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Further Developments in Metal-Catalysed C-C Bond Cleavage in Allylic Dimethyl Malonate Derivatives

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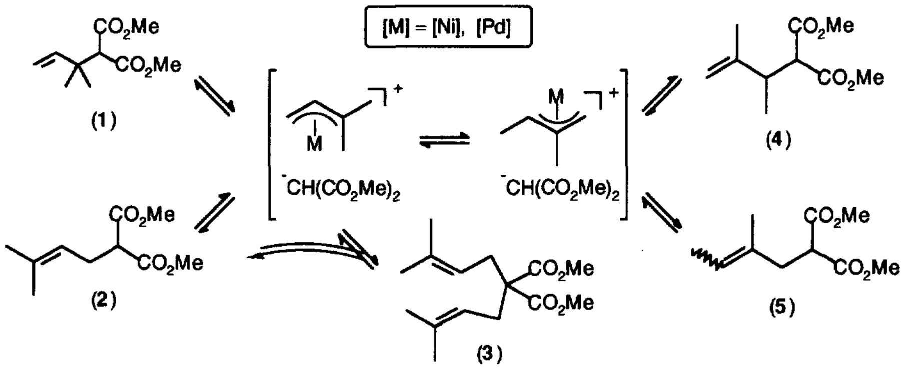
Abstract: *The use of a catalytic amount of nickelbis(1,4-bis(diphenylphosphino)butane) in DMF enables the activation of the C-C bond in dimethyl allylmalonate derivatives to proceed under rather smooth reaction conditions, without added nucleophile. Several examples like isomerization of substituted-allyl malonate derivatives, racemization of chiral products, but also a synthetic application as an inverse disproportionation reaction are described.* © 1997, Elsevier Science Ltd. All rights reserved.

Alkylation of allylic derivatives with nucleophilic reagents is a widespread tool in organic synthesis for the formation of carbon-carbon bonds. This reaction is most often performed in the presence of palladium catalysts,[1] though the use of alternative metals, particularly nickel-based catalysts,[2] has also been emphasised. The alkylation reaction with stabilized nucleophiles was usually assumed to be irreversible under reaction conditions (low temperatures and short reaction times), and thus under kinetic control. However, it has been recently reported that the reversibility of the carbon-carbon bond forming step in these processes proceeded at higher temperatures and longer reaction times.[3] Under the latter conditions, the alkylation reaction is under thermodynamic control, as demonstrated with several rearrangements of mono- and diallylic malonate derivatives into thermodynamically more stable regioisomers.[3] These isomerizations were carried out in THF with a Pd(0)-PBu$_3$ catalyst and in the presence of an equimolar amount of sodium dialkyl malonate as the nucleophile.[3] We report here that such an activation of the C-C bond present in dimethyl allylmalonate derivatives is efficiently performed with nickel-based catalytic systems, and that the addition of a salt or the use of a polar solvant without any added nucleophile is an interesting alternative for this reaction.



Scheme 1

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The first set of examples deals with the isomerization of the branched alkylation product **1**[3] in the presence of Ni(dppb)$_2$ as the catalyst (prepared *in situ* by mixing Ni(COD)$_2$ and 2 equiv of 1,4-bis(diphenylphosphino)butane).[2g] Product **1** was progressively transformed into the linear product **2**, along two other isomerization products, **4** and **5**, as well as diallylation products **3**, whose relative concentrations depend upon the reaction conditions (Scheme 1). The results of systematic studies conducted on this reaction are summarized in Table 1.

