Asymmetric Catalysis

DOI: 10.1002/anie.201408364

Nickel(0)-Catalyzed Enantioselective Annulations of Alkynes and Arylenoates Enabled by a Chiral NHC Ligand: Efficient Access to Cyclopentenones**

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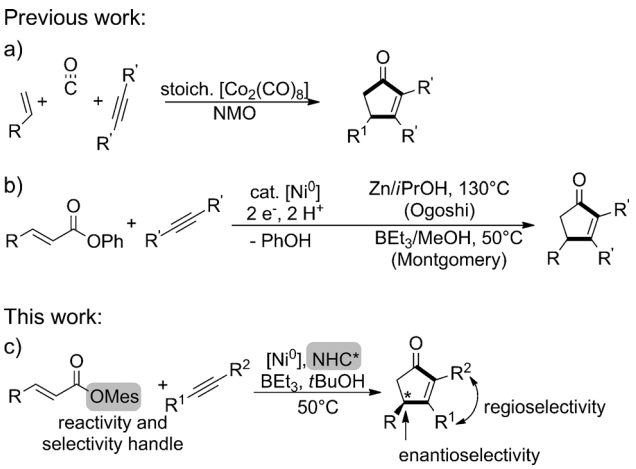
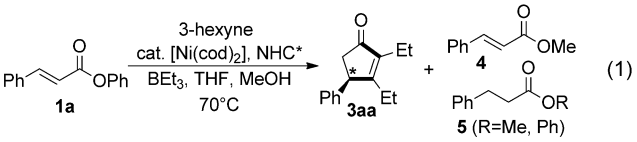
Abstract: *Cyclopentenones are versatile structural motifs of natural products as well as reactive synthetic intermediates. The nickel-catalyzed reductive [3+2] cycloaddition of α,β-unsaturated aromatic esters and alkynes constitutes an efficient method for their synthesis. Here, nickel(0) catalysts comprising a chiral bulky C_1-symmetric N-heterocyclic carbene ligand were shown to enable an efficient asymmetric synthesis of cyclopentenones from mesityl enoates and internal alkynes under mild conditions. The bulky NHC ligand provided the cyclopentenone products in very high enantioselectivity and led to a regioselective incorporation of unsymmetrically substituted alkynes.*

Cyclopentenones are important structural motifs in many natural products and bioactive compounds,[1] and are used as key synthetic intermediates of substituted cyclopentanones.[2] These characteristics promoted the development of a broad variety of synthetic methods to access cyclopentenones.[3] Among them, the Pauson–Khand reaction is a particularly useful three-component process.[4] Asymmetric variants have been devised,[5] however intermolecular reactions with unbiased olefins remain problematic. Although catalytic reactions with cobalt and other transition metals are reported,[6] stoichiometric metal–carbonyl complexes and/or the use of toxic carbon monoxide often make the development of alternative processes attractive.[7,8] In this respect, reductive Ni-catalyzed[9] [3+2] annulations of phenyl enoates and alkynes to give cyclopentenones were recently reported independently by Ogoshi et al.[10] and Montgomery et al.[11] Both substrates, the enoate and the alkyne, are common, stable, and readily accessible building blocks. Along the same the lines, the enoate that serves as three-carbon component omits the use of CO (Scheme 1). Given the relevance of the cyclopentenone scaffold, an efficient catalytic asymmetric variant of this method enabled by a suitable chiral phosphine or carbene ligand is a desirable and synthetically valuable goal. However, despite intense research efforts and the resulting growing number of chiral N-heterocyclic carbenes, only very scarce examples of asymmetric NHC–Ni catalysis have been reported so far.[12] This discrepancy is somewhat surprising, as simple achiral workhorse NHCs, such as IPr and IMes, belong to the most powerful and versatile ligands in Ni catalysis. It might be rationalized by the differences in the steric and electronic characteristics of many chiral N-heterocyclic carbenes with respect to IPr or IMes, often rendering them not competent for the envisaged transformation. These shortcomings represent an important gap in asymmetric catalysis.



Scheme 1. Synthesis of cyclopentenones. a) [2+2+1] cycloaddition (classical Pauson–Khand reaction), b) reductive Ni^0-catalyzed [3+2] cycloaddition, c) asymmetric reductive Ni^0-catalyzed [3+2] cycloaddition.

