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Palladium-catalyzed ring opening of azabicyclic olefins with organoindium reagents: a simple, clean, and efficient synthesis of functionalized cyclopentenes

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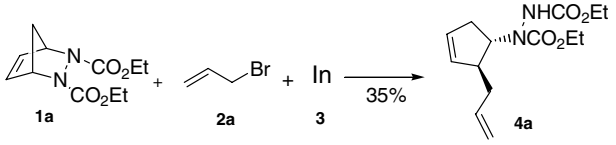
Dedicated with respect to Professor Yoshinori Yamamoto for his inspiration, constant encouragement and scholarly criticism

Abstract—Azabicyclic olefins undergo facile palladium-catalyzed ring opening with organoindium reagents affording *trans*-3,4-disubstituted hydrazinocyclopentenes in good to excellent yields.

Transition metal catalyzed coupling reactions of organometallic compounds with electrophiles provides a general and powerful tool for the formation of carbon–carbon bonds.[1] Among organometallic reagents, organoindiums have gained increasing popularity in organic synthesis. Indium metal exhibits low heterophilicity and can be handled with ease as it is unaffected by air or oxygen and has no toxic side effects. It has been observed that reactions of organoindiums show exceptional regio- and stereoselectivity.[2,3] Regioselective allylation was first reported on alkynes with allylindium reagents.[4] It was also reported that allenes undergo clean regio- and stereoselective allylation.[5] The reactivity of organoindium reagents toward carbon–carbon double bonds however, has received only scant attention. Araki et al. reported the regioselective allylation of electron deficient alkenes with allylindium.[6] Palladium-catalyzed cross couplings of allylindium with organic electrophiles have been reported by Lee et al.[7] They also reported Pd-catalyzed substitution reactions of organoindiums with allyl esters, which yielded both substitution and addition products.[8]

Recently, we developed a general and efficient methodology for the stereoselective synthesis of trans-vicinal disubstituted hydrazinocyclopentenes in good to excellent yields through a one-step ring opening of bicyclic hydrazines[9] with organostannanes and organoboronic acids. As part of our sustained interest in the chemistry of azabicyclic olefins, we undertook an investigation of the palladium-catalyzed reactions of organoindium reagents with these substrates. Our studies began with the reaction of 1 equiv of allylindium, generated in situ from the reaction of allyl bromide and indium, with 1 equiv of azabicyclic olefin[10] **1a** in THF in the presence of $[Pd(allyl)Cl]_2$/dppe/$Yb(OTf)_3$ as the catalyst system. The reaction afforded *trans*-3-allyl-4-hydrazinocyclopentene **4a** in 35% yield. The structure of the product was assigned based on spectroscopic data and was further confirmed by HOMO–COSY analysis and by comparison with the literature data Scheme 1.[9]

Detailed optimization studies were carried out to find the best conditions for this transformation. The catalytic activity of various catalysts were screened among which $[Pd(allyl)Cl]_2$ gave the best yield. The optimized



Scheme 1. $[Pd(allyl)Cl]_2$ (5 mol %), dppe (10 mol %), $Yb(OTf)_3$ (2 mol %), THF, 60 °C, 12 h.

Keywords: Bicyclic hydrazine; Organoindium reagents; Homogeneous catalysis; Cyclopentene derivatives; Palladium catalysis.
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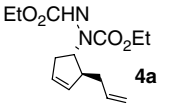
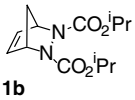
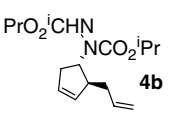
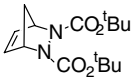
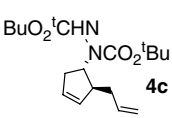
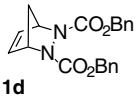
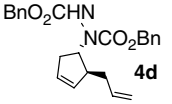
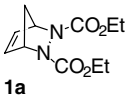
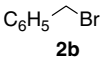
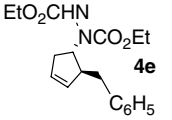
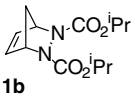
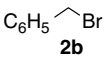
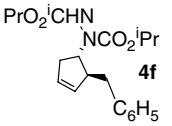
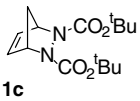
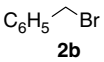
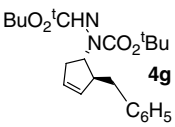
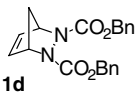
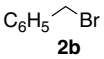
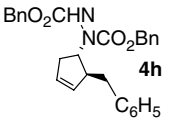
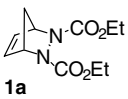
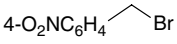
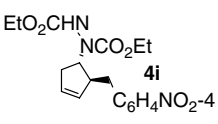
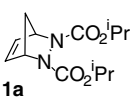
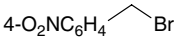
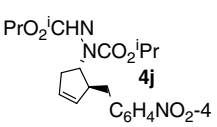
Table 1. Catalyst system optimization studies

