Solvent-Free Carbon-Carbon Bond Formations in Ball Mills

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Abstract: Ball milling has been applied in numerous solvent-free carbon-carbon bond formations. In many cases, these transformations proved superior to the analogous reactions performed in solution. The reaction scope involves purely organic addition and coupling reactions, transformations involving metals (in stoichiometric and catalytic amounts) as well as asymmetric organocatalyses.

1 Introduction

The simple use of a mortar and a pestle to mix reagents can be useful in order to perform organic reactions under solvent-free conditions.[1,2] However, for a more efficient and automated mixing more sophisticated instrumentation has been developed. In that context, ball mills appear to be interesting.[3] In inorganic chemistry and material sciences, ball milling is a well-established technique for the grinding of minerals and the preparation and modification of inorganic solids,[4] both at laboratory and industrial scales.[5] It allows the preparation of nanostructured alloys and the synthesis of new materials.[3a,6]

Various types of ball mills are known including (drum) ball mills, jet-mills, bead-mills, vibration ball mills, planetary ball mills and horizontal rotary ball mills.[3] All of these devices are based on the principle that a starting material is placed between two surfaces and crushed due to impact and/or frictional forces that are caused by collisions between these surfaces. The various mills differ in the method of how the motion causing these collisions is created. Besides the intensive grinding effect, the collisions lead to an energy transfer, which results in an increase of internal temperature and pressure. For achieving better control of these factors, some ball mills have cooling/heating devices. In general, ball mills are able to produce materials with a particle size of ≤ 100 nm.

Whereas in laboratories planetary and vibration ball mills are most commonly used, horizontal rotary ball mills are often found in industrial applications. As all C−C bond formations that are discussed in this review have been performed in one of these three types, they will be briefly described. A planetary ball mill contains a main disk, which can rotate at a high rotational speed and accommodates one to eight grinding bowls. These bowls hold a number of balls as grinding medium and rotate around their own axes in opposite directions relative to the main disc. The rotational speeds are of the order of 100–1000 rpm. Vibration ball mills contain only one or two grinding chambers, which accommodate one or more grinding balls, and it can be shaken at a frequency of 10–60 Hz in three orthogonal directions. Some vibration ball mills have cooling/heating systems, which allow a temperature control while grinding. Other terms found in the literature describing the same milling technique are

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high-speed ball milling (HSM), high-speed vibrational ball milling (HSVM), shaker milling or high-energy ball milling. Horizontal rotary ball mills have the advantage that they can be operated at a high relative velocity of the grinding medium (up to 14 m s^{-1}) that

cannot be reached by other types (up to 5 m s^{-1}).[7] Furthermore, they allow the use of closed circuits and controlled conditions such as vacuum or inert gas. In this type of ball mill a horizontally arranged rotor inside the grinding vessel accelerates the grinding

medium. Thus, an advantage of this device is that it only moves reactants and balls, but not the large masses of the containers as the other mills. These ball mills are especially interesting for industrial applications being available with a grinding chamber capacity of 0.5–400 L and allowing rotation frequencies of up to 1800 rpm as well as control of the reaction temperature by cooling or heating devices. In all three cases, grinding medium and vessels are usually made of chemically inert and non-abrasive material such as hardened steel, tungsten carbide, zirconia, etc.

In chemical synthesis, ball milling modifies the conditions under which a chemical reaction commonly takes place. Generally, there are two possibilities. Either the modification is accomplished by changing the reactivity of the reagents (mechanical activation) or by inducing chemical reactions *via* mechanical breaking of molecular bonds during milling (mechanochemistry).[3b,8] Since none of the C−C coupling reactions dealt with in this review is based on mechanochemical processes, we will exclusively discuss transformations induced by mechanical activation.

Changes in reactivity during ball milling (compared to conventional methods) can mainly be ascribed to the more efficient mixing and the enormous increase of the reagents' surfaces. Both lead to a close contact between the starting materials on a (almost) molecular scale, leading to a reactivity increase. However, other factors such as the increased temperature and pressure can also lead to a change of reactivity. While milling, some extreme conditions occur on the external surfaces of two colliding bodies only for times in the order of microseconds. Although the ball milling process is extremely complicated and not fully understood yet,[9] a model developed by Urakaev and Boldyrev[10] permits one to estimate the magnitude of the extreme shifts in temperature and pressure during this short time scale. Thus factors such as the rotational frequency of the mill, the milling time, the radius of the vessel, size, weight and number of balls, weight and heat capacity of the material, etc. have to be taken into account in order to estimate the energy transfer onto the material, the local, temporary, extreme conditions and the overall rise in temperature and pressure during ball milling. According to this model, local temperatures of 400–1500 K and local pressures of some thousand atmospheres can characterize typical extreme conditions in the ball mill.[10] Especially in the field of material science ball milling has gained importance as these short-time extreme effects allow the generation of metastable phases under macroscopically very mild conditions. Many examples are known where materials that usually require high temperatures (e.g. >800 °C) and pressures to be formed can be synthesized with much less additional heating under ball milling conditions. As a result of

these local effects in the absence of temperature control, one can expect that the average temperature in a ball mill typically rises by approximately 40–60 °C. Without taking the described complex processes into account, ball mills are commonly operated by controlling the average temperature through the application of cooling devices and the local effects roughly through the choice of the rotational speed, time of milling and pause periods, material sizes, weight and number of balls, etc. When using a ball mill without temperature control, breaks (pause periods) during the milling process can help to keep the temperature at a reasonable level.

Ball milling in organic chemistry is less common, and generally it has been applied with the goal to affect highly efficient mixing of reagents under solvent-free conditions. This issue is particularly important in reactions between solids.[11,12]

In a more detailed description, solvent-free reactions can be categorized into three classes: 1) reactions between solids (solid state reactions), 2) reactions between solids with intermediate local melting, and 3) reactions with at least one liquid reagent. The first type benefits the most from a performance under ball milling conditions, which relates to the mechanism of solid state molecular reactions, as recently elucidated by atomic force microscopy (AFM), scanning near-field optical microscopy (SNOM) and grazing incidence diffraction (GID) studies.[11c,12,13] Thus, the successful progression of three different stages is a requirement for a solid state reaction to proceed. First, the crystal lattice must allow for long-range anisotropic molecular migration to form crystal-correlated surface features in a phase rebuilding step.[14] Second, the product lattice must form with a reasonable rate in a phase transformation step. And third, the crystal disintegration step (with formation of the product crystal structure) must provide a fresh surface of the reacting crystals. Thus, solid-solid reactions require continuous fresh contact between the reacting solids, which can more efficiently be achieved by milling , rather than by grinding or sonicating (especially for large-scale reactions).[12]

Importantly, the three-step phase rebuilding solid state mechanism avoids a decrease of reactivity by solvation (as it occurs in solution or melts) and additionally benefits from the crystal packing that leads to a regular self-assembled alignment and approach of the reacting molecules.[5] Consequently, the kinetics of solid state reactions are favorable and melt reactions suffer more often from side reactions. Noteworthy is also that all types of solvent-free reactions take advantage from the high concentrations of the reagents.

The aim of this review is to give an overview on the application of the ball milling technique for the performance of C−C bond forming reactions[15] and especially to demonstrate the potential of the ball milling

methodology in situations where it modifies the behavior in terms of selectivity and reactivity.

2 Metal-Free Transformations

2.1 Aldol Condensations

The aldol condensation reaction is widely used in synthetic organic chemistry to obtain α,β-unsaturated carbonyl compounds.[16] The reaction can be performed in the presence of a simple acid or base catalyst, but usually it is carried out with preformed enolates in order to reach high conversions and good chemoselectivity.

In 1990, Toda and co-workers conducted a comparative study in order to investigate if the reaction is more efficient when performed in the absence of any solvent.[17] For the reaction under solvent-free conditions, the starting materials were ground by pestle and mortar in the presence of a stoichiometric amount of NaOH. These studies showed that, in most cases, the condensation proceeded more efficiently and stereoselectively in the absence of any solvent than in solution. For example, the reaction between *p*-methylbenzaldehyde and acetophenone to give the corresponding condensation product proceeded with 97% yield when performed under solvent-free conditions. In contrast only 11% yield was observed when the reaction was performed in solution following standard reaction conditions. More recently, Li and co-

workers investigated the crossed aldol condensation of various aromatic aldehydes with cycloalkanones to the corresponding double aldol condensation products under solvent-free conditions also using the grinding method.[18] As in the previous work by Toda, the solvent-free condensations proceeded with higher yields, under milder reaction conditions and allowed an easier work-up than the corresponding reactions that were performed in solution (using either a heating method[19] or conventional stirring).[18]