Table 1. Rearrangement of dimethyl (1,1-dimethylallyl)malonate (**1**)[a]

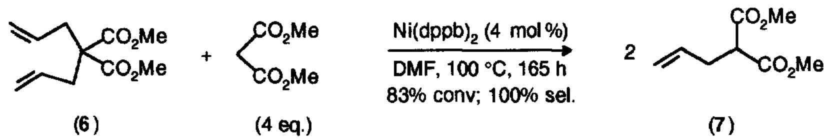
entry	metal catal.[b]	solvent	co-reagent (equiv.)[c]	time (h)[d]	conv **1** (%)[d]	Selectivity (mol %) [e]					TOF° (h^{-1})[f]
						1	**2**	**3**[g]	**4**	**5**	
			starting material[h]			68	31	1	0	0	
1	NiL$_2$	THF	-	55	44	39	44	3	10	3	0.5
2	"	"	NaDMM (2)	0.33	100	0	91	9	0	0	250
3	"	"	NaBF$_4$ (2)	20	99	<1	74	4	16	6	7
4	"	DMF	-	8	100	0	64	6	21	9	13
				51	100	0	73	7	8	12	"
5	"	"	NaDMM (2)	1.5	98	1	88	8	2	1	55
6	PdL$_2$	THF	NaDMM (2)	17.5	98	2	91	7	0	0	5
7	"	DMF	-	22	8	63	34	1	1	1	0.1

[a] [Substrate] / [Ni or Pd] = 25; reaction temperature: 100 °C. [b] Catalyst prepared *in situ* by mixing 0.13 mmol of Ni(COD)$_2$ and 2 equiv. of dppb, or 0.13 mmol of Pd(OAc)$_2$ and 3 equiv. of dppb. [c] Molar equivalents of added co-reagent, with respect to **1**. [d] Optimized reaction time for the specified conversion (mol %) of **1** to isomerization products involving C-C bond activation. [e] Selectivities of the different allylated products with respect to the dimethyl malonate moiety, as determined by quantitative GLC analysis. [f] Initial turnover frequency of Ni or Pd (0-20% conversion) for the isomerization of **1**. [g] In every cases, dimethyl di(3,3-dimethylallyl)malonate (**3**) accounts for at least 95% of diallylation products. [h] See reference 6 for the preparation.

First, when a mixture of the alkylation products (**1**/**2**/**3** = 68/31/1; starting material) was treated with 4 mol % of Ni(dppb)$_2$ in THF at 100 °C for 55 h without any co-reagent, 44% of **1** was isomerized into products **2**-**5** (entry 1). When the same reaction was performed in the presence of 2 equiv. of the sodium salt of dimethyl malonate anion (NaDMM), a total, selective conversion of the branched product (**1**) to the linear product (**2**), along with a small increase in the diallylation compounds (**3**), was obtained within 20 minutes (entry 2). The use of 2 equiv. of NaBF$_4$ also led to the transformation of **1** into **2**, but the reaction was much slower and less selective than the latter, as significant amounts of **4** and **5** were also formed (entry 3). Replacement of THF by DMF as the solvent increased the reaction rate, and a monitoring of the reaction medium demonstrated the evolution of the products concentration with time (entry 4). The addition of 2 equiv. of NaDMM improved once again the reactivity and the selectivity of the reaction (entry 5), but the Ni(dppb)$_2$-NaDMM-DMF system was finally found to be less efficient than the corresponding system in THF (entry 2). The transposition of these results to palladium-catalysis was investigated with Pd(dppb)$_2$ (prepared *in situ* by mixing Pd(OAc)$_2$ and 3 equiv. of dppb). As expected, the catalytic system using THF as the solvent and 2 equiv. of NaDMM proved to be effective, with almost the same excellent selectivity into the linear product (**2**), though much less reactive than the corresponding nickel-based catalytic system (entries 2 and 6). Similarly, Pd(dppb)$_2$ alone exhibited a very low activity in DMF (entry 7). All these Ni and Pd catalytic systems exhibited a similar behavior for the isomerization of dimethyl (1-methylallyl)-malonate.

