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INVESTIGATION OF THE REGIOSELECTIVITY ON THE REACTION OF 2-INDOLYLCYANOCUPRATE WITH *N*-(PROP-2-EN-1-YLIDENE)-AMINIUM CHLORIDE DERIVATIVES

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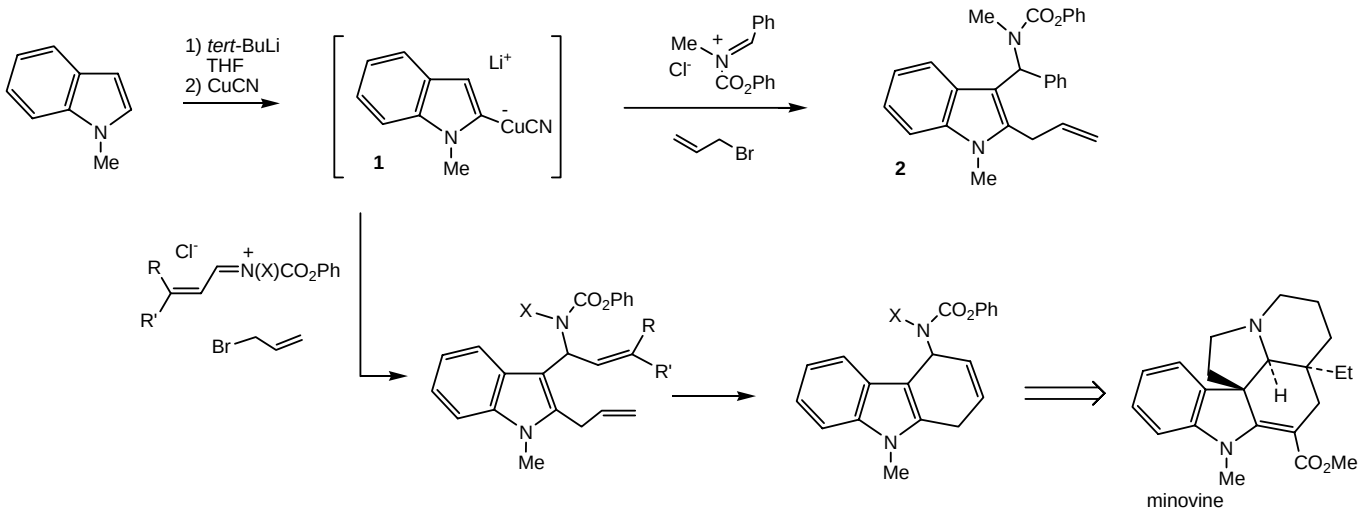
Abstract - Regioselectivity on the reaction of (1-methylindol-2-yl)cyanocuprate with *N*-(prop-2-en-1-ylidene)aminium chlorides was investigated.

Although the chemical lability of organocopper reagents is well recognized as a versatile synthetic tool,[1] the applications of heteroarylcopper reagents for this purpose, as found in the literature, have been limited.[2]

We have previously reported that 2-indolylcyanocuprate (**1**), readily available *in situ* from 2-lithio-1-methylindole and CuCN in THF, reacted with electrophiles to give 2- or 3-substituted indoles in a regioselective manner, depending on the nature of electrophiles used. A one-pot protocol for the regioselective formation of 2,3-disubstituted indole (**2**) was also developed by the successive addition of iminium chloride and allyl bromide to a solution of **1** in THF (Scheme 1).[3]