In agreement with these results, Raston and Scott reported highly chemoselective direct aldol condensations between solid aldehydes and ketones, as well as between solid ketones, under solvent-free conditions using a ball mill (Scheme 1).[20] The solid reagents were simply ground together in a vibration ball mill in the presence of solid NaOH for a total of two minutes over a ten-minute period, allowed to stand overnight and subsequently washed with a dilute aqueous acid solution. This protocol did not require the use of preformed enolates, and the employment of organic solvents was kept at a low level as it was restricted to product recrystallization. However, in order to obtain crystalline products of high purity in good yields, an alternative work-up including an extraction procedure (using an organic solvent) proved to be superior. These aldol condensation reactions proceeded at ambient temperature and afforded the corresponding single crossed products in high yields and chemoselectivities, even in those reactions where a mixture of products was possible.
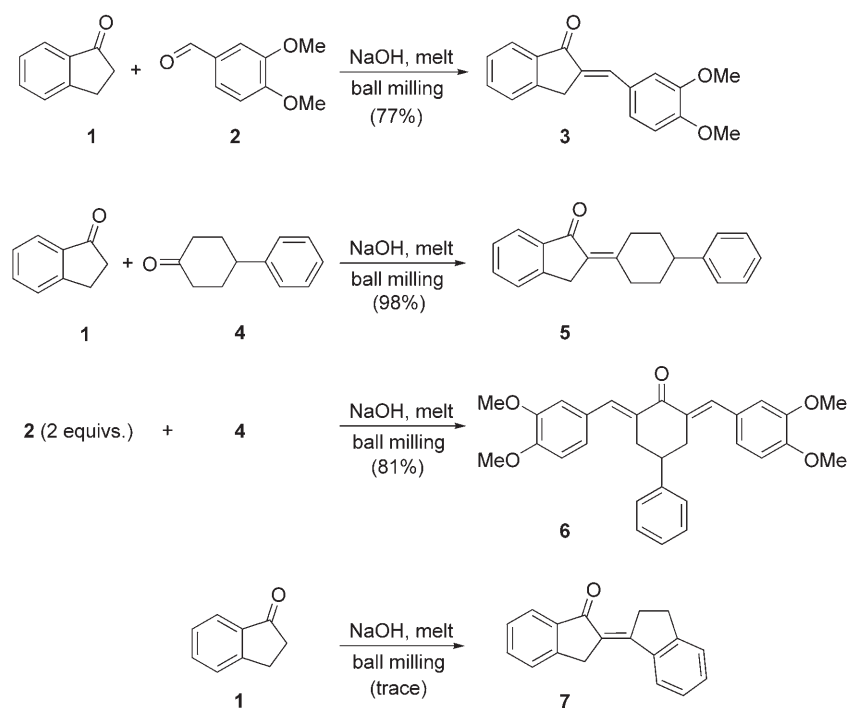
Scheme 1. Solvent-free aldol condensations.

The solids **1**, **2** and **4** were reacted in various combinations in the ball mill under solvent-free conditions. For comparison, all reactions were also carried out in absolute ethanol according to the method of Wattanasin and Murphy.[21] Although combinations of **2** and **4** or **1** and **4** could lead to more than one condensation product, under solvent-free conditions only single products were obtained. The complete chemoselectivity of the reaction under ball milling conditions is particularly noteworthy as it is contrary to that of the corresponding reaction in solution, where a complex mixture of products resulted. Scott and co-workers assumed that this difference in chemoselectivity, which was also observed by Toda, may be explained by the different solibility of the product in the respective reaction medium. It was observed that grinding the carbonyl compounds prior to addition of NaOH yielded in each case a viscous liquid, which solidified during the course of the reaction. From a continuous study examining many substrate combinations, it was concluded that a reaction is only observed in those cases where a phase change occurs and, hence, the existence of a liquid phase is a prerequisite for reaction in these systems.[22] Consequently, under solvent-free conditions the reaction seems to take place in a eutectic mixture of the reagents with a melting point lower than the ambient temperature. The liquid mixture of the reagents yields a solid product that crystallizes from this "reaction solution" as the reaction proceeds. It is assumed that, as the product is insoluble in the reaction medium, it is effectively removed by this change in phase driving the reaction to completion and causing the aldol condensation to be irreversible under these conditions, unlike comparable reactions in solution. Because of the lower acidity of the α-hydrogen atoms of 4-phenylcyclohexanone (**4**) relative to **1**, no products due to the attack of 4-phenylcyclohexanone carbanions are formed. Another advantage of the solvent-free aldol condensation, especially with regard to industrial applications, is that the intermediates formed by grinding together the two carbonyl compounds and the base catalyst may be stored, prior to work-up, without protection from light, oxygen or moisture for months without an impact on the product quality.

Other examples of aldol condensations performed in a vibration ball mill (20–25 Hz) were reported by Kaupp and co-workers, namely waste-free quantitative condensation reactions using ninhydrin (**8**).[23] As its melting point is quite high, these reactions take place in the solid state. The aldol-like condensation of ninhydrin (**8**) with dimedone (**9**) proceeded as a single-step condensation to provide product **10** in quantitative yield (Scheme 2). No further dehydratization was observed even in the presence of gaseous trimethylamine, hydrogen chloride or *p*-toluenesulfonic acid. The reaction in solution produces waste
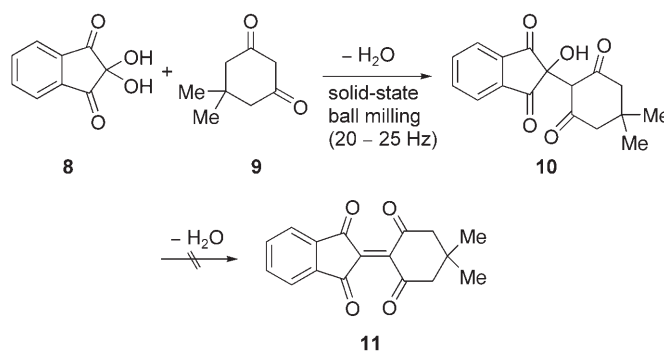

Scheme 2. Quantitative uncatalyzed condensation of ninhydrin with dimedone.

due to lower yields (96% crude, 82% after recrystallization) and work-up requirements,[24] unlike the more sustainable solid state reaction, which proceeds with a quantitative yield. The second elimination step of water to product **11** can be achieved, for instance, in solution using anhydrous dioxane with trifluoroacetic anhydride and pyridine.

2.2 Asymmetric Aldol Reaction Catalyzed by (*S*)-Proline

The proline-catalyzed intermolecular aldol reaction is a well-studied and efficient C−C bond forming reaction, which proceeds *via* enamine intermediates generated *in situ*, thus affording products with high chemo- and stereoselectivity under very mild conditions.[25] With the vision that such metal-free reactions could benefit from the inherent solvent-free conditions of the ball milling technology, Bolm and co-workers recently initiated a program that studied a combination of both approaches.[26] While the reaction has been usually conducted in highly polar solvents, such as dimethyl sulfoxide (DMSO), only few examples of organocatalytic aldol reactions performed in the absence of a solvent could be found in the literature.[27,28] In these examples, high yields and acceptable stereoselectivities could only be achieved with an excess of liquid ketone (≥3 equivalents) which, in most cases, appears to act as both reactant and reaction medium. However, a solvent-free approach using close to equimolar mixtures of reactants had not been studied.
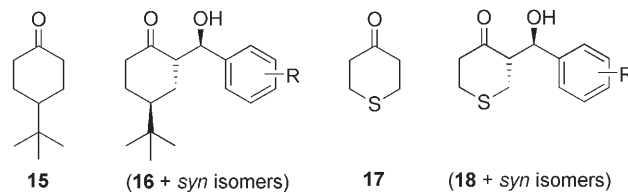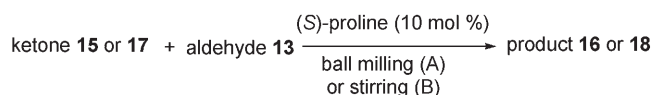
In their study, Bolm and co-workers described that, under solvent-free conditions, an efficient mixing method was vitally important to achieve high yields. In this respect, conventional magnetic stirring appeared insufficient. This limitation could be easily overcome by means of a planetary ball mill (250–400 rpm).[26] In order to keep the temperature rise at a low level, breaks were included during the milling process. The solvent-free ball milling conditions al-

Table 1. The asymmetric aldol reaction under solvent-free conditions.[26]
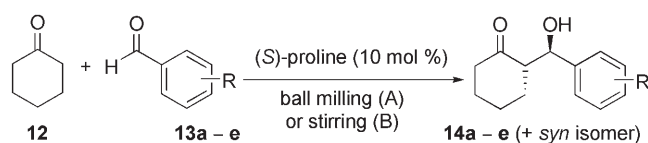
Entry	13/14	R =	Method	t [h]	Yield [%]	anti/syn	ee [%]
1	a	4-NO$_2$	A	5.5	99	89:11	94
2	a	4-NO$_2$	B	24	95	89:11	94
3	b	3-NO$_2$	A	7	94	88:12	>99
4	b	3-NO$_2$	B	16	89	82:18	98
5	c	2-NO$_2$	A	7	97	93:7	97
6	c	2-NO$_2$	B	36	89	91:9	97
7	d	4-Cl	A	20	87	74:26	75
8	d	4-Cl	B	72	85	78:22	67
9	e	2-MeO	A	36	65	66:34	63
10	e	2-MeO	B	96	64	71:29	67

Table 2. The asymmetric aldol reaction between solely solid reactants.[26b]

Entry	Ketone	13/16/18	R =	Method	t [d]	Yield [%]	anti/syn	ee [%]
1	15	a	4-NO$_2$	A	1.4	85	91:9	91
2	15	a	4-NO$_2$	B	5	58	93:7	89
3	15	b	3-NO$_2$	A	1	80	78:22	92
4	15	b	3-NO$_2$	B	5	82	92:9	95
5	15	c	2-NO$_2$	A	1	66	81:19	88
6	15	c	2-NO$_2$	B	6	76	77:23	92
7	15	d	4-Cl	A	1.6	75	92:8	93
8	15	d	4-Cl	B	7	85	87:13	93
9	16	a	4-NO$_2$	A	1.4	79	96:4	90
10	16	a	4-NO$_2$	B	7	47	98:2	96
11	16	b	3-NO$_2$	A	1.5	75	88:12	89
12	16	b	3-NO$_2$	B	7	59	93:7	96
13	16	c	2-NO$_2$	A	1.5	59	82:18	96
14	16	c	2-NO$_2$	B	6	73	93:7	98
15	16	d	4-Cl	A	1.4	72	95:5	85
16	16	d	4-Cl	B	7	77	99:1	82

lowed a highly efficient catalysis to occur, even when solely solid reagents were employed. In all cases, the use of simple (unmodified) (S)-proline (10 mol%) and nearly stoichiometric amounts of ketone and aldehyde (1.1:1) led to the formation of *anti*-aldol products in high yields (up to 99%) with excellent stereoselectivities (up to >99% ee, Table 1). In a comparative study using conventional magnetic stirring, the aldol products were stereoselectively obtained in high yields as well, but the reactions proceeded much more slowly, highlighting the advantage of the ball milling technology.