Entry	Catalyst	Ligand	Lewis acid	Yield (%)
1	$[Pd(allyl)Cl]_2$	dppe	$Yb(OTf)_3$	35[a]
2	$[Pd(allyl)Cl]_2$	PPh_3	$Yb(OTf)_3$	60[b]
3	$[Pd(allyl)Cl]_2$	dppe	$Yb(OTf)_3$	95[b]
4	$Pd(PPh_3)_4$	dppe	$Yb(OTf)_3$	34[b]
5	$Pb(OAc)_2$	PPh_3	$Sc(OTf)_3$	Trace[b]
6	$[Pd(allyl)Cl]_2$	dppe	$Sc(OTf)_3$	70[b]

[a] Reagents and conditions: **1a** (1.0 equiv), **2a** (1.5 equiv), In (1.0 equiv), $[Pd(allyl)Cl]_2$ (5 mol %), dppe (10 mol %), $Yb(OTf)_3$ (2 mol %), THF, 60 °C, 12 h.

[b] Reagents and conditions: **1a** (1.0 equiv), **2a** (3.0 equiv), In (2.0 equiv), $[Pd(allyl)Cl]_2$ (5 mol %), dppe (10 mol %), $Yb(OTf)_3$ (2 mol %), THF, 60 °C, 12 h.

Table 2. Palladium-catalyzed ring opening of azabicyclic olefins with organoindium reagents

Entry	Substrate	Halide	Product	Yield (%)
1	 **1a**	 **2a**	 **4a**	95
2	 **1b**	 **2a**	 **4b**	86
3	 **1c**	 **2a**	 **4c**	88
4	 **1d**	 **2a**	 **4d**	80
5	 **1a**	 **2b**	 **4e**	89
6	 **1b**	 **2b**	 **4f**	80
7	 **1c**	 **2b**	 **4g**	75
8	 **1d**	 **2b**	 **4h**	72
9	 **1a**	 **2c**	 **4i**	43
10	 **1a**	 **2c**	 **4j**	35

Reagents and conditions: **1** (1.0 equiv), **2** (3.0 equiv), **3** (2.0 equiv), $[Pd(allyl)Cl]_2$ (5 mol %), dppe (10 mol %), $Yb(OTf)_3$ (2 mol %), THF, 60 °C, 12 h.

conditions for the reaction were found to be 1 equiv of bicyclic alkene, 3 equiv of allyl bromide, 2 equiv of indium, 5 mol % $[Pd(allyl)Cl]_2$, 10 mol % dppe, and 2 mol % of $Yb(OTf)_3$ in THF as solvent and which gave **4a** in 95% yield.[11] The results of the optimization studies are shown in Table 1.

Benzyl indium reagents generated from the corresponding benzyl bromides also afforded ring opened products in good to excellent yields. Similar reactivity was observed with other bicyclic alkenes and the results are summarized in Table 2. The mechanism of the reaction appears similar to that proposed for the ring opening with organostannanes and organoboronic acids.[9]

In conclusion, we have reported a novel reactivity of organoindium reagents with azabicyclic olefins under palladium catalysis, leading to the stereoselective formation of *trans*-3,4-disubstituted cyclopentenes. The products are versatile synthons with multiple points for functionalization and can be used in the synthesis of a number of biologically active molecules such as glycosidase inhibitors,[12] carbocyclic nucleosides, antiviral, and antitumor[13] agents. Further work to utilize the developed method for the synthesis of carbocyclic nucleosides is in progress and will be reported in due course.

Acknowledgments

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11. *Typical experimental procedure and spectroscopic data for* **4a**: Bicyclic hydrazine **1a** (100 mg, 0.41 mmol), $[Pd(allyl)Cl]_2$ (7 mg, 5 mol %), dppe (15 mg, 10 mol %) and $Yb(OTf)_3$ (5 mg, 2 mol %) were charged in a Schlenk tube and the allylindium reagent generated from allyl bromide (0.106 mL, 1.2 mmol) and indium powder (94 mg, 0.82 mmol) was then added. The reaction mixture was degassed with argon and allowed to stir at 60 °C for 12 h. The extent of the reaction was monitored by TLC and on completion the reaction mixture was evaporated and subjected to column chromatography (silica gel 60–120 mesh, 15% EtOAc–hexane) to afford the product as a colorless viscous liquid in 95% yield. *Spectral data for* **4a**: R_f: 0.35 (30% EtOAc–hexane). IR (Neat) ν_{max} : 3295, 3060, 2981, 2917, 1714, 1691, 1517, 1417, 1294, 1241, 1127, 1061, 760, 716 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.33 (s, 1H), 5.79–5.82 (m, 1H), 5.60–5.67 (m, 2H), 5.01–5.10 (m, 2H), 4.56–4.58 (m, 1H), 4.19 (q, 4H, $J = 7.05$ Hz), 2.85 (br s, 1H), 2.31–2.54 (m, 3H), 2.13–2.16 (m, 1H), 1.27 (t, 6H, $J = 7.08$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.5, 155.8, 136.6, 132.9, 128.8, 116.5, 63.3, 62.7, 62.3, 47.9, 37.8, 35.4, 14.7, 14.6. MS(LR-FAB): *m/z* calcd for $C_{14}H_{23}N_2O_4$ (M+1): 283.1658, found: 283.1660.
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