Scheme 1

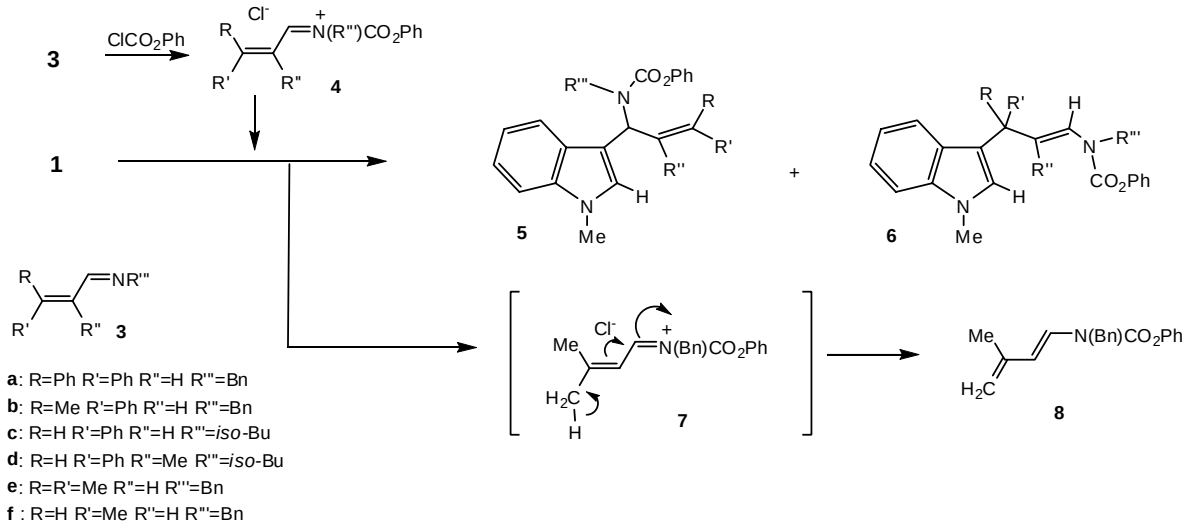
Next, our attention was drawn to the question as to whether *N*-(prop-2-en-1-ylidene)aminium chloride derivatives (**4**) might be applicable to the reaction with **1**, as these functionalities could serve as a convenient synthetic handle for future transformations directed to indole alkaloids. This paper describes the preliminary results of our investigation of the reaction of **1** with **4**.

At first, the feasibility of the reaction of **1** with **4** was tested in accordance with the previous report.[3] To a solution of **4** generated from **3** and $ClCO_2Ph$ in THF, a cooled THF solution of **1** was added at -20 °C, and the mixture was then gradually raised to room temperature. As shown in Table 1, this allowed the isolation of two kinds of 3-substituted indoles, 1,2-adduct (**5**) and/or 1,4-adduct (**6**), with the observed selectivity, possibly due to the dependence on the steric bulk associated with the alteration of substitution pattern in **4**. Sole production of **5a**,**b** was obtained from the reaction using **4a**,**b**, while the reaction using **4c**,**d** allowed the isolation of both **5c**,**d** and **6c**,**d**.

Table 1 Reaction of **1** with **4** generated from **3** and $ClCO_2Ph$

	Yields (%)	
4	**5**	**6**
4a: R=Ph R'=Ph R''=H R'''=Bn	73 (**5a**)	---
4b: R=Me R'=Ph R''=H R'''=Bn	43 (**5b**)	---
4c: R=H R'=Ph R''=H R'''=*iso*-Bu	34 (**5c**)	29 (**6c**)
4d: R=H R'=Ph R''=Me R'''=*iso*-Bu	33 (**5d**)	5 (**6d**)
4e: R=R'=Me R''=H R'''=Bn	---	---

Otherwise, we were confronted with the problem of the reaction using **4e** derived from **3e**, in which the sole isolable product was diene (**8**) instead of the anticipated **5e** and **6e**. The generation of **8** can be explained by assuming a facile deprotonation-isomerization path such as **7** (Scheme 2). The structure of **6** and **8** was confirmed based on NOE experiments.[4]



a: R=Ph R'=Ph R"=H R'"=Bn
b: R=Me R'=Ph R"=H R'"=Bn
c: R=H R'=Ph R"=H R'"=*iso*-Bu
d: R=H R'=Ph R"=Me R'"=*iso*-Bu
e: R=R'=Me R"=H R'"=Bn
f : R=H R'=Me R"=H R'"=Bn

