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Synthesis of 3,4-Disubstituted Maleimides by Selective Cross-Coupling Reactions Using Indium Organometallics[†]

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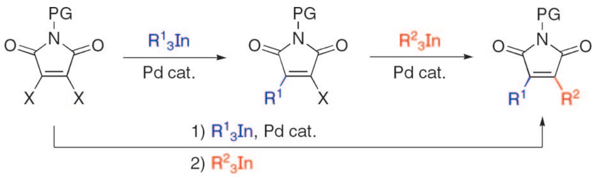
ABSTRACT



X = Cl, Br
PG = protecting group
R^1, R^2 = 2- and 3-indolyl, aryl, heteroaryl, alkynyl, alkyl

Unsymmetrical 3,4-disubstituted maleimides have been synthesized by palladium-catalyzed cross-coupling reactions of indium organometallics with 3,4-dihalomaleimides. The synthesis was performed by stepwise or sequential one-pot palladium-catalyzed cross-coupling reactions with various triorganoindium reagents. This method was used to prepare a wide variety of alkyl, aryl, heteroaryl, and alkynyl 3,4-disubstituted maleimides in good yields and with high selectivity and atom economy.

3,4-Disubstituted maleimides are an important family of natural and synthetic products with valuable pharmacological properties.[1] They are potent agents for the inhibition of protein kinases, especially PKC, an important target in cancer chemotherapy,[2] and some members of this family are in clinical trials as anticancer drugs.[3] Other compounds exhibit antibacterial, antiviral, antimicrobial, and antigenic activities.[4] Furthermore, 3,4-bisindolylmaleimides have found applications as light emitting diodes (LED)[5] and have also been used in the development of photocatalysts immobilized on surfaces.[6]

[†] Dedicated to Professor Luis Castedo on the occasion of his 70th birthday.

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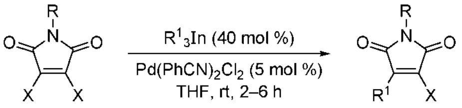
The synthesis of 3,4-disubstituted maleimides has generally been carried out by two main approaches: a linear synthetic sequence based on the formation of the maleimide ring in the last steps of the synthesis[7,8] or by selective functionalization of a 3,4-dihalomaleimide by Grignard addition and cross-coupling reaction.[9,10] Generally, the cross-coupling reactions afford symmetrical 3,4-disubstituted maleimides,[11] and only one example, using alkylzinc reagents, has proved to be selective in the monocoupling reaction.[12]

During the past few years, we have shown that indium organometallics are useful reagents in metal-catalyzed cross-coupling reactions.[13] The main features of triorganoindium reagents (R_3In) in cross-coupling reactions are their high efficiency, versatility, and chemo- and stereoselectivity. Additionally, R_3In are particularly effective in the synthesis of functionalized heterocyclic compounds.[14] In this communication, we report the synthesis of unsymmetrically 3,4-disubstituted maleimides by selective cross-coupling reactions of R_3In with 3,4-dihalomaleimides.

Our study began with an investigation into the reactivity and selectivity of triorganoindium reagents in the palladium-catalyzed cross-coupling reaction with 3,4-dibromomaleimide **1** (Table 1). Initially, the reaction of R_3In with **1**, using the most commonly used commercially available palladium catalysts $Pd(Ph_3P)_4$ or $Pd(Ph_3P)_2Cl_2$, under reflux gave the double cross-coupling product as the major product. Further screening of the reaction conditions showed that on using $Pd(PhCN)_2Cl_2$ (5 mol %) as the catalyst[15] the monocoupling product could be obtained regioselectively at rt in good yields after 2−6 h, using only 40 mol % of the triorganoindium reagent as the nucleophile. For example, the reaction of tri-*n*-butylindium with **1** afforded the monocoupling product **3** in 81% yield (Table 1, entry 1). The reaction of arylindium reagents (4-methoxyphenyl, 1-naphthyl) with **1** gave similar yields and selectivities (78−79%, entries 2 and 3). Interestingly, the 3-bromo-4-indolylmaleimide **6** was prepared by reaction of tri(5-methoxy-3-indolyl)indium with **1**, and this reaction gave 75% yield (entry 4). These results demonstrate the high selectivity of the system R_3In:$Pd(PhCN)_2Cl_2$ in the coupling reactions with 3,4-dibromomaleimides and the high atom economy of R_3In in transferring all three groups to the electrophile.