Herein we report a Ni-catalyzed annulation of a wide range of acrylates and alkynes enabled by a chiral N-heterocyclic carbene for the asymmetric synthesis of cyclopentenones. In addition to the challenge of finding an appropriate chiral (NHC or phosphine) ligand for this transformation, the nature of the reduction system to close the catalytic cycle is critical for the reaction outcome [Eq. (1)]. While Ogoshi's system consisting of zinc powder and *i*PrOH as solvent required very high reaction temperatures of 130 °C,[10] thus impeding efficient asymmetric



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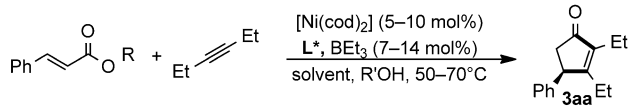
[**] This work was supported by the Swiss National Science Foundation (no. 137666). We thank Dr. R. Scopelliti for X-ray crystallographic analysis of compounds **3 la** and **6**. NHC = N-heterocyclic carbene.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201408364.

reactions, Montgomery's triethylborane/protic solvent protocol[11] allowed homogenous reaction mixtures at lower temperatures. However, in our case, the advantage of using chiral carbene ligands came along with two issues: 1) the competing transesterification of the reactive phenol ester with the added methanol gave unreactive methyl cinnamate **4**, and 2) the direct 1,4 reduction gave saturated esters **5**.

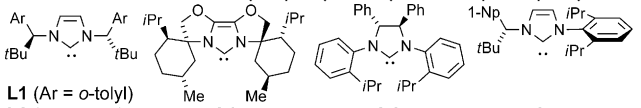
In order to get a first overview over the potential of the ligand, we evaluated a set of chiral N-heterocyclic carbenes using phenyl cinnamate and 3-hexyne as model substrates (Table 1, entries 1–4; for the full optimization study, see the Supporting Information). The ratio **3aa**/**4**/**5** varies significantly, depending on the chiral ligand NHC*. From the tested carbene scaffolds, only the Kündig-type ligands[13] **L1** and **L2** gave the desired enone product **3aa** in reasonable yields and selectivity, while many other carbenes or phosphine ligands failed. With this initial hit, the role of the aromatic ester was investigated next. Electron-poor aryl groups (entry 6) led to a reduced enantioselectivity and a largely increased propensity for transesterification with the methanol additive. Electron-rich aryl groups (entry 5) reacted more sluggishly and alkyl esters (entry 10) were completely unreactive. We found that the steric bulk of the phenol group is highly important for the reactivity and selectivity. In this respect, a larger 2,4,6-trimethyl phenyl group (entry 8) provided the optimal balance, giving **3aa** in 64% yield and 97.5:2.5 e.r. Further increase in the steric bulk with an even larger 2,6-diisopropyl group shut down the formation of **3aa** completely and led almost exclusively to the formation of the 1,4-reduced product (entry 9). Restriction of the amounts of MeOH and BEt_3 had a positive influence and the optimal ratio consisted of five equivalents of alcohol and two equivalents of borane. Switching to CPME (cyclopentyl methyl ether) as the solvent allowed to reduce the reaction temperature, and the bulkier *t*BuOH as proton source almost completely suppressed transesterification and reduction pathways, thus increasing the yield of cyclopentenone to 92%, but slightly reducing the enantioselectivity (entry 11). Given the favorable characteristics of the bulky IPr ligand for the cyclopentenone formation, we explored **L5**, a ligand with a mixed design between **L2** and IPr. Notably, **L5** gave rise to a substantially superior reactivity and selectivity, resulting in **3aa** in 92% yield and 3:97 e.r. (entry 12).[14] Moreover, under these conditions, the catalyst loading could be reduced to 1.25 mol% without affecting the reaction outcome significantly (entry 13). Such loadings are still rather rare for complex Ni^0-catalyzed transformations. **L5** was previously used only once in a single trial in asymmetric catalysis, resulting in a very poor selectivity for Pd-catalyzed oxindole formation.[15] This outcome is in stark contrast to the excellent results of the C_2-symmetric carbene **L2** for the same transformation as reported by Kündig. This striking performance discrepancy for two different reactions is clearly another testimony that one cannot conclude on the power of a chiral ligand for a specific transformation from a few established benchmark reactions.