The generality of the organocatalytic aldol reaction in a ball mill was examined by varying the substrate combinations. In reactions with cyclohexanone, aldehydes with electron-withdrawing substituents afforded products with high stereoselectivities in short reaction times (**14a–c**). More electron-rich groups, however, resulted in lower reactivity and stereoselectivity (**14d** and **14e**). Noteworthy is the fact that the above-mentioned trends of the electronic effects and the dependence of the stereoselectivity on the substrate structure are analogous to those observed in aldol reactions under alternative reaction conditions (e.g., in organic or aqueous solvents and solvent-free conditions). When the same reaction conditions were applied to reactions between solely solid reagents, the *anti*-aldol products **16a–d** and **18a–d** were also obtained with both excellent diastereoselectivities (up to 99:1 *anti/syn* ratio, **18d**, Table 2 and enantioselectivities (up to 98% ee, **18c**). Presumably due to a more difficult mixing in the solid-solid system the reactions proceeded much slower than in the liquid-solid one. However, in agreement with the results achieved in the previous case, in all these reactions between solely solid reagents the application of a mechanical technique was particularly useful. Thus, by means of ball milling,

high conversions were achieved in relatively short times (≤ 1.6 days), in comparison to the use of conventional magnetic stirring (5–7 days).

2.3 Knoevenagel Condensations

The Knoevenagel condensation of aldehydes with active methylene compounds is an important C–C bond forming reaction that provides access to α,β-unsaturated compounds.[29] This reaction usually requires the presence of a base, Lewis acid or a surfactant as catalyst. In recent years, solvent-free Knoevenagel condensations have been developed that take place on solid supports and are promoted by microwave[30] or infrared irradiation.[31] Unfortunately, reactions under these latter conditions do not proceed quantitatively and solvents have to be used for the extraction of the product from the solid supports or catalyst and for the work-up. Additionally, grinding of the reaction mixture in a mortar with a pestle proved to be an efficient method for the Knoevenagel condensation under solvent-free conditions.[32] The disadvantage of this method is that it is not applicable for slow reactions and/or large-scale synthesis.

In 2003, Kaupp and co-workers reported that the use of a more efficient grinding method, the applica-
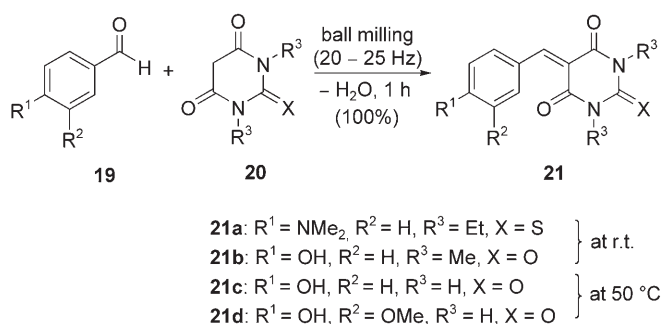
Scheme 3. Quantitative uncatalyzed Knoevenagel condensation of aromatic aldehydes with barbituric acids proceeding in the solid state.

tion of a ball mill, allowed the performance of numerous Knoevenagel condensations under solvent-free conditions using only stoichiometric amounts of the starting materials (Scheme 3 and Scheme 4).[33] Compared to the above-mentioned methods, the most important advantage was that when pure reactants were used the products were always obtained in quantitative yields and a work-up was not required. Consequently, these reactions were completely solvent-free, atom economic and sustainable and no waste was produced. The Knoevenagel condensations were performed either as solid state reactions (Scheme 3) or as melt reactions (Scheme 4) with direct crystallization of the product at the reaction temperature.[34] After 1 h of grinding in a vibration ball mill (20–25 Hz), the desired products were isolated in quantitative yields. The water of the reaction did not interfere as it was taken up by the crystals and removed by evaporation.

The synthetic potential of the ball milling method in Knoevenagel condensations was also shown by scaling-up the synthesis of **21b** and **21c** to stoichiometric 200-g batches in a 2-L horizontal ball mill (15–20 Hz).[5,33] In the former case, water cooling was necessary to keep the temperature at 14–20 °C, whereas in the latter case the reaction was performed without cooling allowing the average temperature of the reaction mixture to rise, but not exceeding 50 °C. In both cases the Knoevenagel condensation product was obtained in quantitative yield.

In the case of the Knoevenagel reaction between aldehyde **13** and cyanoacetamide (**25**) (Scheme 5) an alternative procedure was reported.[33] This solid state reaction was too slow at room temperature and required the presence of a basic catalyst. Thus, both reagents were ball-milled in a vibration ball mill (20–25 Hz) for 10 min and the resulting powder was then treated with trimethylamine (1 bar) for 24 h at room temperature. The catalyst could easily be removed together with the newly formed water of the reaction. Alternatively, the uncatalyzed condensation could be performed as a melt reaction at 150–170 °C for 1 h (without ball milling). Both procedures delivered the product **26** in quantitative yield, and a work-up was not required. Also the reactions of aldehydes **13** with malononitrile (**27**) or methyl cyanoacetate (**28**) to give condensation products **29** and **30**, respectively, did not proceed in the solid state at room temperature. In these cases performing the reactions uncatalyzed as melt reactions at 150–170 °C for 1 h (without ball milling) was the method of choice affording the corresponding products in quantitative yields.

The electron-poor alkenes **23**, **24**, **26**, **29** and **30** were suitable starting materials for Michael additions. For example, it was shown that **29** and dimedone (**9**) reacted quantitatively upon ball-milling at 80 °C followed by heating of the resultant powder to 100 °C to furnish the corresponding Michael adduct (Scheme 6).[12,33] After rearrangement and cyclization, compounds **31** were obtained in quantitative yield.

Suzuki and co-workers applied the ball milling technology to the Knoevenagel condensation of malononitrile (**27**) and methyl cyanoacetate (**28**) with various aldehydes under solvent-free conditions
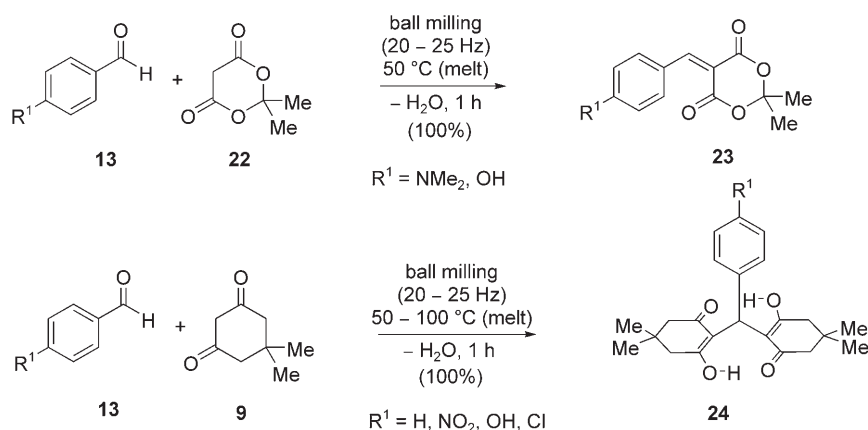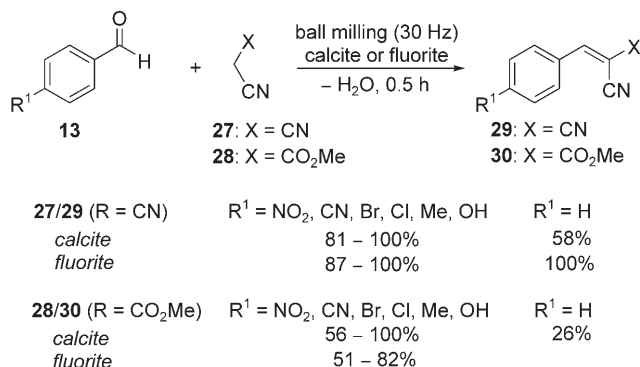

Scheme 4. Quantitative uncatalyzed Knoevenagel condensations proceeding in stoichiometric melts.
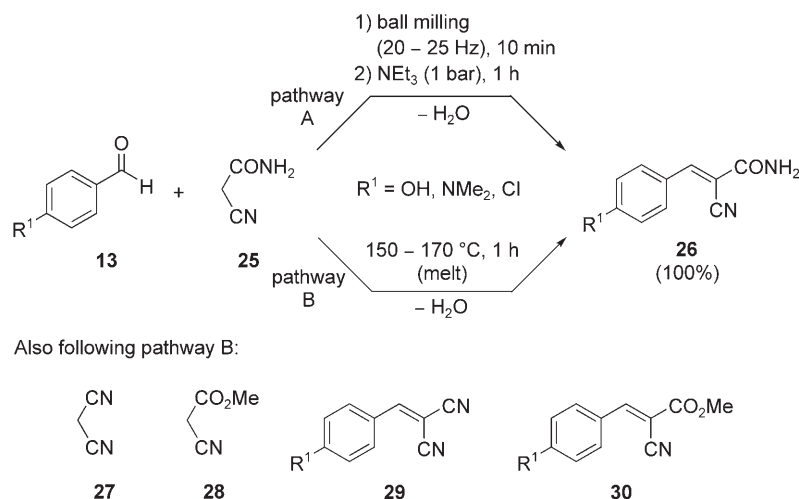
Scheme 5. Quantitative Knoevenagel condensations proceeding either in the solid state or in a melt.
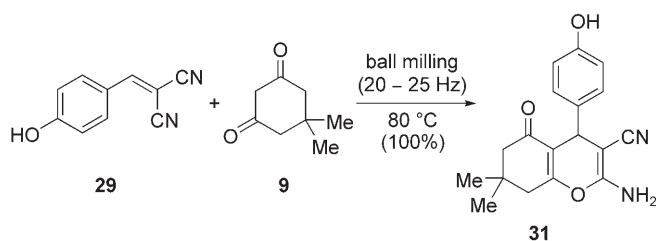
Scheme 6. Quantitative three cascades of alkene **29** with dimedone (**9**) including Michael addition, followed by rearrangement and cyclization.