Scheme 2

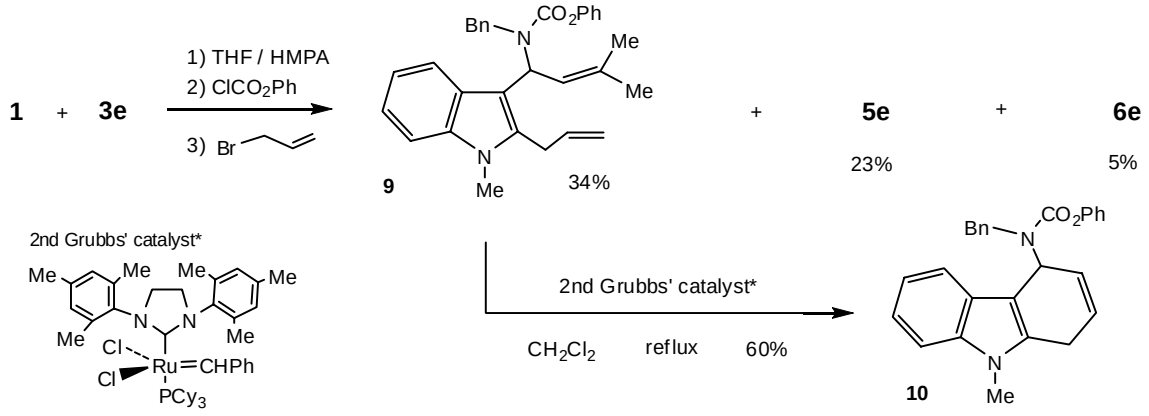
After efforts to effect the reaction, we eventually succeeded in obtaining **5e**[5] and **6e**[5] by way of a one-pot treatment of pre-mixed solution of **1** and **3e** in THF with $ClCO_2Ph$ at -20°C, in which the presence of HMPA in the reaction medium led to a profound improvement in the yield of **5e** (Table 2).[6] This procedure also proved to be effective in increasing the yield of **5b** compared with that in Table 1. The reaction using **3f** produced **6f** in preference to **5f**, which might be due to the less sterically hindered nature of **3f**.

Table 2 Reaction of a mixture of **1** and **3** with $ClCO_2Ph$

			Yields (%)	
3	Additive	Conditions	**5**	**6**
3e	-----	-20°C to rt, 1.5h	20 (**5e**)	14 (**6e**)
3e	HMPA	-20°C to rt, 1.5h	51 (**5e**)	12 (**6e**)
3e	HMPA	-78°C to rt, 6.5h	41 (**5e**)	6 (**6e**)
3b	-----	-20°C to rt, 1.5h	56 (**5b**)	---
3f	-----	-20°C to rt, 1.5h	8 (**5f**)	36 (**6f**)
3f	HMPA	-20°C to rt, 1.5h	7 (**5f**)	33 (**6f**)

Having developed the construction of the requisite **5**, the one-pot formation of 2,3-disubstituted indole (**9**)[7] was next examined. To a mixture of **1** and **3e** in THF containing HMPA was added $ClCO_2Ph$ at -78 °C. After 15 minutes, allyl bromide was sequentially added to the mixture, allowing the isolation of the desired **9,** though in somewhat low yield along with a substantial amount of **5e** and **6e**.

The ring-closing metathesis reaction of **9** in the presence of the 2nd generation Grubbs' catalyst in CH_2Cl_2 under reflux smoothly produced carbazole (**10**).[8]



Scheme 3

In summary, we have developed a protocol for the formation of 3-substituted indoles (**5** and **6**) based on a one-pot treatment of **1** and *N*-(prop-2-en-1-ylidene)amine (**3**) with $ClCO_2Ph$. Further investigations

involving the improvements in the formation of **9** and its application to the indole alkaloid synthesis are in progress.

ACKNOWLEDGEMENTS

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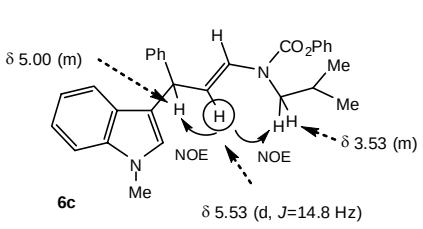
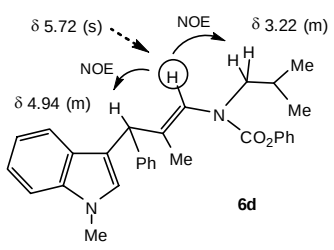
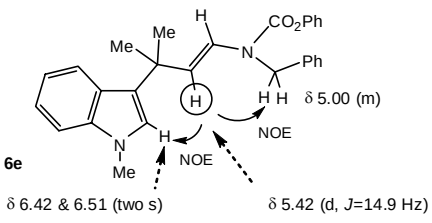
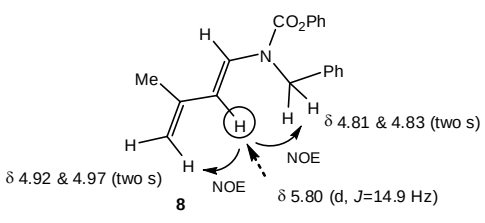
4. NOE Correlations of **6c-e** and **8**:









5. **5e**: ^{1}H-NMR ($CDCl_3$) δ: 1.71 (s, 3H), 1.77 (s, 3H), 3.76 (s, 3H), 4.31 (m, 1H), 4.61 (d, 1H, *J*=16.1 Hz), 5.56 (d, 1H, *J*=8.6 Hz), 6.58 (br s, 1H), 6.90-7.41 (m, 14H), 7.73 (br s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 18.6, 25.8, 32.9, 47.4, 51.6, 109.4, 114.1, 119.6, 119.9, 121.9, 122.1, 125.2, 126.6, 127.1, 128.1, 129.3, 136.3, 137.5, 139.7, 151.6, 155.1. **6e**: ^{1}H-NMR ($CDCl_3$) δ: 1.51 (s, 6H), 3.65 (s, 3H), 4.93 (d, 2H, *J*=17.9 Hz), 5.41 (d, 1H, *J*=14.9 Hz), 6.42 and 6.52 (two s, 1H), 7.00-7.43 (m, 14H), 7.61 (d, 1H, *J*=8.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 29.2, 32.6, 35.8, 48.4, 109.4, 118.5, 121.2, 121.3, 121.8, 123.0, 123.2, 124.2, 125.0, 125.1, 125.7, 126.6, 127.2, 127.3, 128.7, 129.4, 137.2, 137.8, 151.2, 151.4, 153.3.
6. To a solution of **1**[3] (1 mmol) and **3e** (1.5 mmol) in THF (10 mL) and HMPA (1 mL) under an argon atmosphere at -20 °C, $ClCO_2Ph$ (1.5 mmol) was added slowly, and the whole was gradually warmed to rt over 1.5 h. The mixture was diluted with AcOEt, washed with brine, and dried over $MgSO_4$. The solvent was removed, and the residue was separated by medium pressure liquid chromatography (on SiO_2) with AcOEt-hexane (1:15) as an eluent to give **5e** and **6e**.
7. **9**: ^{1}H-NMR ($CDCl_3$) δ: 1.58 (s, 3H), 1.72 (s, 3H), 3.55 (s, 3H), 3.32-3.72 (m, 2H), 4.51 (m, 1H), 4.62 (d, 1H, *J*=16.1 Hz), 4.87 (dd, 1H, *J*=17.1, 1.1 Hz), 5.05 (dd, 1H, *J*=10.5, 1.1 Hz), 5.79-5.92 (m, 1H), 5.88 (d, 1H, *J*=8.6 Hz), 6.49 (d, 1H, *J*=8.6 Hz), 6.89-7.43 (m, 13H), 7.74 (d, 1H, *J*=8.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 18.2, 25.8, 29.1, 29.6, 48.1, 53.1, 109.1, 110.4, 116.4, 119.6, 119.9, 121.0, 121.4, 121.9, 123.1, 125.2, 126.4, 127.0, 127.4, 127.9, 128.7, 129.2, 129.8, 134.5, 136.7, 137.0, 139.6, 151.6, 154.9.
8. **10**: ^{1}H-NMR ($CDCl_3$) δ: 3.36 (d, 2H, *J*=2.6 Hz), 3.68 (s, 3H), 4.07 (d, 1H, *J*=16.0 Hz), 4.39 (d, 1H, *J*=16.0 Hz), 5.92-6.12 (m, 2H), 6.50 (s, 1H), 7.02-7.44 (m, 13H), 7.66 (d, 1H, *J*=7.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 23.4, 29.3, 46.5, 50.9, 51.4, 106.3, 108.6, 119.2, 119.7, 121.5, 121.8, 124.5, 125.2, 125.8, 126.4, 127.1, 127.6, 127.8, 128.1, 129.2, 129.3, 135.7, 137.1, 139.4, 151.4, 155.5.