Table 1: Optimization of the cyclopentenone formation.[a]



Entry	L*	R	Solvent	R'OH	Yield [%][b]	e.r.[c]
1[d]	**L1**	Ph	THF	MeOH	32	76:24
2	**L2**	Ph	THF	MeOH	52	92:8
3[d]	**L3**	Ph	THF	MeOH	1	74:26
4[d]	**L4**	Ph	THF	MeOH	0	–
5	**L2**	4-MeO-C_6H_4	THF	MeOH	53	92:8
6	**L2**	4-CF_3-C_6H_4	THF	MeOH	27	81:19
7	**L2**	3,5-Me_2-C_6H_3	THF	MeOH	82	91.5:8.5
8	**L2**	2,4,6-Me_3-C_6H_2	THF	MeOH	64	97.5:2.5
9	**L2**	2,6-*i*Pr_2-C_6H_3	THF	MeOH	1	97:3
10	**L2**	$CH(Ph)_2$	THF	MeOH	0	–
11[e]	**L2**	2,4,6-Me_3-C_6H_2	CPME	*t*BuOH	92	94:6
12[e]	**L5**	2,4,6-Me_3-C_6H_2	CPME	*t*BuOH	92	3:97
13[f]	**L5**	2,4,6-Me_3-C_6H_2	CPME	*t*BuOH	71	2.5:97.5
14	**L5**	3,5-Me-C_6H_3	CPME	*t*BuOH	60	2:98

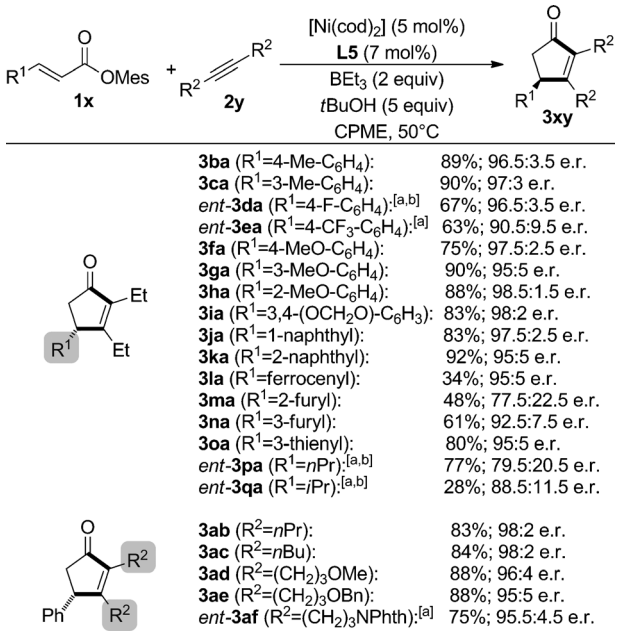
[a] Reaction conditions: enoate (0.10 mmol), 3-hexyne (0.15 mmol), $[Ni(cod)_2]$ (10.0 μmol), **L*** (11.0 μmol), MeOH (0.8 mmol), BEt_3 (0.5 mmol), at 70°C for 17 h. [b] Yields of isolated products. [c] Determined by HPLC on a chiral stationary phase. [d] At 50°C. [e] With $[Ni(cod)_2]$ (5.0 μmol), **L*** (7.0 μmol), *t*BuOH (0.5 mmol), BEt_3 (0.2 mmol), at 50°C. [f] 1.25 mol% catalyst, $[Ni(cod)_2]$ (1.25 μmol), **L5** (1.30 μmol), *t*BuOH (0.5 mmol), BEt_3 (0.2 mmol), at 50°C for 42 h, 79% conversion. CPME = cyclopentyl methyl ether, Np = naphthyl.



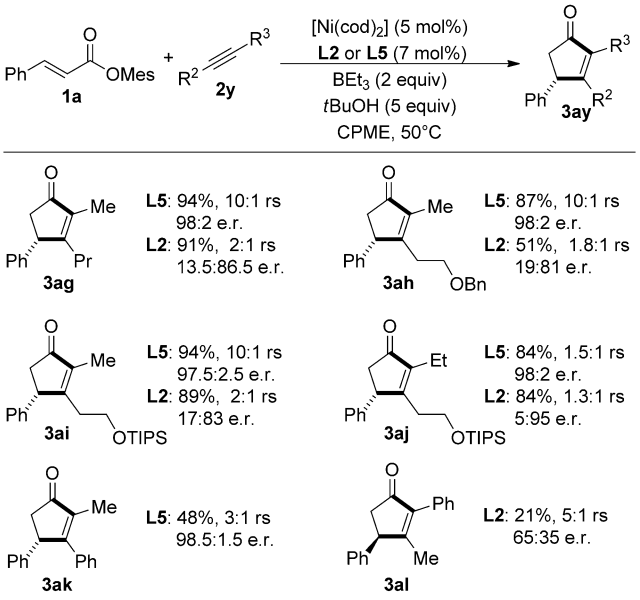
L1 (Ar = *o*-tolyl)
L2 (Ar = 1-Np)
L3
L4
L5