Scheme 7. Knoevenagel condensations catalyzed by the minerals calcite or fluorite.

(Scheme 7).[35] In their study, the rock minerals calcite (CaCO₃) and fluorite (CaF₂) were employed as catalysts, allowing the reaction to be performed at room temperature in the solid state. Consequently this procedure represents an alternative to the ball milling-free and uncatalyzed variant of Kaupp, which proceeded in stoichiometric melts and required reaction temperatures of 150–170 °C (Scheme 5). Although

these minerals have basic properties, they usually cannot be used as inorganic bases due to their insolubility in organic solvents as well as in water. However, under ball milling conditions (vibration ball mill, 30 Hz) both minerals proved effective as mild catalysts for the Knoevenagel condensation. After only 0.5 h of milling in the presence of calcite or fluorite, malononitrile and methyl cyanoacetate readily underwent Knoevenagel condensation with aromatic aldehydes. The corresponding condensation products were obtained in good to excellent yields (Scheme 7). As the reaction vessel was not air-tight, in the case of benzaldehyde and p-tolylaldehyde the addition of a catalytic amount of hydroquinone was necessary to prevent oxidation. Interestingly, when reagent-grade calcium carbonate or fluoride in the form of a fine powder was used, the reaction did not proceed satisfactorily. Therefore the authors assumed that, in order to deprotonate the active methylene compound, the presence of naked ionic species was required. Besides mixing the reagents, the main function of the ball mill is to generate these species *in situ* by crushing the minerals and opening newborn reactive solid surface sites thereby.

By using a vibration ball mill (30 Hz), Wang and co-workers found an elegant way to perform cascade reactions consisting of a Knoevenagel condensation, followed by hydrogenation under solvent-free conditions (Scheme 8).[36] The one-pot reductive benzylization of malononitrile by aromatic aldehydes using the Hantzsch 1,4-dihydropyridine as reductant proceeded almost quantitatively when aldehydes bearing electron-withdrawing groups were employed. Just as in the mineral-catalyzed Knoevenagel condensation, this cascade reaction exhibited a significant substituent effect. When benzaldehyde was used, the desired product was formed with only 68% yield, while the less reactive 4-*N,N*-dimethylaminobenzaldehyde did
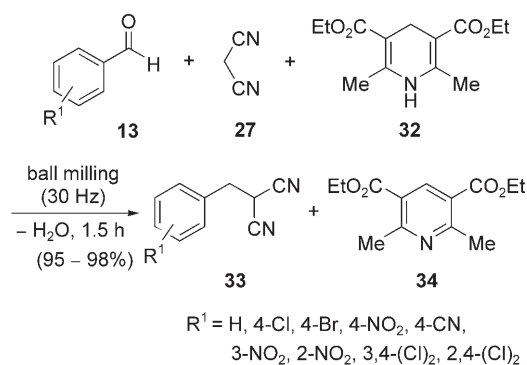
Scheme 8. One-pot reductive benzylizations of malononitrile by aromatic aldehydes using a Hantzsch 1,4-dihydropyridine as organoreductant. [Alternatively, after treatment of the crude product with aqueous HCl (5%) under ultrasonic irradiation followed by filtration, washing with H_2O and drying the yield was reduced to 54–87%].

not react at all. The Hantzsch 1,4-dihydropyridine acts in two different ways: as the reductant and as base catalyst for the Knoevenagel condensation. The application of a ball mill in this cascade reaction was demonstrated to have many advantages. First, a separation of the *in situ* generated benzylidenemalononitriles was not necessary. Second, the reaction could be performed under solid state conditions at room temperature without addition of another base. Third, as the reaction time was relatively short (90 min), 1.02 equivs. of Hantzsch 1,4-dihydropyridine were enough to promote the reaction completely, even in the presence of air. Fourth, the use of an organic solvent was only required during the work-up (Method A). It could be avoided completely when an aqueous work-up was accomplished (Method B), albeit involving a significant decrease in yield. Furthermore, the reduction proceeded with complete chemoselectivity and other functional groups, such as carbonyl, cyano or nitrogroups, were not affected.

2.4 Baylis–Hillman Reaction

The Baylis–Hillman (also known as Morita–Baylis–Hillman) reaction,[37] is an atom-economic transformation that typically involves the reaction between an electron-deficient alkene, an electrophile (usually an aldehyde) and a tertiary amine as catalyst, yielding highly functionalized products. One of the main drawbacks of this powerful C–C bond forming reaction is its slow reaction rate. Thus, the Baylis–Hillman reaction typically requires days to weeks for completion depending on the reactivities of both the activated alkene and the electrophile.

The observation that ball milling facilitates chemical reactions, prompted Mack and Shumba to investigate the Baylis–Hillman reaction under these condi-
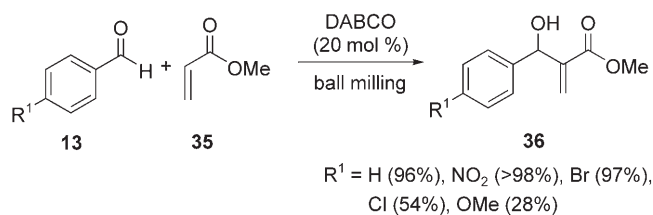

Scheme 9. The Baylis–Hillman reaction in a ball mill.

tions.[38] For this study (Scheme 9), reactions between various *p*-substituted aromatic aldehydes **13** and methyl acrylate (**35**) in the presence of 20 mol% of 1,4-diazabicyclo[2.2.2]octane (DABCO) were performed in a vibration ball mill (max. 60 Hz). A previous report had shown that the reaction between *p*-nitrobenzaldehyde and methyl acrylate with catalytic amounts of DABCO at room temperature takes between 3 and 4 days to obtain the desired product in good yields (70–87%).[39] In contrast, the use of a HSM led to a significant rate enhancement generating the product (**36** with R=NO$_2$) in more than 98% yield in only 0.5 h. However, in the ball milling procedure the temperature was neither controlled nor was it reduced by including breaks into the 0.5 h ball milling time. It may therefore be assumed that the temperature increased significantly during the course of the reaction.

2.5 Michael Reaction

Wang and co-workers described in 2004 the first Michael addition reaction of 1,3-dicarbonyl compounds to α,β-unsaturated ketones catalyzed by K_2CO_3 under solvent-free conditions.[40,41] Hitherto, this reaction was frequently catalyzed by strong bases which often caused some side reactions.[42] Although the use of weaker bases improved the yields, in general longer reaction times or a tedious work-up were required. To circumvent these problems, Wang and co-workers studied the Michael reaction under solvent-free conditions using a vibration ball mill (60 Hz).[40,41] In this manner, only catalytic amounts of a weak base were required to promote the solvent-free Michael reaction
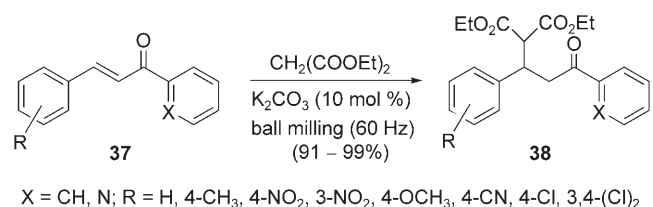
Scheme 10. Michael addition of diethyl malonate to chalcones **37** catalyzed by 10 mol% of K_2CO_3 under the ball milling conditions.
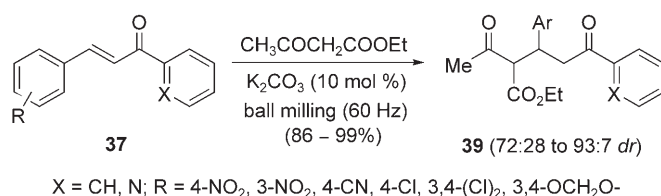
of diethyl malonate with various chalcones and aza-chalcones **37** (Scheme 10).[40] While strong bases such as KF/Al$_2$O$_3$ or NaOH (either in catalytic or stoichiometric amount) showed poor product selectivity, using only 10 mol% of K$_2$CO$_3$, the desired products **38** were isolated in excellent yields after short reaction times (10–60 min). In most cases (with yields of 98–99%), essentially pure products were obtained after washing the reaction mixture with water. In other cases (applying substrates with R = 4-OCH$_3$, 4-Cl) an additional purification by column chromatography was necessary.

Applying this same protocol, Wang and co-workers also described the solvent-free Michael addition of ethyl acetoacetate to chalcones **37**, in which the diastereoselectivity of the reaction was analyzed (Scheme 11).[41] In the presence of 10 mol% of K$_2$CO$_3$, after only 20–40 min, the desired products **39** were again obtained in good to excellent yields (up to 99%) and with high diastereoselectivity in favor of the *anti* diastereomer (up to 93:7 dr).
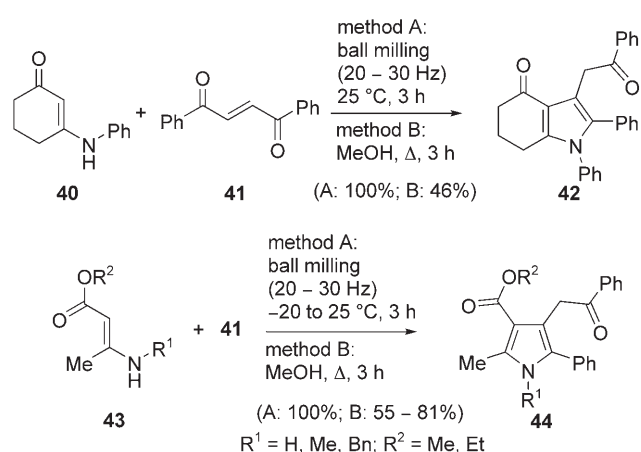
Compared with previously reported methods, the main advantages of the described procedure were milder conditions and shorter reaction times, which may help to avoid side reactions, and thus resulting in high chemoselectivities and quantitative yields. As the described Michael reactions required a high vibration frequency (60 Hz) to proceed nearly quantitatively in such short reaction times, it can be concluded that temperature and pressure effects created by the high vibration speed (3500 rpm) were crucial for the success of this procedure.