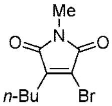
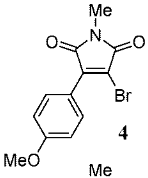
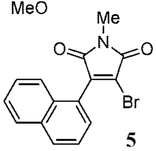
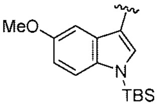
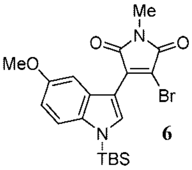
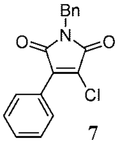
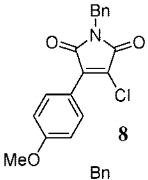
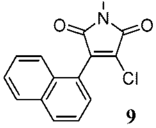
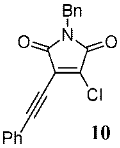
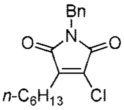
The reactivity of R_3In with 3,4-dichloromaleimide **2** was also studied.[12]Initial studies showed that the reaction occurs

Table 1. Palladium-Catalyzed Mono Cross-Coupling Reactions of Indium Organometallics with **1** and **2**



1, R = Me, X = Br
2, R = Bn, X = Cl

3–6, R = Me, X = Br
7–11, R = Bn, X = Cl

entry	maleimide	R^1	product	yield (%)
1	**1**	*n*-Bu	 **3**	81
2	**1**	4-$MeOC_6H_4$	 **4**	78
3	**1**	1-Naphthyl	 **5**	79
4	**1**		 **6**	75
5	**2**	Ph	 **7**	67
6	**2**	4-$MeOC_6H_4$	 **8**	69
7	**2**	1-Naphthyl	 **9**	71
8	**2**	PhC≡C	 **10**	40[a]
9	**2**	*n*-Hexyl	 **11**	58

[a] The reaction product (**10**) was obtained along with 32% of the symmetrical cross-coupling product.

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(7) (a) Hughes, T. V.; Cava, M. P. *Tetrahedron Lett.* **1998**, *39*, 9629–9630. (b) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053–6058. (c) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *Tetrahedron Lett.* **1999**, *40*, 1109–1112. (d) Roy, S.; Roy, S.; Gribble, G. W. *Org. Lett.* **2006**, *8*, 4975–4977.

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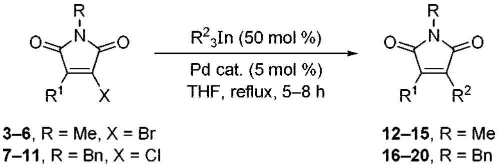
efficiently using $Pd(PhCN)_2Cl_2$ (5 mol %) as the catalyst, although longer reaction times are required and slightly lower yields obtained in comparison to the analogous dibromide. We believe that the lower reactivity favors the double cross-coupling product, which is the secondary product in all reactions.[16]

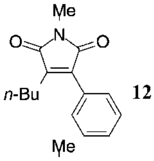
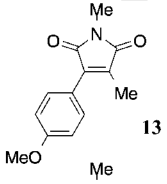
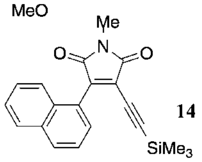
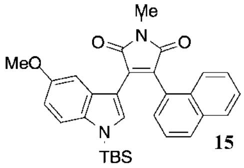
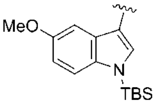
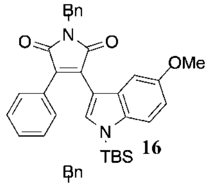
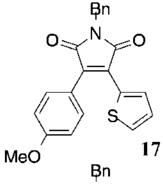
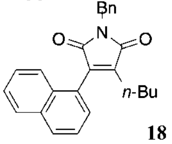
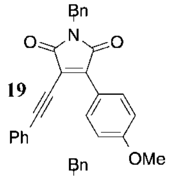
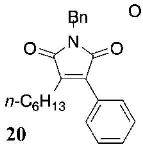
Under these conditions, the reaction of arylindium (phenyl, 4-methoxyphenyl, 1-naphthyl) reagents with **2** produced the selective cross-coupling products **7−9** in good yields (67−71%, Table 1, entries 5−7). The reaction using tri(phenylethynyl)indium afforded the monocoupling product **10** in 40% yield, accompanied by 32% of the symmetrical cross-coupling product (Table 1, entry 8). Interestingly, the reaction with an alkylindium derivative such as tri(*n*-hexyl)indium gave the 3-alkyl-4-chloromaleimide **11** in a satisfactory 58% yield (Table 1, entry 9). Overall, these results demonstrate the high versatility of R_3In (sp, sp^2, sp^3) in cross-coupling reactions with 3,4-dihalomaleimides, and they represent the first general method for the synthesis of 3-halo-4-substituted maleimides by cross-coupling reactions.

To prepare unsymmetrically 3,4-disubstituted maleimides, we explored a second cross-coupling reaction using the previously prepared 3-halo-4-substituted maleimides **3−11**. In the first experiments, the reaction of 3-bromomaleimides **3−6** with R_3In afforded the corresponding products in low yields. Further research showed that good yields could be obtained on using $Pd(DPEphos)Cl_2$ (5 mol %)[17] as the catalyst and by performing the reactions under reflux for 5−8 h. Under these conditions, the 3-bromo-4-substituted maleimides **3−6** reacted with aryl-, alkyl-, or alkynylindium reagents (50 mol %) to give the corresponding 3,4-disubstituted maleimides, i.e., alkyl−aryl (**12** and **13**, 80−89% yield, Table 2, entries 1 and 2), 1-naphthyl−alkynyl (**14**, 84% yield, Table 2, entry 3), or 3-indolyl−1-naphthyl (**15**, 88% yield, Table 2, entry 4).