To explore the generality of the optimized process, we evaluated different substitution pattern on the acrylic ester. A wide range of cinnamic esters were tolerated (Scheme 2). The aromatic portion accommodated the most common electron-donating and electron-withdrawing groups. Irrespective of the position of the substituents (*ortho*, *meta*, or *para*), the yields and selectivities were consistently high. Notably, substrates with condensed arenes, heterocyclic substituents such as 3-furyl, 3-thienyl reliably provide cyclopentenones **3ba**–**3qa**. However, a 2-furyl group reduced both yield and selectivity, presumably because of a chelation of the nickel center with the oxygen atom of the furan. The absolute configuration of the cyclopentenones was unambiguously established by X-ray crystallographic analysis of the ferrocenyl-containing derivative **3la**.[16] Alkyl-substituted acrylates, such as **1p** and **1q**, undergo the annulation reaction, however with lower selectivity. Next, different internal alkynes were evaluated. A variety of dialkyl alkynes with functional groups were well tolerated and provided the cyclopentenones with excellent enantioselectivities. However, diaryl alkynes did not provide the desired cyclopentenones under these conditions.

We next evaluated nonsymmetrical internal alkynes. Especially for these challenging substrates, the advantage of the "mixed-design" carbene **L5** over the C_2-symmetrical carbene **L2** was apparent (Scheme 3). **L5** resulted in dramatically improved regioselectivities, while concomitantly increasing the enantioselectivity. Although aryl alkyl alkynes



Scheme 2. Scope of enantioselective synthesis of cyclopentenones **3**. Reaction conditions: **1** (0.10 mmol), **2** (0.15 mmol), [Ni(cod)$_2$] (5.0 μmol), **L5** (7.0 μmol), *t*BuOH (0.5 mmol), BEt_3 (0.2 mmol), at 50 °C for 17 h. [a] With **L2**. [b] MeOH used instead of *t*BuOH at 70 °C. cod = cycloocta-l,5-diene, Mes = mesityl, Phth = phthaloyl.



Scheme 3. Performance of **L5** versus **L2** with challenging unsymmetrical alkynes. Reaction conditions: **1** (0.10 mmol), **2** (0.15 mmol), [Ni(cod)$_2$] (5.0 μmol), **L*** (7.0 μmol), *t*BuOH (0.5 mmol), BEt_3 (0.2 mmol), at 50 °C. rs = regioselectivity.

turned out to be less reactive, they provided the corresponding enone. Noteworthy, in this case the regiochemistry was reversed with **L5**.[17]

The performance of **L5** prompted us to evaluate its structure more closely, and the corresponding Ni^{II} complex **6** is depicted in Figure 1.[16] Although **6** turned out to be not

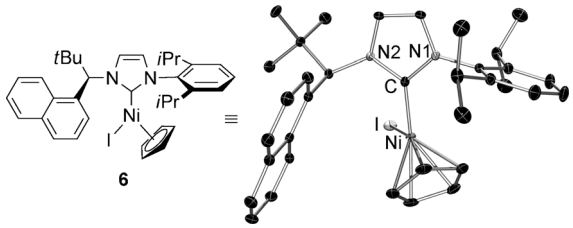
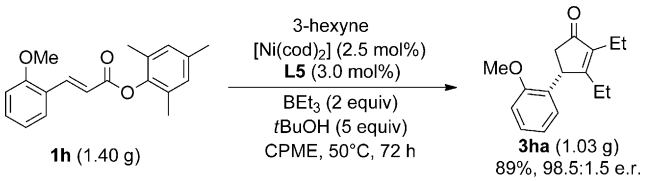


Figure 1. X-ray crystal structure of a Ni^{II} complex **6**.