2.6 Vinylogous Michael Addition in Cascade Reactions

In 1999, Kaupp and co-workers presented an elegant one-pot, multistep synthesis of highly substituted indole **42** and pyrroles **44** by treating keto-enamine **40** or primary and secondary enamine esters **43** with *trans*-1,2-dibenzoylethene (**41**), either in solution or in a heatable/coolable vibration ball mill (Scheme 12).[43] After 3 h of reflux in methanol, the four-step reaction gave the products in only moderate yields (46–81%). However, all desired products were isolated in quanti-
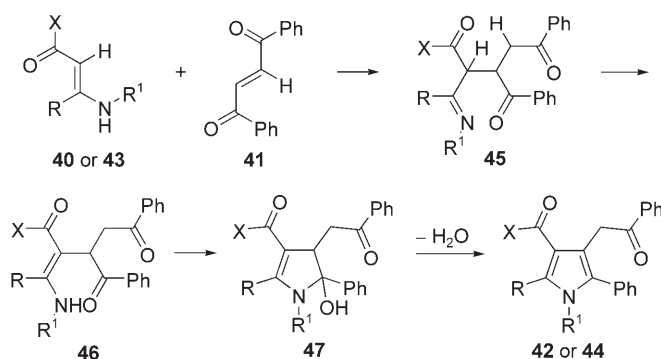
Scheme 12. "One-pot" synthesis of the indole **42** and pyrrole derivatives **44** from easily accessible starting materials.

tative yields when the solid-solid reaction was performed in the ball mill at temperatures from −20 to +25 °C. In these experiments, the solid reagents and a ball were placed in a 10-mL grinding jar (both made of stainless steel), which was then vibrated at 20–30 Hz for 3 h.

This complex cascade reaction is remarkable in view of its high selectivity, by which the C−C showed to be largely preferred over any N−C bond formation reaction. The authors proposed a reaction course by four sequential steps as formulated in Scheme 13. After an initial vinylogous Michael addition (including hydrogen transfer) to give imine **45** and imine/enamine tautomerization affording **46**, the newly formed amino group adds to the more favorably situated carbonyl function leading to the formation of a five-membered ring (intermediate **47**), from which the desired pyrrole was obtained by elimination of water.

Both the chemoselectivity and the same preference in solution and in the solid state reactions were remarkable. (An initial Michael addition of the enamine
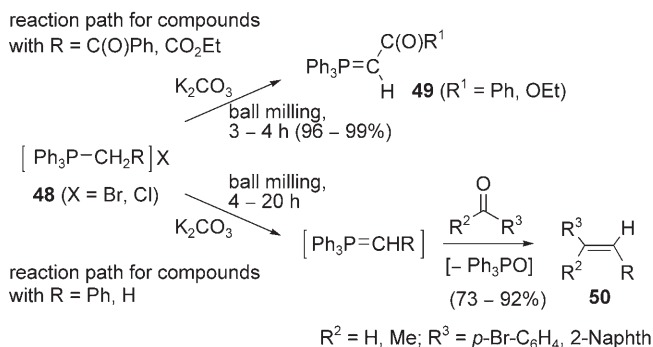
X = CH, N; R = 4-NO$_2$, 3-NO$_2$, 4-CN, 4-Cl, 3,4-(Cl)$_2$, 3,4-OCH$_2$O-

Scheme 11. Michael addition of ethyl acetoacetate to chalcones **37** catalyzed by 10 mol% of K$_2$CO$_3$ under ball milling conditions.

Scheme 13. Sequential steps proposed for the cascade reaction to give the indole-type compound **42** or pyrrole derivatives **44**.

nitrogen, cyclizing addition of the enamine double bond, rearrangement to the enamine, and elimination of water would have exchanged the positions of phenyl and benzoylmethyl groups in the final products.) Noteworthy is that by means of a coolable ball mill the reactions in the solid state could be performed at much lower temperatures than those in solution. Presumably owing to these milder reaction conditions, the ball milling variant afforded all products in quantitative yields.
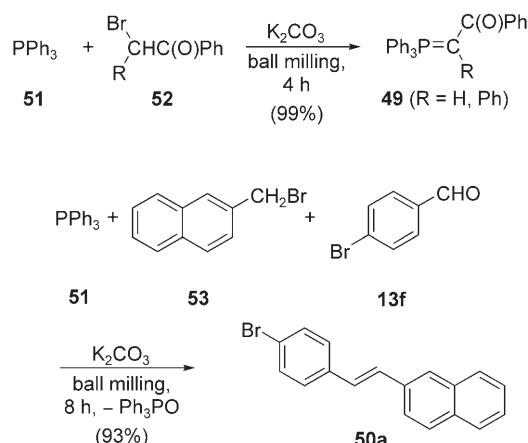
2.7 Wittig Reaction

The Wittig reaction is one of the most versatile synthetic methods for the preparation of olefins from carbonyl compounds.[44] Conventionally, phosphorus ylides are prepared in solution,[45] but in general long reaction times, in particular for stabilized ylides, are required.[46] With the aim to overcome this limitation, Balema, Pecharsky and co-workers reported for the first time the formation of phosphorus ylides under solvent-free conditions.[47] By means of a vibration ball mill (max. 60 Hz), the authors showed an elegant, efficient and easy way to generate in the solid state three major types of phosphorus ylides (stabilized, semi-stabilized and non-stabilized phosphoranes). In their work, stabilized ylides were prepared in nearly quantitative yields after 3–4 h and isolated in a pure form, by ball milling the corresponding solid phosphonium salts with an excess of anhydrous K_2CO_3 in a hardened-steel vial with steel balls under helium (Scheme 14). On the other hand, semi-stabilized and non-stabilized phosphoranes were trapped by a solid organic carbonyl compound and transformed into ethenes and triphenylphosphine oxide in a solvent-free Wittig-type reaction. In the former cases, the more thermodynamically stable *E*-substituted products were formed preferably.

The authors also showed that the mechanical preparation of stabilized phosphorus ylides **49** and olefins **50** (by subsequent solvent-free Wittig reaction) can be
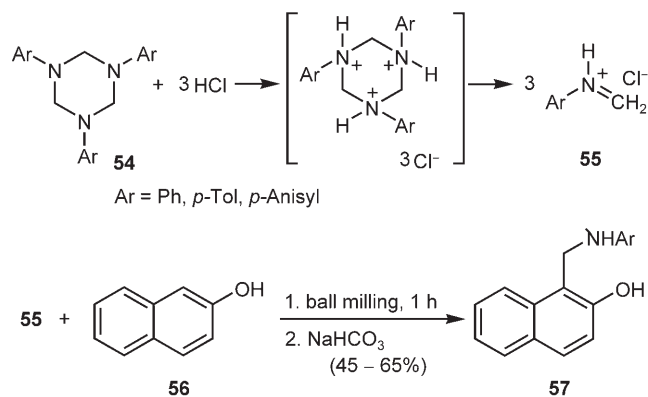

Scheme 15. "One-pot" synthesis of phosphoranes **49** and olefin **50a** in a ball mill.

successfully carried out as a "one-pot" process (Scheme 15). Thus, the desired products could be easily obtained in nearly quantitative yields by ball milling mixtures of triphenylphosphine (**51**), an organic halogenide (**52** or **53**) and a carbonyl compound (such as **13f**) in the presence of K_2CO_3.

2.8 Arylaminomethylation of Iminium Salts

Another example of a metal-free C−C bond forming reaction performed in the ball mill is the arylaminomethylation reaction. In 2000, Kaupp and co-workers described numerous reactions with iminium salts that could be performed quantitatively in the gas-solid or solid-solid phase.[48] Gas-solid reactions of easily available hexahydro-1,3,5-triazines **54** with HCl provided a versatile access to extremely hydrolyzable solid *N*-arylmethyleneimine hydrochlorides **55**. These were then used in arylaminomethylations of β-naphthol (**56**) in a ball mill. After 1 h milling and subsequent base treat-

Scheme 14. The solvent-free preparation of phosphoranes **49** and Wittig products **50** in a ball mill.

Scheme 16. Arylaminomethylation of β-naphthol in a ball mill.

ment of the resulting HCl salts, the corresponding phenylaminomethylnaphthols **57** were obtained in good yields (Scheme 16). Although the authors did not extend the scope of the reaction to other substrates, these initial results appear very promising for further applications of imine hydrochlorides **55** in arylaminomethylation reactions under ball milling conditions.

2.9 Fullerene Cycloadditions

Since the discovery of fullerenes in 1985,[49] great progress has been made in their functionalization affording compounds which are potentially useful for hydrogen storage, optoelectronics and molecular devices.[50] One of the major obstacles for organic functionalization and characterization of fullerenes is their extremely low solubility in organic solvents. Thus, fullerene polymers have been prepared, for example, under photochemical[51] or high temperature/pressure conditions.[52] Recently, it has been found that fullerenes can be reacted in the solid state utilizing vibration ball milling, which offers new possibilities for studying their reactivity.[53]

2.9.1 Fullerene [2+2] Cycloadditions

High temperature/pressure conditions have been used to prepare fullerene polymers by [2+2] cycloadditions.[51,52] To stop the reaction at the dimer or trimer stage is difficult and, commonly, mixtures of products result. In 1997, however, Komatsu and co-workers found that mixing of C_{60} (**58**) and KCN (20 equivs.) in a vibration ball mill (50 Hz, 30 min) led to dumb-bell shaped C_{120} (**60**) in 30% yield (Scheme 17).[53] Interestingly, performing the reaction in the liquid phase

(o-dichlorobenzene/DMF mixture) afforded the cyanated product $C_{60}H(CN)$ (**59**) exclusively.[54] Since the coupling also occurred with catalytic amounts of alkali metals, the authors proposed the reaction to proceed through a fullerene radical anion. Other effective catalysts included potassium salts such as KOH and KOAc, or solid amines.

