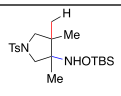
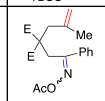
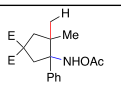
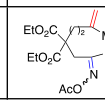
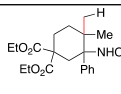
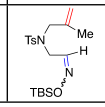
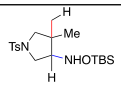


To our delight, C=N bonds could also be used for this Sn-free radical protocol under cobalt catalysis (Table 2). Keto-oximes[22] are attractive precursors for facile access to quaternary carbons, however only limited methods for their production, using Sn reagents,[23] Rh catalysis,[24] and photocatalysis,[25] are known. We expected that stable and readily available oximes could be used for our protocol as radical acceptors.

Table 2 Cyclisation of **6**



6a-j **7a-j** Co cat.

Entry	Substrate		Time (h)	Products (%)	
1		(*Z*)-**6a**: R_1 = H	8		**7a**: 0
2		(*Z*)-**6b**: R_1 = Bn	24		**7b**: 0
3		(*Z*)-**6c**: R_1 = Bz	4		**7c**: 35
4		(*Z*)-**6d**: R_1 = TBS	5		**7d**: 52
5		(*E*)- and (*Z*)-**6d**: R_1 = TBS[1]	5		**7d**: 60
6		(*E*)- and (*Z*)-**6e**: R_1 = Ac[2]	8		**7e**: 61
7		**6f**[3]	5		**7f**: 66
8		**6g**: E = CO_2Et[4]	5		**7g**: 96
9		**6h**: E = CO_2Bn[5]	6		**7h**: 83
10		**6i**[6]	7		**7i**: 0
11		**6j**[7]	24		**7j**: 0

1) A mixture (E:Z = 1:3.1) was used. 2) E:Z = 1:1.5. 3) E:Z = 1:7.3.4) E:Z = 1:5.7. 5) E:Z = 1:2.6. 6) E:Z = 4.8:1. 7) E:Z = 1:1.

First, we investigated the effect of OR groups using (*Z*)-**6a-d**.[26] Although hydrogen and a benzyl group were inert, a benzoyl group promoted the cyclization and **7c** was obtained in 35% yield (entries 1-3). This reaction gave contiguous quaternary carbons on a pyrrolidine ring and the yield was improved to 52% by TBS protection of oxime (**6d**) (entry 4). To evaluate the effect of the stereochemistry of a C=N bond, a mixture of (*E*)- and (*Z*)-**6d** was next used and the corresponding cycloadduct (**7d**) was obtained in 60% yield (entry 5). This result indicates that cyclization efficiency was not influenced by the stereochemistry of a C=N bond**.** An acetyl group was also suitable for enhancing the cyclization efficiency and **7f** was obtained in 66% yield (entry 6). The oxime derived from an aliphatic ketone such as **6f** also cyclized to give **7f** as a single isomer in 66% yield (entry 7). Malonate derivatives as cyclization precursors were efficiently converted to **7g** and **7h** in respective yields of 96% and 83% (entries 8,9). The cyclization efficiency was strongly dependent on ring size, and **6i** was not transformed to **7i** because of a messy reaction (entry 10). In addition, aldoxime **6j** was ineffective for achieving cyclization (entry 11).

Conclusions

In conclusion, we have realized a radical cyclization under Co catalysis. Carbon radicals can be obtained in a regioselective fashion from simple olefins without the use of any Sn reagents or harsh conditions. Various unsaturated bonds such as C=C, C=O and C=N act as radical acceptors to give a wide variety of hetero- and carbocycles and multi-ring systems in a single operation. These achievements may lead to new applications in synthetic chemistry and further studies are currently underway.

Experimental

Typical procedure for Co-catalyzed hydrocyanative cyclization, synthesis of *cis*-**2c**: To a solution of diene (66.1 mg, 0.28 mmol), TsCN (59.9 mg, 0.33 mmol) and $PhSiH_3$ (40.6 µL, 0.33 mmol) in EtOH (1.38 mL) was added Co complex (3.33 mg, 0.006 mmol, 2 mol%) at room temperature. After being stirred for 4 h under argon, the solvent was removed under reduced pressure. The resulting residue was charged on a silica gel pad. Column chromatography (hexane:AcOEt = 20:1) gave *cis*-**2c** (60.3 mg, 0.23 mmol, 82%) as a colorless oil.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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