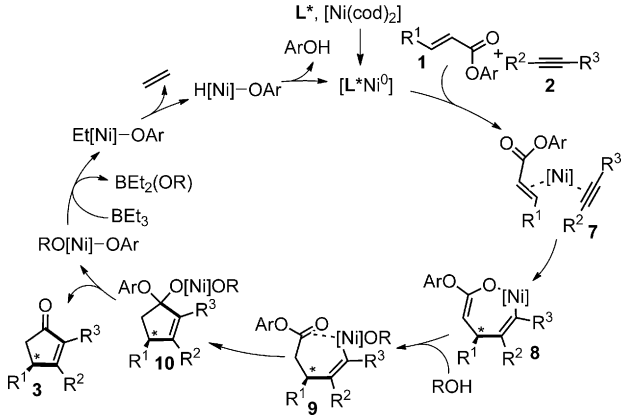
active in the reaction (presumably because of the difficulty to access the corresponding Ni^0 species), it showed that the 2,6-diisopropyl phenyl group provided an increased shielding compared to the chiral side chains. The importance of this increased bulk for a better orientation of the alkyne also manifested itself in the achiral transformations to give **3ag**. IMes with IPr gave 19:1 rs (73 %) and IMes only gave 3:1 rs (84 %). The high enantioselectivity also suggested that only a single chiral side chain of the carbene is involved in the enantioselection, presumably during the facial-selective coordination and incorporation of the enoate (**7**→**8**, Scheme 5).

To demonstrate the practicality of the process, we carried out a gram-scale reaction using substrate **1h** and a catalyst loading of 2.5 mol % nickel (Scheme 4). The desired product **3ha** was isolated in a comparable yield of 89 % and a selectivity of 98.5:1.5 e.r.

The following mechanistic scenario for the cycloaddition is plausible (Scheme 5).[10–11,18] First, both the enoate and alkyne substrates coordinate to the Ni^0 catalyst, which bears the chiral NHC ligand (**7**). Next, the enantioselectivity-determining step of the process is the oxidative cyclization,



Scheme 4. Gram-scale synthesis of cyclopentenone **3ha**.



Scheme 5. Plausible mechanism of the Ni-catalyzed asymmetric cycloaddition.

giving metallocyclic intermediate **8**. Cyclization and subsequent β-alkoxide elimination releases enone **3**. Transmetalation with triethylborane followed by β-hydride elimination gives a nickel hydride.[19] Reductive elimination then closes the catalytic cycle. Such intermediate nickel hydride species might be responsible for the observed side reaction, the straight 1,4 reduction of the enoate substrate.

In summary, we reported a highly enantioselective nickel(0)-catalyzed [3+2] cycloaddition of readily accessible aryl enoates and internal alkynes, giving access to cyclopentenones. A non-C_2-symmetric chiral carbene provides excellent enantioselectivity and superior discrimination in the regioselectivity of unsymmetrical dialkyl alkynes. The reaction proceeds with catalyst loadings as low as 1 mol% and is well suited for gram-scale reactions. The outlined high reactivity and selectivity of this ligand system should enable further asymmetric nickel-catalyzed transformations.

Received: August 19, 2014
Published online: ■■ ■■, ■■■■

Keywords: annulation · asymmetric catalysis · carbenes · cyclopentenones · nickel

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[19] BEt_3 has been shown to undergo partial methanolysis to $B(OMe)Et_2$ (see K.-M. Chen, K. G. Gunderson, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Chem. Lett.* **1987**, 1923–1926). Replacing BEt_3 by $B(OMe)Et_2$ resulted in an inactive catalytic system and no conversion was observed.

Communications

Asymmetric Catalysis

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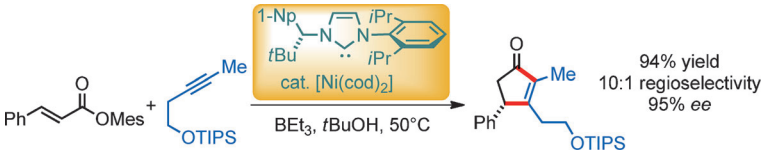
Nickel(0)-Catalyzed Enantioselective Annulations of Alkynes and Arylenoates Enabled by a Chiral NHC Ligand: Efficient Access to Cyclopentenones



Cyclization: Nickel(0) catalysts with a chiral bulky C_1-symmetric N-heterocyclic carbene ligand enabled the efficient asymmetric reductive [3+2] cycloaddition of enoates and alkynes, providing substituted cyclopentenones under mild conditions. The system provided the products in very high enantioselectivity and led to a regioselective incorporation of unsymmetrically substituted alkynes.