Ball milling conditions and the use of 4-aminopyridine as catalyst also led to C_{180} trimers (4% yield).[55] Out of the eight possible structures for the linearly connected isomers, four were separated and identified. In addition, "cyclic" trimer **61** was isolated, and *ab initio* calculations showed it to be the energetically most stable one (Figure 1).

Other dimeric fullerene structures including those having the two fullerene cages connected by a single bond and a silicon or germanium bridge could also be prepared under ball milling conditions.[56a,b] Furthermore, C_{60} was reacted with C_{70} to afford the heterocoupled C_{130}.[57]
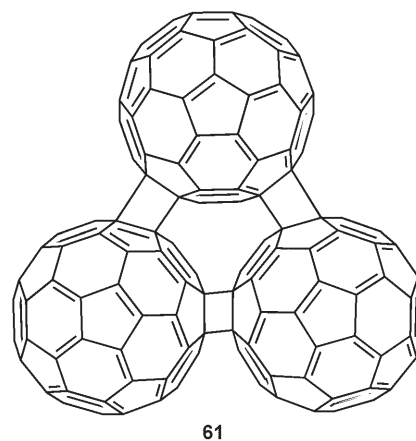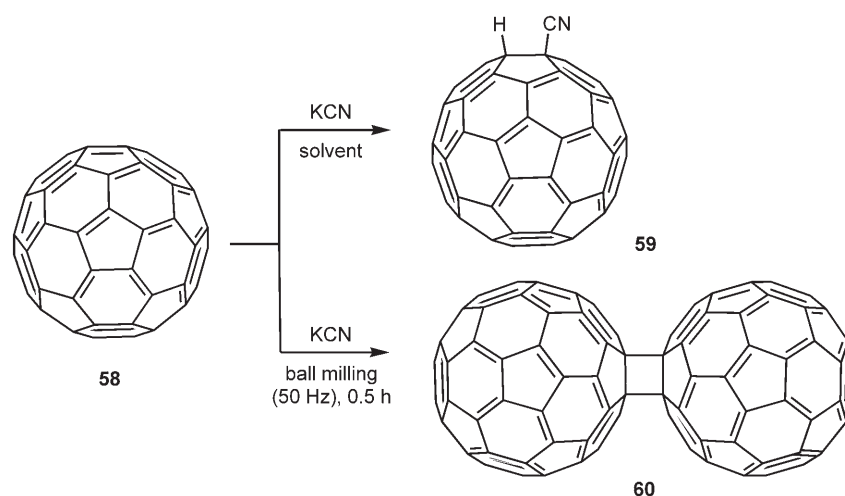

**Figure 1.** The cyclic C_{180} trimer (**61**).

Scheme 17. Dimerization of fullerene C_{60}.

Due to the potential application of fullerenes doped with heteroatoms for hydrogen storage, nitrogen-containing fullerene dimers have been in the interest of Weidinger and co-workers.[58a] Since the starting materials possess only a limited thermal and optical stability, ball milling was chosen as gentle dimerization method. The corresponding hydrogen-doped dimers were later prepared by Komatsu and co-workers.[58b]

2.9.2 Fullerene [4+2] Cycloadditions

[4+2] Cycloadditions have proven very effective for fullerene modifications. In a typical example, C_{60} (**58**) was reacted with anthracene (**62**) in a naphthalene solution at 200 °C for 48 h to give cycloadduct **63** in 39% yield.[59] Other solvents and lower temperatures gave reduced product amounts. Microwave irradiation was also effective, affording **63** in 35% yield.[60] Use of a vibration ball mill (60 Hz) increased the yield significantly, and even after only 1 h a yield of 55% of **63** was obtained.[61] Furthermore, in solution monoadduct **63** was formed exclusively (max. 39% yield), whereas under ball milling conditions a mixture of positional isomers of bisadducts **64** (19% yield) was formed in addition (Scheme 18). A similar behavior was observed in the [4+2] cycloaddition reaction of pentacene, where the monoadduct, bisadduct and the "double C_{60} adduct" were separated in 19%, 15% and 11% yields, respectively. Again, in solution only the monoadduct was observed. As an explanation, the low concentration of C_{60} molecules in solution was proposed. In contrast, in the solid state the molecules
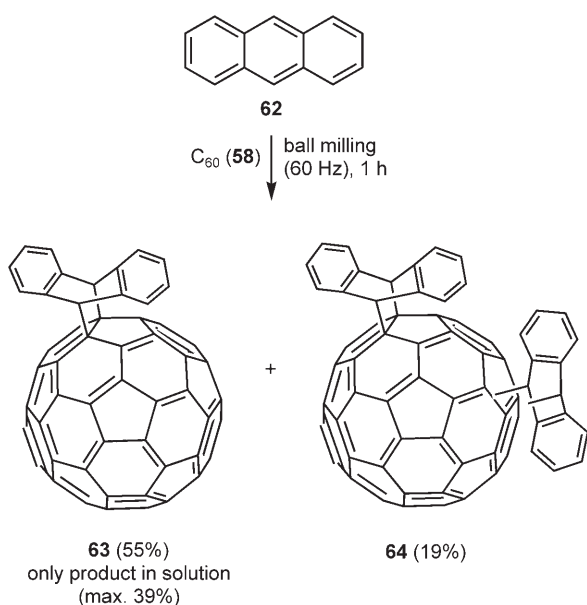
are in close proximity to each other and the probability of a double addition increases.

An example of a cycloaddition where the reaction in solution affords a completely different product than the corresponding solid state reaction, is the [4+2] cycloaddition between phthalazine and C_{60}.[62] In solution, an open-cage fullerene was formed, whereas reaction in a vibration ball mill (60 Hz, 1 h) followed by heating (200 °C, 2 h) led to dimeric bridged **65** as the only compound (in 14% yield; Figure 2) (together with 66% of recovered C_{60}).

The mechanism was proposed to start with a [4+2] cycloaddition of phthalazine, which after nitrogen extrusion gave an *ortho*-quinodimethane type intermediate. A concentration effect was suggested to be the reason for the formation of the different products in solution and in the solid state. Again, in solution the concentration of C_{60} molecules is so low that the intermediate undergoes intramolecular rearrangements. In solid state other C_{60} molecules are present that "trap" this intermediate in an another [4+2] cycloaddition to give **65**. Applying the same ball milling conditions (60 Hz, 1 h) followed by thermal treatment (150 °C, 2 h), a similar reaction conducted with di(2-pyridyl)-1,2,4,5-tetrazine instead of phthalazine afforded novel dimeric fullerenes incorporated in a 2,3-diazabicyclo[2.2.2]oct-2-ene framework.[63]

2.9.3 1,3-Dipolar Cycloadditions of Fullerenes

Methylene bridges can be incorporated into the fullerene skeleton by 1,3-dipolar cycloaddition with ethyl diazoacetates **66** to give a labile fulleropyrazoline **67**. Extrusion of nitrogen by heat or photoirradiation leads to two possible products, **68** and **69**, respectively (Scheme 19).[64]

This 1,3-dipolar cycloaddition was performed by Wang and co-workers in a vibration ball mill.[65] By milling a mixture of C_{60}, glycine ethyl ester hydrochloride and sodium nitrite in a 1:1:2 ratio (60 Hz, 30 min), the stable fullerene-fused 2-pyrazoline **70** was obtained in 48% yield (Scheme 20). Presumably,
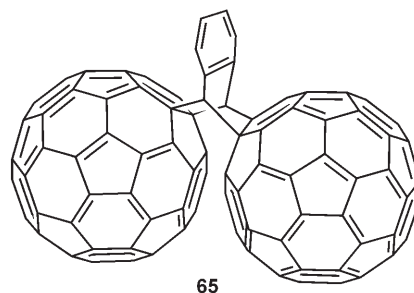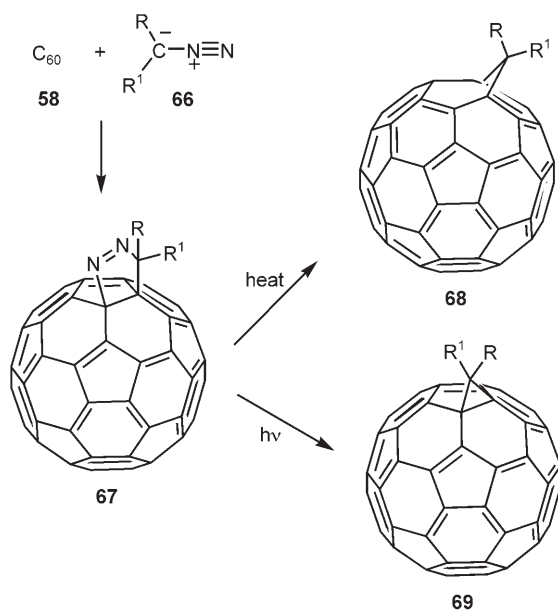

Scheme 18. The [4+2] cycloaddition of fullerene C_{60} and anthracene.

Figure 2. The cycloaddition product from C_{60} and phthalazine under ball milling conditions, followed by heating.

Scheme 19. The 1,3-dipolar cycloaddition with ethyldiazo-acetate.

the initially formed fulleropyrazoline intermediate of type **67** (R = H, R^1 = COOEt) was labile and isomerized under the ball milling conditions to the observed product **70**.

Although this reaction was performed on only a 0.02 mmol scale and **66** was generated *in situ*, a word of caution should be added here. Mixtures of **58** and **66** can be explosive under ball milling conditions, and cautious grinding should only be done with hand and noise protection.