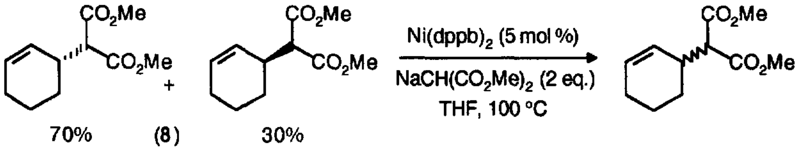
These results clearly demonstrate: (*i*) the superiority of nickel over comparable palladium-based catalysts, at least for this example; (*ii*) that the addition of an external nucleophile (NaDMM) is not a prerequesite for achieving the isomerization process, though that system is the most active one. The increase in the isomerization rate in the presence of a spectator salt ($NaBF_4$) or better a polar solvent (DMF) when no external nucleophile was added probably stems from the stabilisation of the DMM anion, i.e. the leaving group in the allylic C-C bond cleavage (Scheme 1). More, the formation of products **4** and **5**, which were not observed with Pd catalysts,[3] can be rationalised on the basis of the isomerization of the primary π-allyl complex (obtained from alkylation products **1** and **2**) to the secondary π-allyl complex (Scheme 1).

Several other reactions were developed in addition to the previous examples with the aim to enlarge the scope of the nickel- and palladium-catalyzed allylic C-C bond cleavage. Thus, the synthesis of dimethyl allylmalonate (**7**) was performed in high yield and total selectivity via the reverse disproportionation reaction between dimethyl diallylmalonate (**6**) and DMM, in the presence of $Ni(dppb)_2$ as the catalyst (eqn 2). As aforementioned, the reaction could be carried out without any co-reagent at an appreciable rate in DMF (50% yield in 42 h; 75% in 110 h).[4]



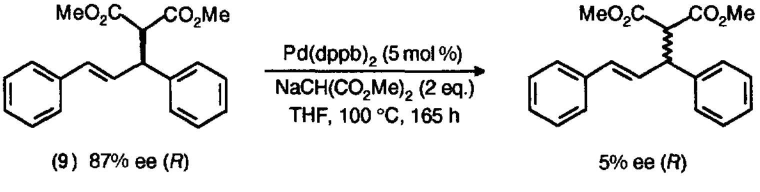
(2)

Another reaction of fundamental interest is the possible racemisation of chiral alkylation products obtained via asymmetric catalysis.[5] Namely, a sample of dimethyl (*R*)-cyclohex-2-enylmalonate (**8**, initially 40% ee)[6] could be almost totally racemised using the $Ni(dppb)_2$-NaDMM-THF system (eqn 3).[7] In the same way, the racemisation of dimethyl E-(*R*)-(1,3-diphenylallyl)malonate (**9**, initially 87% ee)[8] proceeded smoothly at 100 °C with the $Pd(dppb)_2$-NaDMM-THF system (eqn 4);[7] Surprisingly, the latter reaction could not be achieved in the presence of a nickel-based catalyst, because of a rapid catalyst poisoning.



(3)

t (h)	ee **8** (*R*)
0	40
2	31
22	9
85	2



(4)

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3. Nilsson, Y. I. M.; Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1993**, *115*, 6609-6613.
4. In a typical experiment, to Ni(COD)$_2$ (36 mg, 0.13 mmol) was added a solution of dppb (112 mg, 0.26 mmol) in DMF (12.5 ml) under nitrogen. After 15 min stirring, dimethyl diallylmalonate (**6**) (0.69 g, 3.25 mmol), DMM (1.73 g, 13 mmol, 4 eq.) and ethylbenzene (0.21 g, 2 mmol) as an internal standard were added. The solution was stirred at 100 °C and the reaction was monitored by GC analysis of aliquot samples. After 165 h, **7** was isolated from the reaction mixture by chromatography and fully characterised by NMR and MS techniques.
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6. Bricout, H.; Carpentier, J.-F.; Mortreux, A. *Tetrahedron Letters* **1996**, *37*, 6105-6108.
7. Several control experiments ((i) without metal precursor and dppb, and (ii) without metal precursor but in the presence of dppb) showed that no racemization at all occurs without the Ni- or Pd-based catalyst. The use of NaDMM is essential for a reasonable activity.
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