Further evidence for the high efficiency of indium organometallics in these reactions was provided by the synthesis

Table 2. Palladium-Catalyzed Cross-Coupling Reactions of Indium Organometallics with 3-Bromo- and 3-Chloro-4-Substituted Maleimides **3−11**



entry	3-halo-maleimide	R^2	product	yield (%)
1	**3**	Ph	 **12**	89^a
2	**4**	Me	 **13**	80^a
3	**5**	$Me_3SiC{\equiv}C$	 **14**	84^a
4	**6**	1-Naphthyl	 **15**	88^a
5	**7**		 **16**	88^b
6	**8**	2-Thiophenyl	 **17**	82^b
7	**9**	*n*-Bu	 **18**	87^b
8	**10**	4-$MeOC_6H_4$	 **19**	90^b
9	**11**	Ph	 **20**	91^b

[a] Reactions performed with $Pd(DPEphos)Cl_2$ (5 mol %) as catalyst. [b] Reactions performed with $Pd(Ph_3P)_4$ (5 mol %) as catalyst.

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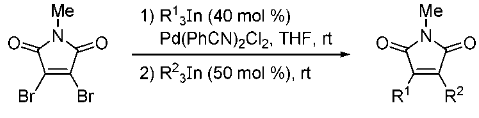
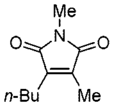
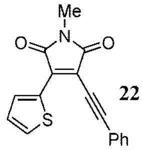
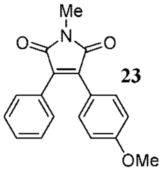
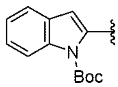
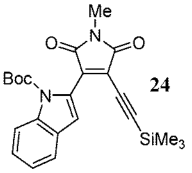
(15) This catalyst has been already useful in selective palladium-catalyzed cross-coupling reactions: Zhang, L.; Meng, T.; Fan, R.; Wu, J. *J. Org. Chem.* **2007**, *72*, 7279–7286.

Table 3. Sequential Cross-Coupling of Triorganoindium Reagents with **1**



1 → **21–24**

entry	R^1, R^2	product	yield (%)
1	R^1 = *n*-Bu R^2 = Me	 **21**	87
2	R^1 = 2-Thiophenyl R^2 = PhC≡C	 **22**	89
3	R^1 = Ph R^2 = 4-MeOC$_6$H$_4$	 **23**	68
4	R^1 =  R^2 = Me$_3$SiC≡C	 **24**	86

of unsymmetrically 3,4-disubstituted maleimides by reaction of R$_3$In with the 3-chloro-4-substituted maleimides **7**−**11**. The yields were relatively poor on using the same reaction conditions as before, but the use of Pd(Ph$_3$P)$_4$ (5 mol %) as catalyst and performing the reactions in a sealed tube at 80 °C for 8 h led to increases in the yields. The cross-coupling reactions of heteroaryl- (3-indolyl, 2-thiophenyl), aryl-, and alkylindium reagents afforded the corresponding 3,4-disubstituted maleimides (**16**−**20**) in good yields (82−91%, Table 2, entries 5−9). Unfortunately, the cross-coupling reactions of trivinylindium with bromo- or chloromaleimides gave unstable cross-coupling products in low yields.

One particular feature of the cross-coupling reactions using indium organometallics is their suitability for the construction of two different carbon−carbon bonds in a one-pot procedure.[14b,18] For this reason, we explored the possibility of synthesizing unsymmetrically 3,4-disubstituted maleimides in a one-pot procedure. It was found that the reaction of dibromomaleimide **1** with 40 mol % of R$_3$In in the presence of Pd(PhCN)Cl$_2$ (5 mol %) in THF at rt, followed by the addition of a different indium organometallic reagent after completion of the first coupling (TLC test), afforded, after 12 h at rt, the disubstituted product in good yields. These results show that a variety of aryl-, heteroaryl-, alkyl-, and alkynylindium reagents can be coupled efficiently with **1**, and the results are summarized in Table 3 (68−89%). To the best of our knowledge, this constitutes the first one-pot approach to 3,4-disubstituted maleimides by cross-coupling reactions.

In summary, a new method for the synthesis of 3,4-disubstituted maleimides using palladium-catalyzed cross-coupling reactions with indium organometallics was developed. The synthesis was performed by selective stepwise or sequential one-pot procedures from 3,4-dibromo- or 3,4-dichloromaleimides. The reactions give good yields, have high selectivity, and have a high atom economy with respect to the organic groups. Following this method, a wide variety of unsymmetrically 3,4-disubstituted maleimides possessing alkyl, aryl, heteroaryl (including 3-indolyl), and alkynyl groups in their structure were synthesized. Further applications of this method in the synthesis of novel maleimides are now under investigation.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data, and copies of NMR spectra for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) In the reactions with **1** and **2**, the use of an excess of R$_3$In (>40 mol %) increases the yield of the symmetrical cross-coupling products.

(17) DPEphos = bis([*o*-(diphenylphosphino)phenyl] ether. (a) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081–3089. (b) Huang, Z.; Qian, M.; Babinski, D. J.; Negishi, E. *Organometallics* **2005**, *24*, 475–478.

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