Another typical example of a 1,3-dipolar cycloaddition involving fullerenes is the Prato reaction. There, fullerenes react with azomethine ylide intermediates, which are readily generated from *N*-substituted glycines or other amino acids with aldehydes or ketones, to give compounds of type **71** (Figure 3).[66] As reported by Wang and Komatsu, the Prato reaction can also be performed in a ball mill (60 Hz, 1 h) using *N*-methyl- or *N*-ethylglycine in combination with various substituted benzaldehydes to afford **71** (with R^2 = H)
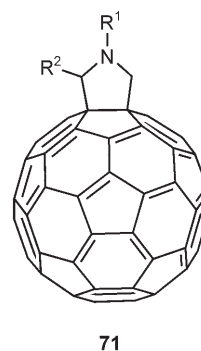

Figure 3. The product from a Prato reaction.

in moderate yields (20–30%).[67] It was also found that *N*-methylglycine can react even without the presence of any carbonyl compound to give *N*-methylful-leropyrrolidine (**71** with R^1 = Me, R^2 = H).

2.10 Other Metal-Free Reactions of Fullerenes

Another versatile method for creating methylene bridges in fullerenes is the Bingel reaction, starting from active methylene compounds such as α-halogenated esters and a base leading to cyclopropanated fullerenes. This reaction was performed in a vibration ball mill (60 Hz, 0.5 h) by Komatsu and Wang,[68a,b] and, surprisingly, under these solvent-free conditions the reaction with C$_{60}$, diethyl bromomalonate and DBU did not proceed at all. In contrast, however, the
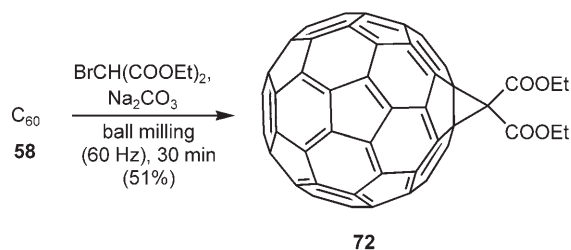
Scheme 21. The Bingel reaction of C$_{60}$ under ball milling conditions.
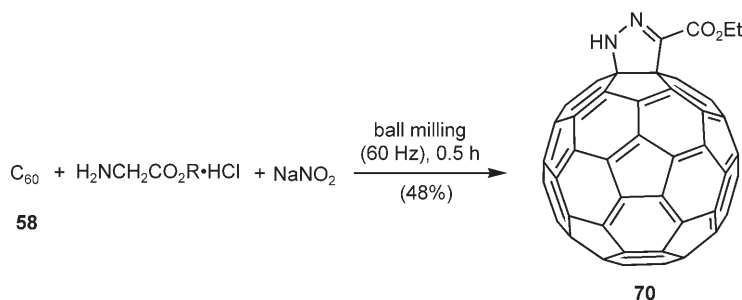
Scheme 20. The fullerene-fused 2-pyrazoline product **70** obtained in a 1,3-dipolar cycloaddition.

desired product **72** was obtained in 51% yield, when Na$_2$CO$_3$ was used as the base (Scheme 21). Furthermore, 7% of bisadducts were observed. This is the first example of a solid state Bingel reaction using a weak inorganic base. It was also possible to conduct the reaction on a large scale (0.5 g of C$_{60}$) leading to **72** with an essentially unchanged yield.

Since methanofullerenes can also be synthesized directly from malonate esters in the presence of DBU and CBr$_4$,[69] Komatsu and Wang investigated this reaction variant as well. Whereas under standard conditions the Bingel product **72** was obtained from diethyl malonate, 1,4-bisadduct **73** was formed, when the reaction was performed in the absence of CBr$_4$. With ethyl acetoacetate as the substrate, dihydrofuran-fused C$_{60}$ derivative **74** was obtained (Figure 4).

For both products, the authors suggested an oxygen-induced one-electron oxidation of the initially formed functionalized C$_{60}$ anion to its radical. To support this hypothesis, a reaction in the absence of air was run and, indeed, no formation of the products was observed.

3 Stoichiometric and Catalytic Metal-Mediated Transformations

3.1 The Suzuki Reaction

The first synthesis of unsymmetrical biaryls by cross-coupling reactions of arylboronic acids with aryl halides was reported by Suzuki, Miyaura and Yanagi in 1981.[70] Since then, this reaction has been carried out using various palladium catalysts, bases, and solvents, the combinations of which significantly affect the product yields and selectivities.[71] Applying this well-known methodology Axelsson and co-workers described the first solvent-free variant in 2000.[72] By means of a planetary ball mill, the authors reported the coupling of phenylboronic acid (**75**) with a series of aryl bromides **76**, using 2 equivs. of the boronic

acid, 5 mol% of Pd(PPh$_3$)$_4$ as the catalyst, and 3 equivs. of K$_2$CO$_3$ as the base. Solid NaCl (35 equivs.) was used as an additive in this procedure, in order to improve the mechanical properties of the reaction mixture. Interestingly, the Suzuki reaction afforded the desired products **77** in the highest yields when electron-rich bromides such as 3-bromoanisole or 3-bromoaniline were used as substrates (Scheme 22). In contrast, the Suzuki coupling of electron-deficient aryl or heteroaryl halides, such as 4-bromobenzonitrile, 4-bromopyridine hydrochloride, 3- or 5-bromopyridine, which were previously successfully coupled in solution,[71,73] did not proceed at all under the ball milling conditions. In general, no reaction occurred or very poor yields were obtained when nitro-substituted aryl halides (bromides and iodides) were used. These reactivity trends are remarkable and complementary to the normal scope of the Suzuki reaction performed in solution.

3.2 The Heck–Jeffery Reaction

Another versatile palladium-catalyzed coupling reaction for the formation of C–C bonds is the Heck reaction, where an aryl halide and an olefin are coupled to form styrenic derivatives. This reaction shows a broad functional group tolerance, allowing access to a large variety of compounds.[74] For example, Frejd and co-workers studied the palladium-catalyzed coupling of 2-amidoacrylates with aryl halides using the so-called Jeffery conditions[75] to obtain aromatic (Z)-didehydroamino acid derivatives. Various protected aromatic amino acids were obtained after catalytic hydrogenation.[76] However, the methodology for these Heck–Jeffery couplings involved extensive reaction times in N,N-dimethylformamide (DMF) at elevated temperatures and a subsequent tedious work-up. In order to find a more efficient method, in 2004 Frejd and co-workers investigated a solvent-free ball milling variant for the coupling of aryl halides with amidoacrylates to afford substituted dehydroalanines (Scheme 23).[77] In this study, the methyl and the
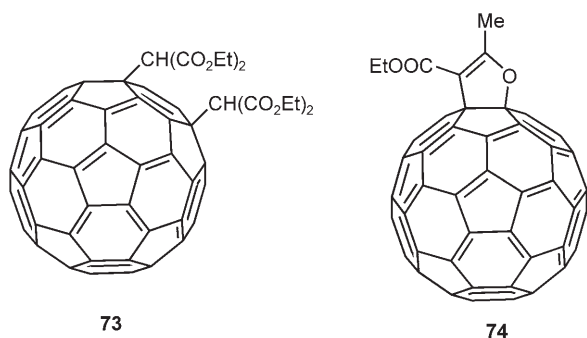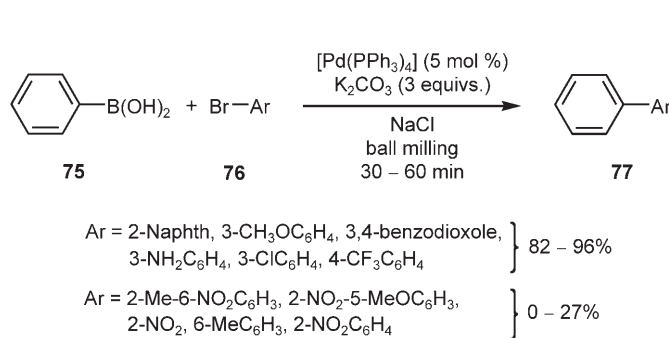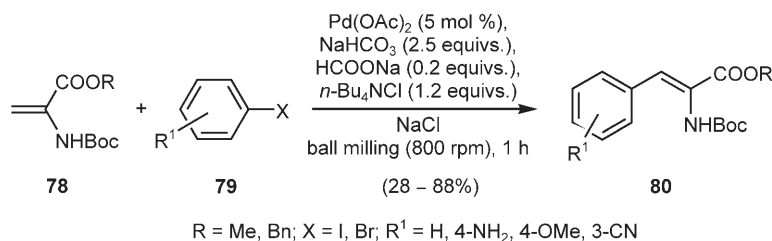

Figure 4. Unexpected products from the Bingel reaction under ball milling conditions in the absence of CBr$_4$.

Scheme 22. Suzuki coupling of phenylboronic acid with aryl bromides in a ball mill.
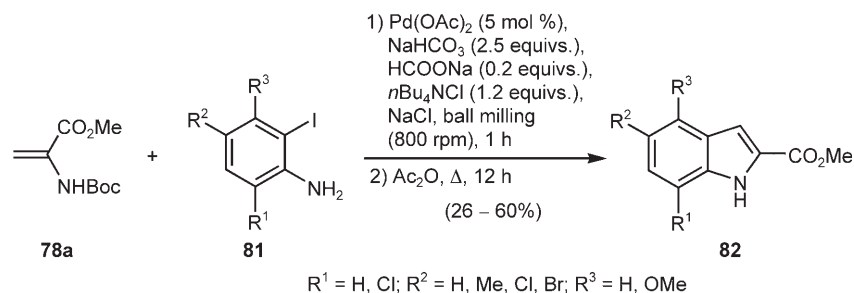
Scheme 23. Heck–Jeffery coupling of amido acrylates **78** with various aryl halides **79** in a ball mill.

benzyl esters of 2-*tert*-butoxycarbonylaminoacrylic acid (**78**) were ball-milled in a planetary ball mill (800 rpm, 1 h) with various aryl halides **79** under argon in a stainless steel vessel containing eight stainless steel balls. In general, aryl halides possessing electron-donating groups or with no other substitution proved to be the best coupling partners. As an advantage of this methodology, the use of DMF as the solvent was avoided, and the desired conjugated arenes **80** could be obtained in moderate to high yields (up to 88%) after only 60 min (compared to 8–40 h when reactions were performed in DMF).[74,75] Coupling of iodobenzene with the amidoacrylates **78**, afforded the corresponding products in 76 and 77% yield (R = Me and Bn, respectively). Using bromobenzene led to lower yields (57%), regardless of the amidoacrylate. No reaction progress was observed with chlorobenzene (after 1 h). With electron-deficient aryl or heteroaryl halides, which were previously coupled in DMF solution with moderate yields (20–47%),[76a,b] either poor conversion or no reaction was observed. Noteworthy is that this reactivity pattern corresponds to the one observed in the study of the Suzuki cross coupling (see Section 3.1).

In a subsequent study the same authors further investigated the utility of ball milling in this reaction. Since the best yield was initially observed in the coupling between 4-iodoaniline and the methyl ester of **78**, they examined the coupling of various halogen-substituted anilines with that particular amido acrylate.[78] As a result, they found that iodoanilines were the only substrates that coupled successfully, whereas all bromoanilines failed to react. As previously described,[76] electron-withdrawing substituents on the aryl iodide had a detrimental effect on the yields in the coupling reactions. Probably due to the proximity of the amino substituent to the iodide, poorer yields were obtained for 2-iodoanilines. The authors also observed that in some cases when 2-iodoanilines **81** were used, the resulting substituted α-amino dehydrophenylalanine derivatives spontaneously cyclized under mildly acidic or thermal conditions to form 2-carboxy-substituted indole derivatives **82** (Scheme 24).

The palladium-catalyzed coupling reaction between 2-iodoaniline and amidoacrylate **78a** in the ball mill for 1 h, followed by refluxing in acetic anhydride overnight gave the corresponding indole **82** in 60% yield. Interestingly, when the coupling was conducted under conventional conditions using *N*-methyl-2-pyrrolidone as solvent, no coupling product was formed after 24 h at 80 °C. In this case, heating to 130 °C was required to give the product in 50% yield. This is remarkable, as the temperature attained in the ball mill after one hour of milling seldom rises to this level, yet it is sufficient to form the product. Apparently, this result shows again that the conditions created during ball milling can alter reactivities, and that ball milling can successfully be applied in challenging synthetic transformations. However, in order to evaluate the impact of the elevated temperature on the alternation of the reaction behavior and to compare it to those effects that are not reproducable in solution (e.g., momentary pressure and temperature effects in the ball mill), it would be essential to repeat the reaction under ball milling conditions with a precise temperature control.

Scheme 24. Heck–Jeffery coupling of various iodoanilines **81** with the amidoacrylate **78a** in a ball mill.
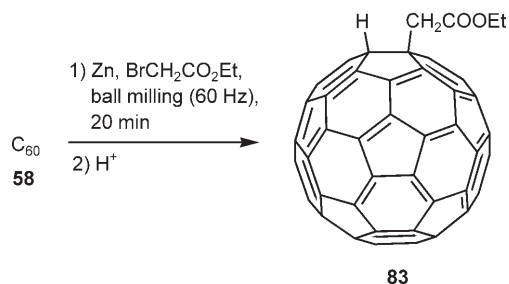
3.3 Nucleophilic Additions to Fullerenes

As fullerenes are electrophilic, they can readily be attacked by nucleophiles. The most basic reactions of such a kind are the addition of alkyllithium or Grignard reagents, reported to proceed in solution by Hirsch and co-workers.[79] A Reformatsky-type nucleophilic addition has been reported to proceed also in a vibration ball mill by Komatsu and co-workers.[80] (Interestingly, the solution version of this reaction is still unknown.) Reacting C_{60} (**58**), ethyl bromoacetate and zinc dust in the ball mill (60 Hz, 20 min) affords the desired product **83** in 17% yield, along with some other products such as the bisadduct and the cyclopropanated product (Scheme 25).

Conducting the reaction with different alkyl and aryl bromides in the presence of alkali metals (Na, K, or Li) afforded the corresponding alkylated or arylated fullerenes after 0.5 h in the ball mill (60 Hz) in 6–24% yield.

3.4 Oxidative Coupling of β-Naphthol

1,1′-Binaphthyl-2,2′-diol, BINOL (**84**), is the best known representative of axially chiral molecules and was first prepared as a racemate in 1873 by von Richter.[81] Since this date, its preparation has been widely studied.[82] A well-established method for the direct synthesis of binaphthols is the oxidative coupling of β-naphthols in the presence of a metal such as Fe(III), Mn(III), Cu(II), or Ti(IV), with chemical yields commonly up to 90%. Although generally performed in solution, some oxidative coupling reactions of phenols in the presence of $FeCl_3 \cdot 6H_2O$ proceed faster and more efficiently in the solid state.[83,84] For example, when a mixture of β-naphthol (**56**) and $FeCl_3 \cdot 6H_2O$ was finely powdered using a mortar and pestle and subsequently kept at 50°C for 2 h, racemic BINOL was obtained in 95% yield after treatment of the reaction mixture with dilute HCl.[83b,84] In contrast, keeping a solution of β-naphthol and $FeCl_3 \cdot 6H_2O$ in 50% aqueous MeOH at reflux for 2 h gave BINOL in only 60% yield. Some authors found it difficult to control the heating of a finely powdered mixture of β-naphthol and $FeCl_3 \cdot 6H_2O$ at 50°C.[83c,84] With the aim to overcome this limitation, Tanner and co-workers studied the solid-state synthesis of BINOL and, in 1997, they reported an easy and practical method for its preparation by means of a planetary ball mill.[85] The success of this method relied on the simultaneous intimate mixing of β-naphthol and $FeCl_3 \cdot 6H_2O$ in combination with a gentle heating of the reaction mixture (Scheme 26). For an effective mixing it was important to avoid the formation of a melt. Therefore, the procedure involved the use of solid NaCl as an additive, which improved the mechanical properties of the reaction mixture. Following this simple method, after only 1 h of milling and subsequent treatment of the reaction mixture with concentrated HCl, the desired product **84** was obtained in 87% yield (recrystallized material).

3.5 Radical Additions to Imines Mediated by Mn(III)

Over the past decades, manganese(III)-mediated free radical reactions have been extensively explored. Since they exhibit remarkable advantages over traditional peroxide or light-initiated processes, they have found widespread applications in organic synthesis.[86] In 2004, Wang and co-workers reported the first manganese(III)-mediated radical addition to imines.[87] In organic chemistry, manganese(III) acetate $[Mn(OAc)_3]$ has commonly been used in the generation of carbon-centered radicals from various carbonyl compounds and their oxidative addition to alkenes. However, since $Mn(OAc)_3$ is poorly soluble in organic solvents, harsh reaction conditions together with a tedious separation procedure are normally required.[88] In order to establish efficient and milder reaction conditions, Wang and co-workers investigated novel manganese(III) acetate dihydrate $[Mn(OAc)_3 \cdot 2H_2O]$-mediated intermolecular radical additions of 1,3-cyclohexanediones to *in situ* generated imines under solvent-free conditions, promoted by the ball milling technique. In this study, a variety of solid aromatic aldehydes **13** were reacted in a vibration ball mill (30 Hz) with solid 4-methylaniline (**85**) affording quantitatively the corresponding imines after 1 h. These *in situ* generated imines were then directly

Scheme 25. Reformatsky-type reaction of C_{60} under ball milling conditions.
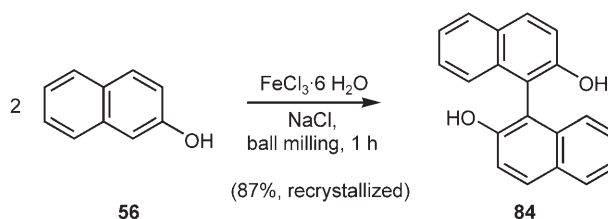
Scheme 26. Oxidative coupling of β-naphthol in a ball mill.
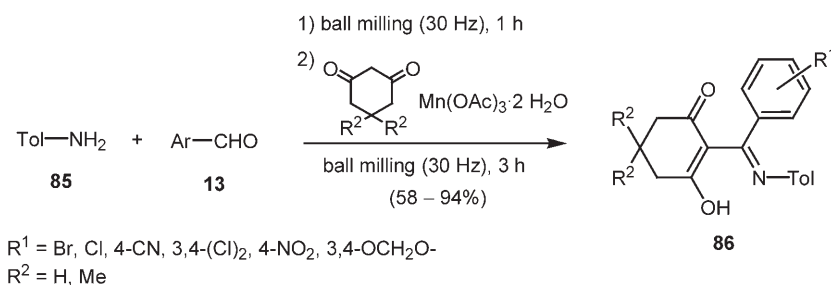
Scheme 27. Solid-state radical reactions of 1,3-cyclohexanediones with *in situ* generated imines in a ball mill.

reacted with 1,3-cyclohexanediones in the presence of $Mn(OAc)_3 \cdot 2 H_2O$ using a ball mill (Scheme 27).

Thus, after a total of only 4 h the final products **86** were obtained in good to excellent yields (58–94%). Interestingly, traditional $Mn(OAc)_3$-mediated radical reactions in organic solvents usually gave less than 70% yield. The efficiency of the ball milling procedure may be ascribed to an enhanced reaction rate resulting from ultimately higher concentrations of reactants and the high mechanical energy that can drive the reaction.

4 Conclusions

In conclusion, conducting reactions using mechanical milling techniques is an effective method for mixing reactants leading to various C–C bond forming reactions. Often, cleaner reaction profiles and higher yields are obtained, and the use of harmful organic solvents can be avoided (except in the work-up). Sometimes, running the reactions in a solid-state also leads to new and unexpected products, not available from the liquid-phase reactions.

Acknowledgements

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